Effects of High- and Low-Efficacy Therapy in Secondary Progressive Multiple Sclerosis

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Abstract
Objective
To compare the clinical effectiveness of high- and low-efficacy treatments in patients with recently active and inactive secondary progressive multiple sclerosis (SPMS) after accounting for therapeutic lag.

Methods
Patients treated with high-efficacy (natalizumab, alemtuzumab, mitoxantrone, ocrelizumab, rituximab, cladribine, fingolimod) or low-efficacy (interferon beta, glatiramer acetate, teriflunomide) therapies after SPMS onset were selected from MSBase and Observatoire Français de la Sclérose en Plaques (OFSEP), 2 large observational cohorts. Therapeutic lag was estimated for each patient from their demographic and clinical characteristics. Propensity score was used to match patients treated with high- and low-efficacy therapies. Outcomes after the period of therapeutic lag was disregarded were compared in paired, pairwise-censored analyses.

Results
One thousand patients were included in the primary analysis. Patients with active SPMS treated with high-efficacy therapy experienced less frequent relapses than those on low-efficacy therapy (hazard ratio [HR] 0.7, p = 0.006). In patients with inactive SPMS, there was no evidence for a difference in relapse frequency between groups (HR 0.8, p = 0.39). No evidence for a difference in the risk of disability progression was observed.

Conclusion
In treated patients with SPMS, high-efficacy therapy is superior to low-efficacy therapy in reducing relapses in patients with active but not those with inactive SPMS. However, more potent therapies do not offer an advantage in reducing disability progression in this patient group.
Although the use of disease-modifying therapy (DMT) has altered long-term outcomes in patients with relapsing-remitting multiple sclerosis (MS),1,2 the outlook for treating secondary progressive MS (SPMS) has been more guarded.3-6 Nevertheless, clinicians often decide to treat patients with SPMS, particularly if there is evidence of overt inflammatory activity.7

For the first time in more than a decade, a new therapy with the potential to mitigate long-term disability has been licensed for the treatment of SPMS. In the Exploring the Efficacy and Safety of Siponimod in Patients With Secondary Progressive Multiple Sclerosis (EXPAND) trial, siponimod, a selective sphingosine-1-phosphate modulator, reduced the risk of disability accumulation, particularly in patients with relapses in the 2 years before study entry.8 A recent observational study from MSBase showed that patients with SPMS and evidence of episodic inflammation (but not those without) experience slower accrual of disability if treated consistently.7 Thus, both the evidence from clinical trials and registry data suggest that immunotherapy is warranted in patients with active SPMS. Whether high-efficacy therapy is superior to low-efficacy therapy in achieving these benefits is uncertain. A delayed onset of treatment effect, called therapeutic lag, may obscure therapeutic benefits if not accounted for particularly in cohorts enriched for patients with higher disability scores.9-12

The utility of observational data in the analysis of treatment outcomes has been well demonstrated in a number of cohorts and registries.13-15 In this study, we aimed to compare the effectiveness of high- and low-efficacy therapies in mitigating disability worsening and relapses in patients with active and inactive SPMS after accounting for therapeutic lag.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The MSBase registry13 (World Health Organization International Clinical Trials Registry Platform identifier: ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee and by the local ethics committees in all participating centers. The Observatoire Français de la Sclérose en Plaques (OFSEP) cohort15 (World Health Organization International Clinical Trials Registry Platform identifier: NCT02889965) was collected in accordance with French Commission Nationale Informatique et Libertés and French regulations of observational research. Written informed consent was obtained from enrolled patients as required.

Population and Database

Longitudinal clinical data were extracted from MSBase (166 centers in 37 countries) and OFSEP (39 French centers) in December 2019. We retrospectively identified patients with SPMS as per a previously validated, objective definition (Figure 1).16 The minimal dataset consisted of patient age, sex, MS onset, date of treatment start and stop (when applicable), treating center, and disability scores (quantified by Expanded Disability Status Scale [EDSS]) at baseline and at least 2 subsequent visits recorded ≥6 months apart after the estimated period of therapeutic lag (described below). To accommodate a delayed onset of treatment effect, treatments were required to be continued for at least the estimated duration of therapeutic lag for disability progression (described below, Table 1).

Therapy

We selected patients treated with a high-efficacy (natalizumab, alemtuzumab, mitoxantrone, ocrelizumab, rituximab, cladribine, fingolimod) or a low-efficacy (interferon beta-1a, interferon beta-1b, glatiramer acetate, teriflunomide) DMT after SPMS onset. To create a clear distinction between the high- and low-efficacy DMT groups, dimethyl fumarate was excluded from this analysis. Baseline was defined as the first commencement of a DMT after SPMS onset. Patients were analyzed in high- or low-efficacy treatment groups with an intention-to-treat design (all subsequent events were analyzed, regardless of changes in treatment status). Potential carryover effects of previous therapy were minimized by the
exclusion of patients treated with mitoxantrone within the last 2 years or alemtuzumab within the past 5 years or previous recipients of autologous hematopoietic stem cell transplantation.

**Therapeutic Lag**

Using a validated, objective differential-calculus derived method, we have previously reported that after treatment start, the onset of treatment effect on disability progression (Td) and relapses (Tr) is influenced by baseline EDSS score and annualized relapse rate (ARR); sex is an additional determinant of Td and MS phenotype of Tr (further details of the determinants of lag are included in Figure e-1, doi.org/10.5061/dryad.jwstiq82).

From combinations of these 3 characteristics, individualized estimates of Td and Tr were calculated with the following formulas (Table 1):

\[
Td = \sqrt{(T_{D_{EDSS}} - Td)^2 + (Td_{ARR} - Td)^2 + (Td_{sex} - Td)^2} \\
Tr = \sqrt{(T_{R_{EDSS}} - Tr)^2 + (Tr_{ARR} - Tr)^2 + (Tr_{MS\ phenotype} - Tr)^2}
\]

where Td is therapeutic lag for disability progression, Tr is therapeutic lag for relapses, Td is mean therapeutic lag for disability progression, and Tr is mean therapeutic lag for relapses.

The estimated lag durations with this method were consistent with results obtained when lag was directly calculated in sufficiently populated patient groups (Figure e-2, doi.org/10.5061/dryad.jwstiq82). Only events that occurred after the estimated therapeutic lag period were included in the analysis.

**Classification of SPMS**

Patients were classified as having active SPMS if they had a relapse or physician-reported neuroradiologic disease activity (new/enlarging T2 or gadolinium-positive lesions) in the 2 years before the start of study therapy. All other patients were classified as having inactive SPMS. Confirmation of relapses with a change in disability score was not required.

Data were recorded mostly at tertiary MS centers, during the course of a clinical visit, into the iMed or the MSBase online data entry system (MSBase) or EDMUS (OFSEP). Data quality assurance procedures were applied as described elsewhere and detailed in Table e-1, doi.org/10.5061/dryad.jwstiq82.

**Study Outcomes**

The primary study outcomes were relapses and disability progression after the start of study therapy.

Disability was assessed with the EDSS by Neurostatus accredited raters at each site. Disability progression was defined as an increase in EDSS score of 1.5 steps if the EDSS score is 0, 1 step if the EDSS score is 1 to 5.5, and 0.5 step if EDSS score is ≥6; confirmed over ≥6 months (in the absence of a relapse in the 30 days preceding confirmation); and sustained for the rest of the follow-up period. 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 at least 30 days after a previous relapse. A secondary study outcome was the proportion of patients requiring a wheelchair, defined as reaching an EDSS score ≥7 with confirmation over ≥6 months (in the absence of a relapse in the preceding 30 days).

All outcomes were studied in 2 subgroups: patients with active SPMS in the 2 years before treatment start and patients without evidence of disease activity in the prior 2 years (inactive SPMS).

**Matching and Statistical Analysis**

Matching and statistical analysis were conducted with R (3.6.2; R Foundation for Statistical Computing). Individual patients were matched on their propensity of receiving high- vs low-efficacy DMTs with the MatchIt package. Propensity scores were calculated with a multivariable logistic regression model of treatment allocation that used age, sex, EDSS score, number of relapses in the preceding 12 months, number of relapses in the preceding 24 months, MS duration, SPMS duration, country, and year (Figure e-3, doi.org/10.5061/dryad.jwstqjq82). The positivity assumption was satisfied (Table e-3). Patients were matched without replacement in a 3:1 ratio using nearest-neighbor matching within a caliper of 0.1 SD of the propensity score. Covariate balance was assessed by standardized mean difference. Standardized mean difference <0.1 was taken to indicate a negligible difference in the mean or prevalence of a covariate between groups. Subsequent analyses used weighted estimates to adjust for variable matching ratios. Pairwise censoring was used to control attrition bias, and all analyses were performed with paired models.

Cumulative hazard of confirmed disability progression or relapses was assessed with conditional proportional hazards models for recurrent events with robust estimation of variance and a frailty term for matched pairs (adjusted for visit density for disability progression). Time to confirmed EDSS score of 7.0 was evaluated with a Cox proportional hazards model. Only progression events that occurred after the estimated lag duration for disability progression and relapses that occurred after the estimated lag for relapses were included in the respective analyses. Patients were censored at last available follow-up. Within each matched patient pair, on-treatment follow-up was determined as the shorter of the 2 follow-up periods. Proportionality of hazards was evaluated with the Schoenfeld global test. Kaplan-Meier plots were used to visualize time-to-event data.

Five sensitivity analyses were carried out: (1) using a combined cohort with an exact match for active/inactive SPMS; (2) including only patients with baseline EDSS score <6; (3) changing the definition of active SPMS to having had relapses in the 24 months before baseline; (4) repeating the analysis without accounting for therapeutic lag; and (5) repeating the analysis with a fixed 3-year presumed duration of therapeutic lag.

| EDSS score | Annualized relapse rate | Sex | MS phenotype | Estimated duration of therapeutic lag, wk |
|------------|-------------------------|-----|--------------|----------------------------------------|
| <6         | <1                      | Female | —             | 27                                     |
| <6         | <1                      | Male  | —             | 46                                     |
| <6         | ≥1                      | Female | —             | 44                                     |
| <6         | ≥1                      | Male  | —             | 57                                     |
| ≥6         | <1                      | Female | —             | 42                                     |
| ≥6         | <1                      | Male  | —             | 56                                     |
| ≥6         | ≥1                      | Female | —             | 54                                     |
| ≥6         | ≥1                      | Male  | —             | 66                                     |
| <2         | <2                      | —     | SPMS          | 16                                     |
| ≥2 and <6  | ≥2                      | —     | SPMS          | 15                                     |
| ≥2 and <6  | <2                      | —     | SPMS          | 16                                     |
| ≥6         | <2                      | —     | SPMS          | 15                                     |
| ≥6         | ≥2                      | —     | SPMS          | 16                                     |

Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; SPMS = secondary progressive MS.
Data Availability

MSBase is a data processor and warehouses 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 each OFSEP and MSBase principal investigator (the data controllers), who need to be approached individually for permission.

Results

Of 7,359 patients with SPMS, a total of 1,000 patients (510 with active SPMS, 490 with inactive SPMS) from 88 centers fulfilled the inclusion criteria and were included in the study (Figure 1 and Table e-2, doi.org/10.5061/dryad.jwstqjq82). Of the 1,000 patients objectively identified as having SPMS, 565 (437 MSBase, 128 OFSEP) had a physician classification of relapsing-remitting MS. Details of the excluded patients are summarized in Table e-3, doi.org/10.5061/dryad.jwstqjq82.

Before matching, standardized differences in baseline characteristics between treatment groups were greater in the inactive SPMS cohort (Table e-4, doi.org/10.5061/dryad.jwstqjq82). Logistic regression models were used to calculate the probability of being treated with high- vs low-efficacy therapy in each cohort (Table e-5, doi.org/10.5061/dryad.jwstqjq82). Before matching, patients treated with high-efficacy treatment tended to be younger and to have higher EDSS scores. In both groups, year of baseline and country-specific practice influenced treatment choice. Country and year of treatment, with the number of patients receiving high- and low-efficacy DMT, are available in Table e-6, doi.org/10.5061/dryad.jwstqjq82.

Characteristics of the patients retained after matching are shown in Table 2. The matching procedure retained 80% of the active SPMS and 71% of the inactive SPMS cohorts and resulted in a 94.9% to 95.6% improvement in balance between the matched groups (Figure e-4, doi.org/10.5061/dryad.jwstqjq82). A close match was obtained on the individual determinants of treatment allocation (standardized differences ≤20% for most variables, indicating >85% overlap between groups).32

Outcomes were assessed after the estimated lag duration for relapses and disability progression (Table 1). The results of the primary and secondary analyses are shown in Figure 2. In patients with active SPMS, the cumulative hazard of relapses was lower if treated with high-efficacy compared with low-efficacy DMT (hazard ratio [HR] 0.7, 95% confidence interval [CI] 0.5–0.9; Figure 2A.a). No difference in the cumulative hazard of relapses was seen in patients with inactive SPMS (HR 0.8, 95% CI 0.6–1.2; Figure 2B.a).

We did not find evidence for a difference in cumulative hazards of confirmed disability progression between the high- and low-efficacy cohorts for both the active SPMS (HR 1.1, 95% CI 0.8–1.5; Figure 2A.b) and inactive SPMS (HR 1.3, 95% CI 0.9–1.8; Figure 2B.b.) groups. Similarly, we did not observe any difference in the proportion of patients free from disability progression in either the active SPMS (HR 0.9, 95% CI 0.7–1.2) or inactive SPMS (HR 1.2, 95% CI 0.7–1.8) groups.

We did not find evidence for a difference in the risk of reaching confirmed EDSS score of ≥7 according to treatment allocation (active SPMS: HR 0.8, 95% CI 0.5–1.3, Figure 2A.c; inactive SPMS: HR 1.7, 95% CI 0.9–3.1, Figure 2B.c).

The results of the primary analysis were fully replicated in the sensitivity analyses (Table e-7, doi.org/10.5061/dryad.jwstqjq82). In particular, the results were consistent when we repeated the analysis without accounting for therapeutic lag or when we assumed a uniform 3-year duration of therapeutic lag. A 3-year duration was selected as a conservative estimate on the basis of the upper bounds of the estimated lag duration.

Discussion

In this observational, propensity score–matched analysis of treatment outcomes in patients with SPMS from MSBase and OFSEP, we found that high-efficacy therapy was superior to low-efficacy therapy in reducing relapses in patients with evidence of episodic inflammatory activity in the 2 years before starting therapy. There was no evidence for a difference in the risk of disability progression in patients with SPMS treated with high- and low-efficacy DMT.

The treatment of patients with SPMS has been disappointing, with both high- and low-efficacy therapies generally failing to reduce the rate of disability accrual.33,34 When an effect of therapy in SPMS was reported, it was suggested that mainly patients with evidence of superimposed inflammatory activity during the progressive disease course benefit from therapy. In the EXPAND clinical trial, the benefit of siponimod on disability progression was driven by the group of patients with relapses in the 2 years before study inclusion.3 In the subgroup without relapses, treatment failed to show a statistically significant benefit. Similarly, in the Effect of Natalizumab on Disease Progression in Secondary Progressive Multiple Sclerosis (ASCEND) trial of natalizumab in SPMS, consisting of patients with inactive SPMS and a median 4.9 years since their last relapse, natalizumab did not show any effect on disability progression.3

The results from clinical trials are corroborated by the results from observational data. In our previous study using the MSBase cohort, being on any treatment at the time of SPMS conversion modified the risk of becoming wheelchair dependent in a sensitivity analysis unadjusted for postbaseline relapse rate but not in the fully adjusted analysis.5 Moreover, patients with SPMS and ongoing relapses were less likely to experience disability worsening if they spent a greater proportion of time on DMT.7 DMT had little effect on disability progression in those with SPMS without relapses.
Table 2 Demographic, Clinical, and Paraclinical Characteristics of the Matched Patients

|                         | Active SPMS |                               | Inactive SPMS |                               |
|-------------------------|-------------|--------------------------------|---------------|--------------------------------|
|                         | High efficacy (n = 254) | Low efficacy (n = 154) | Cohen d | High efficacy (n = 151) | Low efficacy (n = 198) | Cohen d |
| Patients, n (% female)  | 254 (72) | 154 (71) |                           | 151 (71) | 198 (71) |                          |
| Registry, n (%)         |            |            |                            |            |            |                            |
| MSBase                  | 181 (71.3) | 111 (72.1) |                          | 104 (69.9) | 134 (67.7) |                          |
| OFSEP                   | 73 (28.7)  | 43 (27.9)  |                           | 47 (31.1)  | 64 (32.3)  |                          |
| Age, mean (SD), y       | 45.21 (6.80) | 45.94 (10.27) | 0.08 | 47.54 (9.01) | 47.62 (8.48) | 0.01 |
| Disease duration, mean (SD), y | 13.74 (5.63) | 13.87 (8.91) | 0.02 | 16.69 (8.99) | 16.71 (7.10) | 0.002 |
| SPMS duration, mean (SD), y | 1.80 (1.59)  | 1.88 (2.36)  | 0.04 | 1.78 (2.19)  | 1.95 (2.18)  | 0.08 |
| Disability, EDSS score step, mean (SD) | 5.37 (0.82) | 5.36 (1.20) | 0.03 | 5.63 (1.07) | 5.50 (1.00) | 0.13 |
| Relapses in 12 mo before baseline, mean (SD), n | 0.82 (0.62) | 0.70 (0.70) | 0.18 | 0.00 (0.00) | 0.00 (0.00) | <0.001 |
| Relapses in 24 mo before baseline, mean (SD), n | 1.37 (0.73) | 1.22 (1.00) | 0.17 | 0.00 (0.00) | 0.00 (0.00) | <0.001 |
| Relapse-free 12 mo before baseline, n (%) | 93 (36.6) | 66 (42.9) | 151 (100.0) | 198 (100.0) |                          |
| Relapse-free 24 mo before baseline, n (%) | 39 (15.4) | 34 (22.1) | 151 (100.0) | 198 (100.0) |                          |
| MRI: new or contrast-enhancing lesions, n (%) |            |            |                            |            |            |                            |
| Imaging available within 2 y of baseline | 144 (56.7) | 66 (42.9) | 49 (22.5) | 47 (23.7) |                          |
| Absent                  | 66 (45.8)* | 36 (54.5)* | 49 (100.0)* | 47 (100.0)* |                          |
| Present                 | 78 (54.2)* | 30 (45.5)* | 0 (0.0)* | 0 (0.0)* |                          |
| Treatment at inclusion, n (%) |            |            |                            |            |            |                            |
| Alemtuzumab             | 2 (0.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) |                          |
| Mitoxantrone            | 43 (16.9) | 0 (0.0) | 56 (37.1) | 0 (0.0) |                          |
| Natalizumab             | 105 (41.3) | 0 (0.0) | 27 (17.9) | 0 (0.0) |                          |
| Ocrelizumab             | 3 (1.2) | 0 (0.0) | 3 (2.0) | 0 (0.0) |                          |
| Rituximab               | 4 (1.6) | 0 (0.0) | 4 (2.6) | 0 (0.0) |                          |
| Cladribine              | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) |                          |
| Fingolimod              | 96 (37.8) | 0 (0.0) | 61 (40.4) | 0 (0.0) |                          |
| Teriflunomide           | 0 (0.0) | 16 (10.4) | 0 (0.0) | 27 (13.6) |                          |

Continued
Table 2 Demographic, Clinical, and Paraclinical Characteristics of the Matched Patients (continued)

|                          | Active SPMS | Low efficacy (n = 154) | Cohen d | Inactive SPMS | Low efficacy (n = 198) | Cohen d |
|--------------------------|------------|------------------------|---------|--------------|------------------------|---------|
|                          | High efficacy (n = 254) | Low efficacy (n = 154) |         |              | High efficacy (n = 151) | Low efficacy (n = 198) |         |
| Glatiramer acetate       | 0 (0.0)    | 48 (31.1)              | 0.05    | 0 (0.0)      | 64 (32.4)              | 0.05    |
| Interferon beta-1a intramuscular | 0 (0.0)    | 17 (11.0)              | 0.00    | 0 (0.0)      | 9 (4.5)                | 0.00    |
| Interferon beta-1b       | 0 (0.0)    | 39 (25.3)              | 0.00    | 0 (0.0)      | 65 (32.8)              | 0.00    |
| Pegylated interferon beta-1a | 0 (0.0)    | 3 (1.9)                | 0.00    | 0 (0.0)      | 4 (2.0)                | 0.00    |
| Interferon beta-1a subcutaneous | 0 (0.0)    | 31 (20.1)              | 0.00    | 0 (0.0)      | 29 (14.6)              | 0.00    |
| Preceding treatment, n (%) |            |                        |         |              |                        |         |
| High efficacy            | 50 (19.7)  | 18 (11.7)              |         | 42 (27.8)    | 28 (18.1)              |         |
| Low efficacy             | 187 (73.6) | 97 (63.0)              |         | 83 (55.0)    | 116 (50.8)             |         |
| None                     | 17 (6.7)   | 39 (25.3)              |         | 26 (17.2)    | 54 (31.2)              |         |
| Time since discontinuation of preceding therapy, median (IQR), d | 44 (7, 223) | 102 (3, 539)          | 0.23    | 34 (8, 109) | 40 (1, 459)            | 0.30    |
| Prebaseline proportion of time on treatment, mean (SD) | 0.44 (0.20) | 0.31 (0.28)           | 0.55    | 0.40 (0.29) | 0.30 (0.26)            | 0.34    |
| Followed up within 1 y of MS onset, n (%) | 45 (17)    | 29 (18)                |         | 29 (19)      | 29 (15)                |         |
| ARR during year 0–5, median (IQR) | 0.8 (0.6, 1.0) | 0.6 (0.4, 0.8)        | 0.50    | 0.5 (0.3, 0.8) | 0.6 (0.2, 1.15)       | 0.24    |
| Postbaseline follow-up, median (IQR), y b | 4.2 (2.5, 6.0) | 4.2 (2.5, 6.0)        | 0.00    | 4.1 (2.5, 5.9) | 4.1 (2.5, 5.9)        | 0.00    |
| Persistence in treatment group, median (IQR), y b | 2.2 (1.5, 3.6) | 2.1 (1.5, 3.3)        | 0.06    | 2.1 (1.5, 3.3) | 2.5 (1.8, 4.1)        | 0.29    |
| Estimated duration of therapeutic lag (disability progression), mean (SD), d | 325 (75) | 329 (70)               | 0.05    | 276 (74)     | 277 (69)               | 0.02    |
| Baseline year, mean (SD) | 2010 (4.6) | 2009 (4.5)             | 0.19    | 2010 (5.4)   | 2010 (5.6)             | 0.01    |

Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; IQR = interquartile range; MS = multiple sclerosis; OFSEP = Observatoire Français de la Sclérose en Plaques; SPMS = secondary progressive MS.

Prebaseline refers to time from the first recorded visit to baseline. Prebaseline proportion of time on treatment = prebaseline time treated/prebaseline follow-up.

* Proportion of patients with available MRI.

* Follow-up and persistence after pairwise censoring, as per the primary analysis.
These studies compared the outcomes between patients with SPMS treated with immunotherapies and those who were untreated. No prior studies compared the effectiveness of different classes of DMT in SPMS. Our observation that high-efficacy therapies are superior to low-efficacy therapies only in reducing relapses in patients with recently active SPMS provides valuable guidance for the choice of immunotherapy in SPMS. When the goal of treatment is to alleviate ongoing relapse activity, more potent therapy is justified, whereas to mitigate the risk of disability progression in SPMS, both high- and low-efficacy immunotherapies show comparable effectiveness.

The so-far largely disappointing results of trials of immunotherapies in SPMS have been attributed to many factors. One...
of the potential reasons is the delay in the onset of treatment effect, called therapeutic lag. The concept of therapeutic lag was suggested on the basis of the observation that in a trial of interferon beta-1b in primary progressive MS, disability outcomes favored treatment over placebo at year 7 but not year 2 after randomization. Lag was explored further in a post hoc analysis of the placebo-controlled Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS (SPECTRIMS; interferon beta in SPMS) and PROMiSe (Glatiramer Acetate in Primary Progressive multiple sclerosis) trials, in which treatment was reported to benefit disability progression with a 2- to 2.5-year delay. This analysis suggested an empirical solution with the delay to treatment effect estimated in proportion to the degree of preexisting disability. The method to estimate therapeutic lag requires a consider-able number of events (relapses or disability progression events) to ensure accuracy and reproducibility of the estimate. Therefore, we were able to directly estimate therapeutic lag duration only in the most populous patient subgroup (such as female patients with an EDSS score ≤6 and ARR ≥1). To estimate lag in the less represented groups (such as female patients with an EDSS score ≥6 and ARR ≥1), we have used an indirect estimation of therapeutic lag. This approach assumes a cumulative effect of patient and disease factors on the duration of lag. Where both direct and indirect estimates were available, these estimates were closely aligned. If minor inaccuracies were present in the indirect estimates of lag, the comparisons of the effectiveness of 2 treatment classes were robust to such error. This was demonstrated by the sensitivity analyses performed without accounting for a delayed treatment effect and with a fixed conservative estimate of lag for all patients. Drugs with other mechanisms of action are anticipated to have different lag durations than those represented.

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The limitations of this study are inherent in the observational nature of the studied dataset. Due to the low numbers of patients treated with individual drugs, we combined exposure to therapies into high- and low-efficacy groups to maximize analytical power. It is therefore possible that individual therapies within each group may have an effect on disability outcomes in SPMS. This remains to be explored in a dedicated analysis. We defined SPMS activity on the basis of relapses and MRI activity in the 2 years before the start of treatment because relapses alone may underestimate inflammatory activity. Because a significant number of patients, particularly in the inactive SPMS group, did not have imaging available in the 2 years before baseline, the radiologic evidence of focal inflammation may have been underestimated. Nevertheless, our findings remained consistent in a sensitivity analysis in which active SPMS was defined on the basis of relapses only. This study included 565 patients classified as having SPMS as per an objective algorithm who were classified by the treating clinician as having relapsing-remitting MS. Misclassification of SPMS in observational data is, however, not uncommon, particularly in patients treated with DMT. Continued treatment eligibility may therefore influence the decision to adjust MS phenotype. The use of an objective SPMS definition thus enabled inclusion of a consistent patient cohort among multiple international sites. An intrinsic limitation of our study lies in the EDSS metric as a disability outcome. Limitations of the EDSS include floor and ceiling effects, nonlinearity, interrater and intrarater variability, and a lower sensitivity to change at higher scores. While imperfect, it remains the most commonly collected measure of disability in routine practice that reflects standard neurologic examination and is widely used in clinical trials and observational studies. It is reassuring that our findings were corroborated with the use of a robust disability milestone such as wheelchair dependency.

Observational data are prone to a number of biases. In this analysis, we used propensity score–based methods, with rigorous attention to attrition, reporting, indication bias, and the positivity assumption. While propensity score methods do not eliminate unmeasured confounders, our results remain consistent in all sensitivity analyses with varying inclusion criteria and across several complementary endpoints. While we have adjusted for factors in the 2 years before baseline, our analysis did not adjust for events that occurred in the earlier stages of MS (i.e., the 45 patients with active SPMS treated with high-ef- ficacy therapy who were followed up since MS onset had higher ARR in the first 5 years of MS than those treated with low-efficacy therapy). The reported findings are relevant to the population of patients with SPMS treated in MS centers who were deemed eligible for immunotherapy by their neurologists.

Despite the lack of evidence guiding treatment selection, anti-inflammatory DMTs are not infrequently used in the treatment of patients with SPMS. This study, together with the previously published work, suggests that overt inflammatory activity in progressive MS remains a treatable target. In patients with SPMS for whom a decision has been made to start therapy, the presence of clinical or radiologic
inflammation in the prior 2 years helps to identify individuals in whom high-efficacy therapy may more effectively ameliorate relapses. However, the present data did not provide evidence for superiority of the most potent immunotherapies over lower-efficacy therapies in controlling disability. Therefore, the decision to use immunotherapy in patients with active SPMS should carefully consider the amount of preceding relapsing activity and the risk-vs-benefit profiles of different therapeutic options.

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Disclosure
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Sanofi-Genzyme, Novartis, Merck, and Biogen; served on a steering committee for Brain Atrophy Initiative from Sanofi-Genzyme; received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL, and Merck; and received research support from Biogen. Go to Neurology.org/N for full disclosures.

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### Appendix (continued)

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