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Determinants of therapeutic lag in multiple sclerosis

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Abstract

Background: A delayed onset of treatment effect, termed therapeutic lag, may influence the assessment of treatment response in some patient subgroups.

Objectives: The objective of this study is to explore the associations of patient and disease characteristics with therapeutic lag on relapses and disability accumulation.

Methods: Data from MSBase, a multinational multiple sclerosis (MS) registry, and OFSEP, the French MS registry, were used. Patients diagnosed with MS, minimum 1 year of exposure to MS treatment and 3 years of pre-treatment follow-up, were included in the analysis. Studied outcomes were incidence of relapses and disability accumulation. Therapeutic lag was calculated using an objective, validated method in subgroups stratified by patient and disease characteristics. Therapeutic lag under specific circumstances was then estimated in subgroups defined by combinations of clinical and demographic determinants.

Results: High baseline disability scores, annualised relapse rate (ARR) $\geqslant$ 1 and male sex were associated with longer therapeutic lag on disability progression in sufficiently populated groups: females with expanded disability status scale (EDSS) < 6 and ARR < 1 had mean lag of 26.6 weeks (95% CI = 18.2–34.9), males with EDSS < 6 and ARR < 1 31.0 weeks (95% CI = 25.3–36.8), females with EDSS < 6 and ARR $\geqslant$ 1 44.8 weeks (95% CI = 24.5–65.1), and females with EDSS $\geqslant$ 6 and ARR < 1 54.3 weeks (95% CI = 47.2–61.5).

Conclusions: Pre-treatment EDSS and ARR are the most important determinants of therapeutic lag.

Keywords: Neurology, multiple sclerosis, observational study, therapeutic lag

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Introduction

After starting a disease-modifying therapy (DMT), there is a delay to full clinically apparent treatment effect, referred to as 'therapeutic lag'.[1–5] As treatment decisions are often made in the face of ongoing disease activity, accurate expectations of timing of treatment effect is clinically relevant.[6] Using an objective, differential calculus-derived method, the duration of therapeutic lag has been estimated to range between 12–30 weeks for relapses and 30–70 weeks for disability progression.[7]

It has been suggested that the duration of therapeutic lag is not uniform among patients and may increase proportionate to the degree of pre-existing disability.[3] A randomised placebo-controlled trial of interferon beta-1b in primary progressive multiple sclerosis (PPMS) failed to detect a beneficial treatment response after 2 years.[8] When patient outcomes were revisited at year 7, after a 5-year treatment-free period, cognitive and upper limb outcomes in patients initially randomised to interferon beta-1b were superior to those randomised to placebo.[4] This suggests that in progressive MS, therapeutic lag may obscure a detectable effect of therapy if not accounted for analytically. As yet, therapeutic lag has not been incorporated into clinical trial design. Understanding the effect of individual disease characteristics on the duration of therapeutic lag might aid personalised DMT decision-making.

In this study, we apply an objective, externally validated method to measure the duration of therapeutic lag with respect to disability progression and relapses. We aim to explore the associations of the duration of therapeutic lag with patient and disease characteristics.

Methods

The MSBase registry[9] (WHO ICTRP, ID ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee and by the local ethics committees in all participating centres. Written informed consent was obtained from enrolled patients as required. The Observatoire Français de la Sclérose en Plaques (OFSEP) cohort[10] (WHO ICTRP, ID NCT02889965) was collected in accordance with French *Commission Nationale Informatique et Libertés* and French law relative to observational research.

Population and data collection

Longitudinal clinical and demographic data were extracted from the MSBase registry (125 centres in 37 countries) and OFSEP registry (39 French centres) in December 2018. Inclusion criteria consisted of: MS diagnosis as per the 2005[11] or 2010[12] McDonald Criteria, commencement of and persistence on a DMT for at least 12 months, minimum 3-year pre-treatment follow-up, yearly visits during the treatment epoch (defined below) and availability of the minimum data set. The minimum data set consisted of patient age, sex, disease phenotype, disability (quantified by the expanded disability status scale (EDSS)) at baseline and two subsequent timepoints at least 6 months apart, MS duration, documentation of relapses and date of treatment start and cessation (where applicable).

The prospective follow-up period was defined as time from first to the last available EDSS. Study baseline was defined as the start of the index DMT. All DMTs were eligible for study inclusion. A treatment epoch was defined as time including 3 years prior to baseline and 1 year (for the effect of relapses) and 3 years (for the effect on disability, see below) after baseline. In patients in whom multiple eligible baselines were identified, multiple eligible treatment epochs per patient were studied. Each treatment epoch was treated as independent.

All data were prospectively collected during routine clinical care predominantly from tertiary MS centres and entered near real-time into the iMed patient record or online data entry system for MSBase or EDMUS patient record for OFSEP. Standardised data quality processes were applied as previously described.[13]

Study outcomes

This study evaluated the time from treatment start to its full clinically manifest effect ('therapeutic lag') on disability progression and relapses in subgroups of patients with MS.

Disability progression was defined as an EDSS score increase of 1 point (1.5 points where EDSS is 0, 0.5 points if EDSS $\geqslant$ 6), confirmed over $\geqslant$ 6 months (in the absence of a relapse in the 30 days prior to confirmation) and sustained for the remainder of the treatment epoch.[14] 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.[15] The first episode of demyelination was considered a relapse. For analysis of disability, patients were required to be treated for at least 1 year, and all disability progression events recorded during a 3-year period were analysed, irrespective of treatment status. For the analysis of relapses, patients were required to have 1-year on-treatment follow-up and relapses

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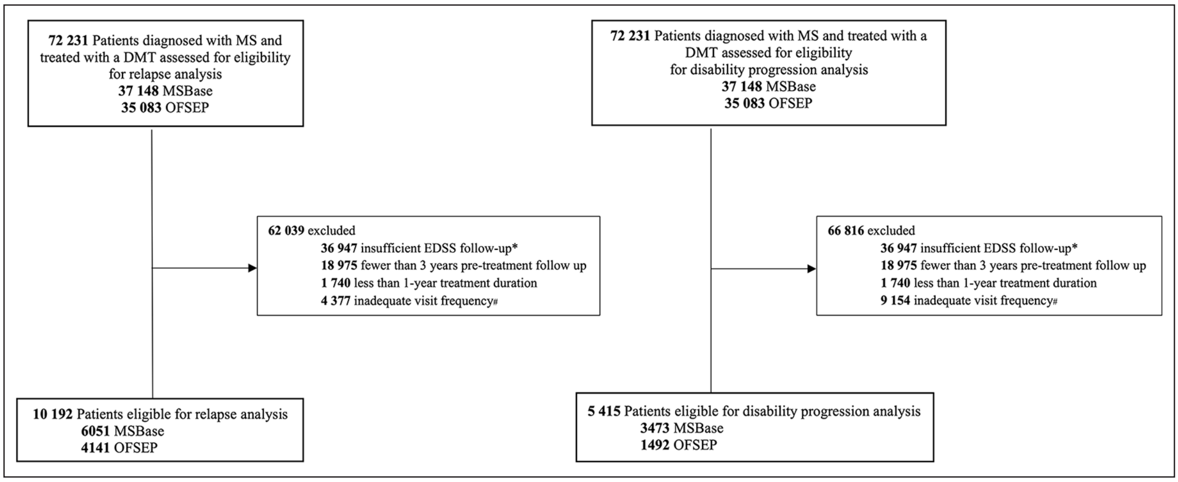

Figure 1. CONSORT diagram.
MS: multiple sclerosis; RRMS: remitting–relapsing MS; CIS: clinically isolated syndrome; DMT: disease modifying therapy.
*Patients excluded owing to 'insufficient EDSS follow-up' did not have a baseline visit with a recorded EDSS measurement within 6 months pre or 1 month post therapy commencement or had fewer than 2 post baseline visits 6 or more months apart.
#Patients excluded due to 'inadequate visit frequency' did not have at least yearly visits with EDSS recorded during the treatment epoch. A treatment epoch was defined as time including 3 years prior to treatment start and 1 year (for the effect on relapses) and 3 years (for the effect on disability) after treatment start.

recorded during this year were included in the analysis. Differences in analytical approaches are motivated by observations that DMTs effects on relapses are more immediate than the effect on disability.[7]

Classification of MS phenotype was analysed as documented by the treating physician. In addition, secondary progressive MS (SPMS) was analysed as defined by an objective algorithm, which identifies SPMS with 87% accuracy in a timely manner.[16] Annualised relapse rate (ARR) was calculated as the number of relapses in the three years before baseline. MS duration and onset were calculated from the first MS symptom.

By separately plotting the incidence of relapses and disability progression events in subgroups stratified by patient and disease characteristics, the duration of therapeutic lag was calculated by identifying the first local minimum of the first derivative after treatment start (Supplementary Figure 1).[7] This local minimum represents the timepoint at which stabilisation of the effect of treatment is reached on disability progression (T_d) and relapses (T_r). Therapeutic lag estimates were recalculated by non-parametric bootstrap with 10,000 repetitions.

Statistical analysis

Statistical analysis was conducted using R (version 3.5.3).[17] Point and interval estimates of distribution were expressed as means with 95% confidence intervals (CIs) or medians with quartiles, as appropriate. Therapeutic lag (T_d and T_r) was calculated for patient subgroups stratified by their demographic and clinical characteristics. As discussed elsewhere,[7] a critical number of events are required to identify a stable, reliable estimate of therapeutic lag. Therefore, we only considered results from subgroups in whom more than 300 events were recorded (disability progression events or relapses), and for which T_d or T_r was identified in more than 80% of the bootstrap repetitions. Categorisation of continuous variables was performed by first computing quantiles and then aggregating the overlapping quantiles (Supplementary Table 1).

Studied potential baseline determinants of therapeutic lag were selected based on the results of prior studies (Supplementary Table 1).[1,3,18–20] A prior analysis explored therapeutic lag in different DMTs: time to treatment effect for disability progression ranged between 30 and 52 weeks for all included therapies apart from interferon beta-1a IM (mean = 70.4, 95% CI = 59.8–81.0) and time to treatment effect for relapses ranged between 9.4 and 19.8 weeks for all included therapies apart from dimethyl fumarate (mean = 30.2, 95% CI = 26.6–33.7).[7] Therefore, treatment identity was not considered to be a confounder of the estimated therapeutic lag and its effect on therapeutic lag was not evaluated in this study, unless dimethyl fumarate or interferon beta-1a IM were over-represented in any studied subgroup. In this circumstance, the analysis was repeated after the exclusion of dimethyl fumarate (relapses) or interferon beta-1a (disability progression) treatment epochs.

Table 1. Characteristics of the study population.

Source	Disability progression cohort			Relapse cohort		
	Overall	MSBase	OFSEP	Overall	MSBase	OFSEP
	n = 5415	n = 3473	n = 1492	n = 10,192	n = 6051	n = 4141
Female, n (%)	4142 (76)	2570 (74)	1134 (76)	7583 (74)	4478 (74)	3105 (75)
Treatment epochs, n	6551	4304	2247	12553	7606	4947
Age of MS onset, years[a]	27.9 (8.6)	27.8 (8.6)	28.2 (8.5)	28.4 (8.7)	28.2 (8.7)	28.6 (8.7)
Age at start of index DMT, years[a]	40.0 (9.5)	39.7 (9.4)	40.7 (9.7)	40.8 (9.7)	40.3 (9.6)	41.5 (9.9)
Disease duration, years[b]	10.6 [6.9, 15.7]	10.5 [6.7, 15.4]	10.9 [7.1, 16.1]	10.8 [6.9, 16.1]	10.5 [6.7, 15.7]	11.2 [7.4, 16.6]
Disability, EDSS step[b]	3.0 [2.0, 4.5]	3.0 [2.0, 4.0]	3.5 [2.0, 4.5]	3.0 [1.5, 4.0]	2.5 [1.5, 4.0]	3.0 [2.0, 4.5]
Pyramidal score, step[a]	1.8 (1.2)	1.8 (1.2)	1.6 (1.3)	1.7 (1.2)	1.8 (1.2)	1.6 (1.2)
Annualised relapse rate[b]	0.7 [0.3, 1.0]	0.7 [0.3, 1.0]	0.7 [0.3, 1.0]	0.3 [0.0, 1.0]	0.3 [0.3, 1.0]	0.3 [0.0, 1.0]
Disease course (%)						
Clinically isolated syndrome	82 (1.3)	43 (1.0)	39 (1.7)	195 (1.6)	85 (1.1)	110 (2.2)
Relapsing–remitting	5646 (86.2)	3780 (87.8)	1866 (83.0)	10819 (86.2)	6715 (88.3)	4104 (83.0)
Secondary progressive	745 (11.4)	419 (9.7)	326 (14.5)	1378 (11.0)	691 (9.1)	687 (13.9)
Primary progressive	78 (1.2)	62 (1.5)	16 (0.7)	161 (1.3)	115 (1.5)	46 (0.9)
DMT started at baseline (%)						
Injectable therapies	3159 (48.2)	2228 (51.7)	931 (41.4)	5030 (40.1)	3393 (44.6)	1637 (33.1)
Oral therapies	1747 (26.7)	1130 (32.5)	617 (27.5)	4677 (37.3)	2718 (35.7)	1959 (39.6)
Infusion therapies	1645 (25.1)	946 (22.0)	699 (31.1)	2846 (20.0)	1495 (24.7)	1351 (27.3)
DMT in 6 months preceding baseline (%)						
None	1507 (23.0)	955 (22.2)	552 (24.6)	2753 (21.9)	1630 (21.4)	1123 (22.7)
Injectable therapies	3914 (59.7)	2640 (61.3)	1274 (56.7)	7107 (56.6)	4578 (60.2)	2529 (51.2)
Infusion therapies	878 (13.4)	514 (11.9)	364 (16.2)	1695 (13.5)	839 (13.9)	856 (20.7)
Oral therapies	252 (3.9)	195 (4.5)	57 (2.5)	998 (8.0)	559 (7.3)	439 (10.6)
Reason for discontinuation of preceding DMT (%)						
No preceding treatment	1507 (23.0)	955 (22.2)	552 (24.6)	2753 (21.9)	1630 (21.4)	1123 (22.7)
Convenience	231 (3.5)	131 (3.0)	100 (4.5)	564 (4.5)	275 (3.6)	289 (5.8)
Lack of efficacy	1680 (25.6)	1042 (24.2)	638 (28.4)	3014 (24.0)	1710 (22.5)	1304 (26.4)
Lack of tolerance	882 (13.5)	455 (10.6)	427 (19.0)	1805 (14.4)	873 (11.5)	932 (18.8)
Pregnancy (including planned)	82 (1.3)	51 (1.2)	31 (1.4)	185 (1.5)	100 (1.3)	85 (1.7)
Scheduled stop	589 (9.0)	292 (6.8)	297 (13.2)	1213 (9.7)	547 (7.2)	666 (13.5)
Other	47 (0.7)	10 (0.2)	37 (1.6)	142 (1.1)	36 (0.5)	106 (2.1)
Reason not available	1533 (23.4)	1368 (31.8)	165 (7.3)	2877 (22.9)	2435 (32.0)	442 (8.9)

DMT: disease-modifying therapy; MS:: multiple sclerosis.
[a]Mean (standard deviation).
[b]Median [quartiles].
Injectable therapies: glatiramer acetate, interferon beta-1b IM, interferon beta-1b SC and interferon beta-1b.
Oral therapies: fingolimod, dimethyl fumarate, teriflunomide and cladribine.
Infusion therapies: natalizumab, ocrelizumab, alemtuzumab, rituximab and mitoxantrone.

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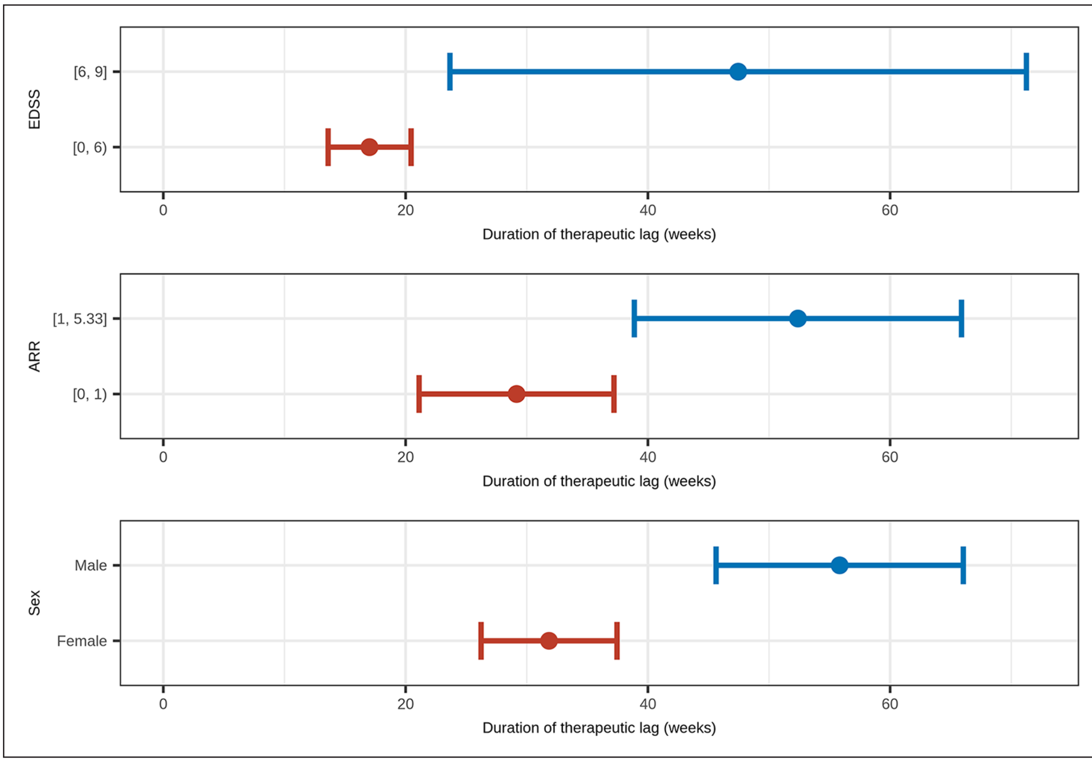

Figure 2. Individual determinants of therapeutic lag for disability progression.
EDSS: expanded disability status scale; ARR: annualised relapse rate.
Opening square bracket: inclusive bracket.
Closing parenthesis: exclusive bracket.

Second, the patient characteristics identified by the above analysis as relevant determinants of T_d and T_r were included in pairwise analyses, in which therapeutic lag was estimated in groups defined by combinations of two characteristics. Third, combinations of determinants that consistently drove differences in therapeutic lag duration in the pairwise analyses were included in the final set of analyses in which groups were defined by combinations of multiple relevant patient characteristics. As mentioned above, we only considered results from sufficiently represented subgroups.

Results

Patients and follow-up

A total of 5415 patients (3473 MSBase, 1492 OFSEP) were included in the analysis of determinants of therapeutic lag for disability progression and 10,192 patients (6051 MSBase, 4141 OFSEP) in the determinants for relapses (Figure 1). Supplementary Table 2 shows the number of patients per contributing centre.

Although population characteristics were largely similar between registries, more patients in MSBase were commenced on an injectable therapy at baseline than those in OFSEP (disability cohort: MSBase 51.7%, OFSEP 41.4%; relapse cohort: MSBase 44.6%, OFSEP 33.1%) (Table 1). Details of the index DMT for each of the studied determinants of therapeutic lag are shown in Supplementary Table 4.

Therapeutic lag for disability progression

We identified three potential determinants of the duration of therapeutic lag for disability progression: disability (EDSS $<$ 6, 17.2 weeks, 13.6–20.5 (mean, 95% CI); EDSS $\geqslant$ 6, 47.5, 23.7–71.3), relapse frequency (ARR $<$ 1, 29.2, 21.1–37.2; ARR $\geqslant$ 1, 52.4, 38.9–65.9) and sex (female, 31.8, 26.2–37.5; male 55.8, 45.6–66.0) (Figure 2). Patient and disease characteristics which did not influence T_d are shown in Supplementary Figure 2. For interferon beta-1a IM, in which we have previously shown longer T_d than the rest of the DMTs, we have assessed the differential use between the compared groups of patients (Supplementary Table 4a). As no substantial difference was apparent adjustment for treatment with interferon beta-1a IM was not necessary. All three individual determinants (EDSS, ARR and sex)

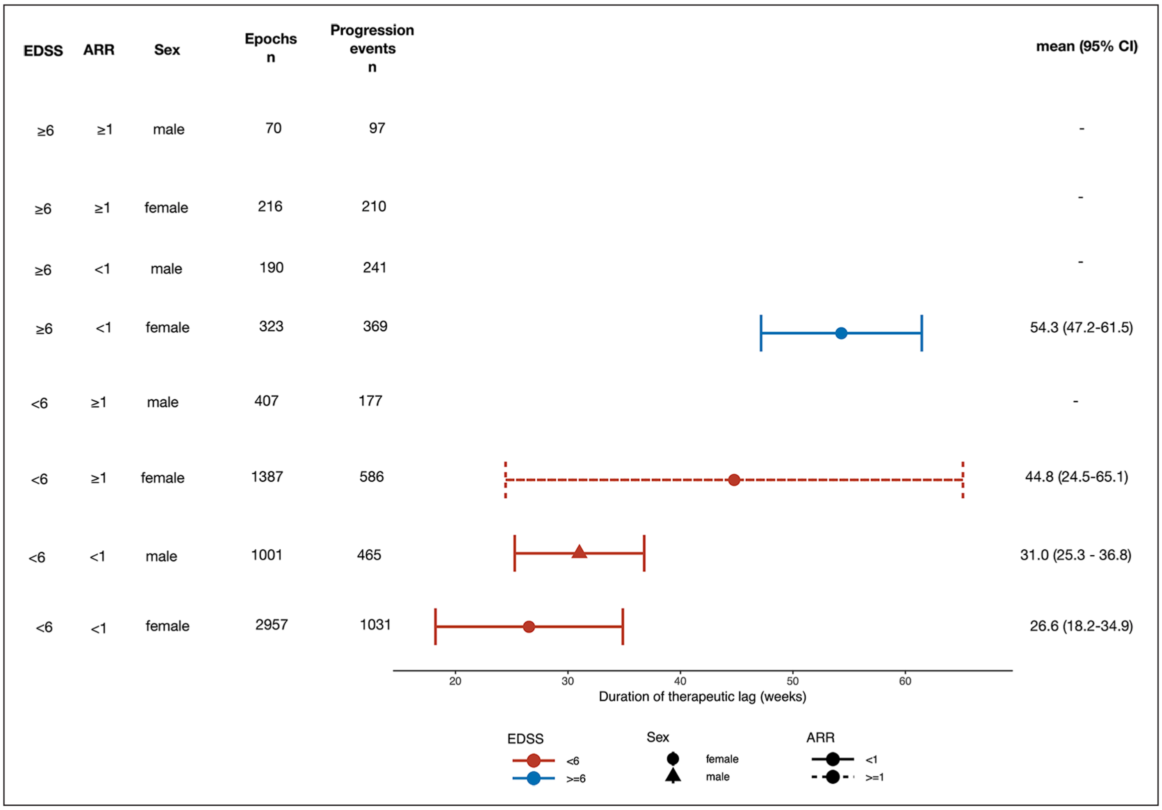

Figure 3. Interactions among the three determinants of therapeutic lag for disability progression (T_d).
EDSS: expanded disability status scale; ARR: annualised relapse rate; CI: confidence interval.
T_d was not calculated in groups of determinants with fewer than 300 progression events.

contributed to differences in T_d when combined in pairwise analyses (Supplementary Table 5) and were included in the final set of analyses exploring all combinations of the three determinants. In these final models, T_d was calculated in four sufficiently represented groups (Figure 3). In females with ARR $<$ 1 and EDSS $<$ 6, the mean T_d was 26.6 weeks (95% CI = 18.2–34.9). This was 27.7 weeks shorter than the mean T_d among females with ARR $<$ 1 and EDSS $\geqslant$ 6 (54.3, 95%CI = 47.2–61.5) and not substantially different from males with ARR $<$ 1 and EDSS $<$ 6 (31.0, 95% CI = 25.3–36.8).

Therapeutic lag for relapses

Baseline EDSS (EDSS $<$ 2, 9.2 weeks, 7.0–11.4 (mean, 95% CI); EDSS $\geqslant$ 2 and $<$6, 12.1, 11.1–13.2; EDSS $\geqslant$ 6, 16.9, 13.8–19.9), ARR (ARR $<$ 2, 14.9, 13.4–16.4; ARR $\geqslant$ 2, 11.1, 9.3–12.8), sex (female, 14.3, 12.7–15.9; male, 9.8, 7.2–12.4), physician-defined MS phenotype (physician RRMS: 9.6, 7.5–11.6; physician SPMS: 14.7, 10.8–18.6) and algorithm-defined MS phenotype (algorithm RRMS: 10.0, 8.0–12.0; algorithm SPMS: 14.8, 11.8–17.7) were identified as potential determinants of T_r (Figure 4); determinants which did not influence T_r are shown in Supplementary Figure 3. T_r was estimated in patients with RRMS and SPMS but not in patients with clinically isolated syndrome (CIS) or PPMS due to low total number of relapses (195 and 192, respectively). As T_r estimates for the algorithm-defined MS phenotype showed less overlap than for physician-defined MS phenotype, the former were used in subsequent analyses. For dimethyl fumarate, in which we have previously shown longer T_r than the rest of the DMTs, we have assessed the differential use between the compared groups of patients (Supplementary Table 4b). As no substantial difference was apparent adjustment for treatment with dimethyl fumarate was not necessary. Pairwise analyses of the individual determinants suggested that baseline EDSS, ARR and MS phenotype were independently associated with T_r (Supplementary Table 6) and were included in the set of analyses exploring all combinations of the four determinants. In these final models, T_r was calculated in seven sufficiently represented groups (Figure 5). Most notably, T_r was shorter in patients with RRMS and an EDSS $<$ 6 compared to the other represented groups. In patients with RRMS and ARR $<$ 2, T_r was approximately 5 weeks shorter in patients with an

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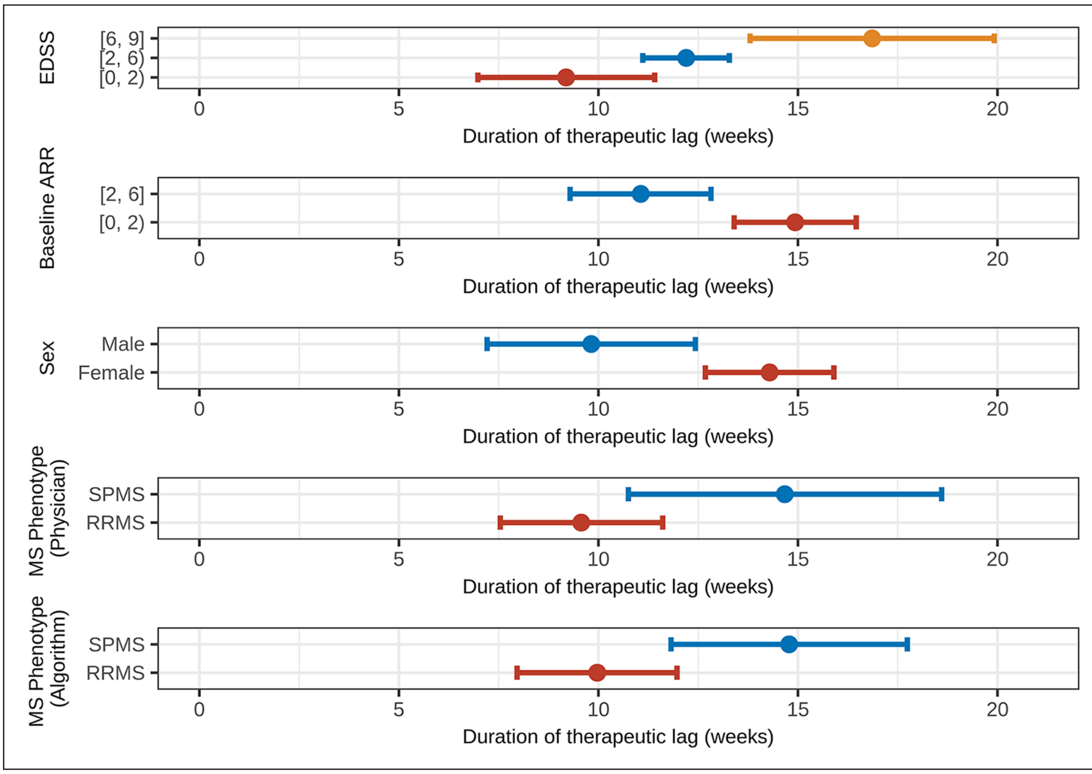

Figure 4. Individual determinants of therapeutic lag for relapses.
EDSS: expanded disability status scale; ARR: annualised relapse rate; RRMS: relapsing remitting MS; SPMS: secondary progressive MS.
Opening square bracket: inclusive bracket.
Closing parenthesis: exclusive bracket.

EDSS < 6 compared to ⩾6. Detailed estimates of T_r in patient groups are shown in Figure 5.

Discussion

This study from the two largest MS registries showed that the time from commencing MS immunotherapy to its full clinically manifest effect (here termed therapeutic lag) is prolonged especially in patients with greater disability. Other contributing factors include low relapse frequency prior to commencement of therapy (associated with shorter therapeutic lag for disability progression events) and sex (with a mildly shorter time to maximum treatment effect on disability progression among females). Therapeutic lag for relapses was mildly prolonged in SPMS.

In contrast with evidence that DMTs reduce long term disability progression in RRMS, results in progressive MS have been comparatively disappointing. Beyond the pathologic differences in each disease stage, proposed methodological reasons have included patient selection, outcome selection, clinical trial design and therapeutic lag. Therapeutic lag was anecdotally observed when differences in disability outcomes occurred at year 7, but not year 2, of a randomised double-blind placebo-controlled trial of interferon beta-1b in PPMS.[4] Our results show that T_r and T_d increase with baseline EDSS. Similarly, a post hoc analysis of the SPECTRIMS (interferon beta-1a in SPMS)[21] and PROMISE (glatiramer acetate in PPMS)[22] trials reported that treatments influenced disability progression with a 2 to 2.5-year delay and that therapeutic lag duration increased with baseline EDSS.[3] While these findings mirror our own, there were differences in the methodology used to estimate lag duration. Whereas the post hoc analysis of the two clinical trials approximated the duration of *therapeutic lag (years) = baseline EDSS – 3 years*, we used an objective method based on differential calculus, suitable for calculation of therapeutic lag in sufficiently large subgroups, which we have validated in two non-overlapping registries.[7]

The role of MS phenotype in therapeutic lag was explored using both physician- and algorithm-defined definitions of SPMS; both definitions of MS phenotype led to similar estimates of lag. In the 'multivariable' model that accounted for interactions among the individual determinants of T_r, the addition of MS phenotype contributed

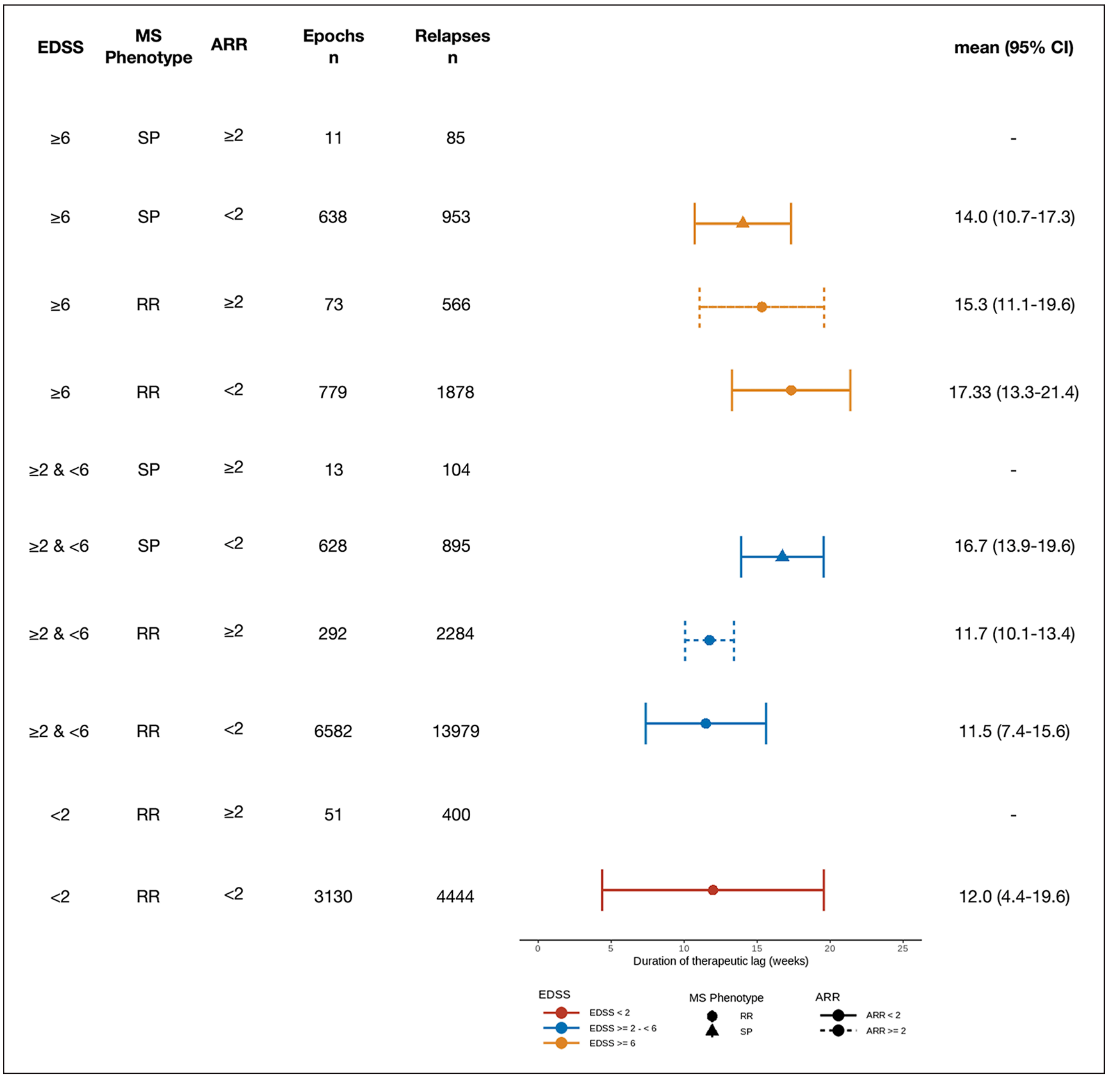

Figure 5. Interactions among the three determinants of therapeutic lag for relapses (T_r).
EDSS: expanded disability status scale; SP: secondary progressive; RR: relapsing-remitting; ARR: annualised relapse rate; CI: confidence interval.
T_r was not calculated in groups of determinants with fewer than 300 relapses or in which T_r was not identified in more than 80% of bootstrap replications.

only minimally to the differences in the duration of T_r within the sufficiently populated groups, that is, T_r was only 5 weeks longer in secondary progressive compared to relapsing-remitting patients with EDSS 2–6 and ARR ⩽ 2. MS phenotype did not significantly contribute to the duration of T_d. The observation that therapeutic lag duration was influenced by EDSS more consistently than MS phenotype supports the hypothesis that MS is a continuum, with elements of neuroaxonal loss and progression throughout its disease course, rather than a disease consisting of clearly separable phases.[23–26]

Whereas one prior study[18] showed no difference in the time to the effect of natalizumab on relapses between patients with and without highly active MS (⩾2 relapses in the year before baseline), ARR was a significant modifier of therapeutic lag for both disability progression and relapses in our analysis. Patients with ARR ⩾ 2 had a mean 4 week shorter T_r than those with ARR < 2. Considering the anti-inflammatory mechanisms of current DMTs for MS, it is not unexpected that they show more pronounced, and earlier, effect on the absolute drop in relapse incidence in patients with higher pre-treatment ARR – a clinical presentation of episodic, therapeutically modifiable inflammatory activity.[19] Conversely, our observation that higher pre-treatment ARR prolongs therapeutic lag for disability progression is consistent with previous research that showed a positive association between high ARR and worse disability outcomes in MS.[27,28] Therefore, lowering of relapse activity below the critical level to enable stabilisation of (or recovery from) disability is expected to be prolonged among patients in whom the pre-treatment level of relapse activity was high.

While male sex is associated with faster disability accrual,[14,29–32] the role of sex in therapeutic lag has not previously been explored. Male sex was weakly associated with longer T_d, but sex was not found to consistently drive differences in T_r.

Studies of observational data are subject to a number of potential limitations and biases, including selection bias and unmeasured confounders. Variable data quality was controlled through the use of a validated data quality control process.[13] Selection and reporting bias was addressed through inclusion of two non-overlapping data sources from predominantly academic MS centres (MSBase, a global registry, and OFSEP, a national cohort) with near-real time data acquisition and prospectively defined observational plans. Detailed discussion of limitations related to the method used for therapeutic lag estimation is found elsewhere.[7] T_d and T_r were only estimated for subgroups in which more than 300 relapses or progression events occurred as the underlying method is dependent on a critical mass of events to consistently identify the first local minimum of the first derivative of relapse incidence.[7] Where an insufficient number of events were present analyses were discontinued. There are therefore groups of determinants, particularly in the assessment of T_d in groups defined by multiple interacting patient characteristics, for which therapeutic lag could not be calculated. In an effort to maximise analytical power, we have combined data from the two largest MS registries. It is also reassuring that the sufficiently powered groups included in the analysis represent the most common clinical scenarios encountered in practice. Because the method requires that therapeutic lag is estimated within discrete groups, we have categorised continuous determinants. While this may lead to some loss of information, we have ensured that the groups defined on categorised variables are internally consistent with regards to the duration of therapeutic lag.

As this study did not include patients treated within 3 years of MS onset, or patients treated for less than 1 year, our conclusions cannot be generalised to these patient groups. Moreover, carryover effects of prior therapies were not considered. Too few patients with PPMS or CIS were included to explore the duration of therapeutic lag in these MS phenotypes; the characteristics of these patients are included for descriptive purposes only.

The EDSS has a number of limitations as a marker of disability progression;[33] we have utilised this disability scale due to its widespread use in registry data, enabling combining information from two separate registries. We have aimed at improving intra- and inter-rater reliability by using specialist neurologist EDSS raters[34] and a robust definition of disability progression.[14] Only clinical markers of therapeutic lag have been studied in this analysis as observational data, with semiquantitative imaging information acquired at varying intervals, is not suited to assess the radiological onset of treatment effect. Furthermore, drugs with other mechanisms of action are anticipated to have different lag durations than those represented.[2]

As MS is a heterogeneous disease, it is highly desirable to personalise the evaluation of clinical treatment response based on patients' individual characteristics.[35] It has been recommended that a magnetic resonance imaging (MRI) assessment is performed in the months after starting a treatment with the aim of creating a new radiological 'baseline'.[36] Similarly, we suggest establishing a new baseline for clinical outcomes after the lapse of therapeutic lag. In the present study, we identified disability and relapse activity prior to commencing MS immunotherapy as factors that most consistently influence the duration of therapeutic lag for disability progression and relapses. Sex has additional influence on the lag of the effect of therapy on disability progression, and MS phenotype contributes to the duration of therapeutic lag with regards to relapses. Moreover, our findings are relevant to reanalysis of clinical trials in patients with more advanced disease and design of clinical trials in progressive MS. Treatment outcomes in cohorts enriched with patients with higher disability scores and relapse activity should be interpreted with the expected duration of therapeutic lag in sight.

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Data availability statement

MSBase is a data processor, and warehouses data are from individual principal investigators who agree to share their data sets on a project-by-project basis. Data access to external parties can be granted upon reasonable request at the sole discretion of each OFSEP and MSBase Principal Investigator (the data controllers), who will need to be approached individually for permission.

Declaration of Conflicting Interests

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Supplemental material

Supplemental material for this article is available online.

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