doi:10.1093/brain/awaa231 BRAIN 2020: 143; 2742–2756 | 2742

BRAIN
A JOURNAL OF NEUROLOGY

Delay from treatment start to full effect of immunotherapies for multiple sclerosis

Izanne Roos,[1,2] Emmanuelle Leray,[3] Federico Frascoli,[4] Romain Casey,[5,6,7,8] J. William L. Brown,[9] Dana Horakova,[10] Eva K. Havrdova,[10] Maria Trojano,[11] Francesco Patti,[12,13] Guillermo Izquierdo,[14] Sara Eichau,[14] Marco Onofrj,[15] Alessandra Lugaresi,[16,17] Alexandre Prat,[18] Marc Girard,[18] Pierre Grammond,[19] Patrizia Sola,[20] Diana Ferraro,[20] Serkan Ozakbas,[21] Roberto Bergamaschi,[22] Maria José Sá,[23] Elisabetta Cartechini,[24] Cavit Boz,[25] Franco Granella,[26,27] Raymond Hupperts,[28] Murat Terzi,[29] Jeannette Lechner-Scott,[30,31] Daniele Spitaleri,[32] Vincent Van Pesch,[33] Aysun Soysal,[34] Javier Olascoaga,[35] Julie Prevost,[36] Eduardo Aguera-Morales,[37] Mark Slee,[38] Tunde Csepany,[39] Recai Turkoglu,[40] Youssef Sidhom,[41] Riadh Gouider,[41] Bart Van Wijmeersch,[42] Pamela McCombe,[43,44] Richard Macdonell,[45,46] Alasdair Coles,[9] Charles B. Malpas,[1,2] Helmut Butzkueven,[47,48,49] Sandra Vukusic[5,6,7] and Tomas Kalincik[1,2] on behalf of the MSBase* and OFSEP investigators*

*Appendix 1.

In multiple sclerosis, treatment start or switch is prompted by evidence of disease activity. Whilst immunomodulatory therapies reduce disease activity, the time required to attain maximal effect is unclear. In this study we aimed to develop a method that allows identification of the time to manifest fully and clinically the effect of multiple sclerosis treatments ('therapeutic lag') on clinical disease activity represented by relapses and progression-of-disability events. Data from two multiple sclerosis registries, MSBase (multinational) and OFSEP (French), were used. Patients diagnosed with multiple sclerosis, minimum 1-year exposure to treatment, minimum 3-year pre-treatment follow-up and yearly review were included in the analysis. For analysis of disability progression, all events in the subsequent 5-year period were included. Density curves, representing incidence of relapses and 6-month confirmed progression events, were separately constructed for each sufficiently represented therapy. Monte Carlo simulations were performed to identify the first local minimum of the first derivative after treatment start; this point represented the point of stabilization of treatment effect, after the maximum treatment effect was observed. The method was developed in a discovery cohort (MSBase), and externally validated in a separate, non-overlapping cohort (OFSEP). A merged MSBase-OFSEP cohort was used for all subsequent analyses. Annualized relapse rates were compared in the time before treatment start and after the stabilization of treatment effect following commencement of each therapy. We identified 11 180 eligible treatment epochs for analysis of relapses and 4088 treatment epochs for disability progression. External validation was performed in four therapies, with no significant difference in the bootstrapped mean differences in therapeutic lag duration between registries. The duration of therapeutic lag for relapses was calculated for 10 therapies and ranged between 12 and 30 weeks. The duration of therapeutic lag for disability progression was calculated for seven therapies and ranged between 30 and 70 weeks. Significant differences in the pre- versus post-treatment annualized relapse rate were present for all therapies apart from intramuscular interferon beta-1a. In conclusion we have developed, and externally validated, a method to objectively quantify the duration of therapeutic lag on relapses and disability progression in different therapies in patients more than 3 years from multiple sclerosis onset. Objectively defined periods of expected therapeutic lag allows insights into the evaluation of treatment response in randomized clinical trials and may guide clinical decision-making in patients who experience early on-treatment disease activity. This method will subsequently be applied in studies that evaluate the effect of patient and disease characteristics on therapeutic lag.

Received January 05, 2020. Revised April 30, 2020. Accepted June 01, 2020

1 CORe, Department of Medicine, University of Melbourne, Melbourne, 3050, Australia
2 Melbourne MS Centre, Department of Neurology, Royal Melbourne Hospital, Melbourne, 3050, Australia
3 Rennes University, EHESP, REPERES (Pharmaco-epidemiology and Health services research) - EA 7449, Rennes, France
4 Faculty of Science, Engineering and Technology, School of Science, Department of Mathematics, Swinburne University of Technology, Melbourne, 3122, Australia
5 University of Lyon, Claude Bernard University Lyon 1, F-69000 Lyon, France
6 Hospices Civils de Lyon, Service de Neurologie, sclérose en plaques, pathologies de la myéline et neuro-inflammation, F-69677 Bron, France
7 Observatoire Français de la Sclérose en Plaques, Lyon Neuroscience Research Centre, INSERM 1028 et CNRS UMR 5292, F-69003 Lyon, France
8 EUGENE DEVIC EDMUS Foundation against multiple sclerosis, state-approved foundation, F-69677 Bron, France
9 Department of Clinical Neurosciences, University of Cambridge, Cambridge, CB2 0QQ, UK
10 Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, 12808, Czech Republic
11 Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari, Bari, 70122, Italy
12 GF Ingrassia Department, University of Catania, Catania, 95123, Italy
13 Policlinico G Rodolico, 95123, Catania, Italy
14 Hospital Universitario Virgen Macarena, Sevilla, 41009, Spain
15 Department of Neuroscience, Imaging, and Clinical Sciences, University G. d'Annunzio, 66100 Chieti, Italy
16 IRCCS Istituto delle Scienze Neurologiche di Bologna, UOSI Riabilitazione Sclerosi Multipla, Bologna, 40139, Italy
17 Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
18 CHUM MS Center and Universite de Montreal, Montreal, H2L 4M1, Canada
19 CISSS Chaudière-Appalache, Lévis, Levis, G6X 0A1, Canada
20 Department of Neuroscience, Azienda Ospedaliera Universitaria, Modena, 41100, Italy
21 Dokuz Eylul University, Konak/Izmir, 35220, Turkey
22 IRCCS Mondino Foundation, Pavia, 27100, Italy
23 Centro Hospitalar Universitário de São João and Universidade Fernando Pessoa, 4249-004 Porto, Portugal
24 UOC Neurologia, Azienda Sanitaria Unica Regionale Marche - AV3, Macerata, 62100, Italy
25 KTU Medical Faculty Farabi Hospital, Karadeniz Technical University, Trabzon, 61080, Turkey
26 Department of Medicine and Surgery, University of Parma, Parma, 43126, Italy
27 Department of General Medicine, Parma University Hospital, Parma, 43126, Italy
28 Zuyderland Ziekenhuis, Sittard, Sittard, 6131 BK, The Netherlands
29 Medical Faculty, 19 Mayis University, Kurupelit, Samsun, 55160, Turkey
30 School of Medicine and Public Health, University Newcastle, 2308, Australia
31 Department of Neurology, John Hunter Hospital, Hunter New England Health, Newcastle, 2305, Australia
32 Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Contrada Amoretta, Avellino, 83100, Italy
33 Cliniques universitaires Saint-Luc, Brussels, 1200 BXL, Belgium
34 Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases, Istanbul, 34142, Turkey
35 Instituto de Investigación Sanitaria Biodonostia, Hospital Universitario Donostia, San San Sebastián, Spain, 20014, Spain
36 CSSS Saint-Jérôme, Saint-Jérôme, QC J7Z 0H6, Canada
37 Hospital Universitario Reina Sofia Cordoba (IMIBIC), 14004 Cordoba, Spain
38 Flinders University, Adelaide, 5042, Australia
39 Department of Neurology, Faculty of Medicine, University of Debrecen, Debrecen, 4032, Hungary
40 Haydarpasa Numune Training and Research Hospital, Selimiye Mahallesi, Istanbul, 34668, Turkey
41 Department of Neurology, Razi Hospital, 2010, Tunis, Manouba, Tunisia
42 Rehabilitation and MS-Centre Overpelt and Hasselt University, Hasselt, 3900, Belgium
43 University of Queensland, St Lucia, 4072, Australia
44 Royal Brisbane and Women's Hospital, Herston, 4029, Australia
45 Department of Neurology, Austin Health, Heidlberg, 3084, Australia
46 Faculty of Medicine and Dental Health Sciences, University of Melbourne, Melbourne, 3050, Australia
47 Central Clinical School, Monash University, Melbourne, 3004, Australia
48 Department of Neurology, The Alfred Hospital, Melbourne, 3004, Australia
49 Department of Neurology, Box Hill Hospital, Monash University, Melbourne, 3128, Australia

Correspondence to: Tomas Kalincik
CORe, Department of Medicine, University of Melbourne, 300 Grattan St, Melbourne, 3050, Australia
E-mail: tomas.kalincik@unimelb.edu.au

Keywords: multiple sclerosis; therapeutic lag

Abbreviations: ARR = annualized relapse rate; DMT = disease modifying therapy; EDSS = Expanded Disability Status Score; OFSEP = Observatoire Français de la Sclérose en Plaques; T_d = therapeutic lag for disability; T_r = therapeutic lag for relapses

Introduction

Multiple sclerosis is a complex neuroimmunological disease characterized by an interplay of inflammation and neurodegeneration throughout the disease course. Initiation or switch of therapy for multiple sclerosis is frequently prompted by disease activity, presenting as relapses, worsening of disability or new/active lesions on MRI. Whilst it is known that multiple sclerosis therapies reduce relapse rates and disability accrual (Tramacere *et al.*, 2015; Lizak *et al.*, 2017; Brown *et al.*, 2019) the time of onset of treatment effect is often inferred from available information concerning pharmacodynamics of a given agent, typically available from preclinical or post-marketing trials. The delay in full biological effect of treatment, however, does not immediately translate into a delay to full clinical effect. This delay from starting a therapy to reaching its full clinical effect is termed 'therapeutic lag' (Giovannoni *et al.*, 2017). Information about therapeutic lag is highly relevant to decisions regarding the use of multiple sclerosis therapies, in particular during the early weeks after the commencement of therapy.

The influence of therapeutic lag on treatment response has been briefly explored in multiple sclerosis. A *post hoc* analysis of two originally negative trials in progressive multiple sclerosis, the SPECTRIMS and PROMISE trials [Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS (SPECTRIMS) Study Group, 2001; Wolinsky *et al.*, 2007], suggested that treatment benefit on 3-month confirmed disability progression develops after a 2–2.5-year delay and is dependent on the degree of pre-existing disability (Sormani and Giovannoni, 2016). Thus, in clinical trials, the effect of therapy may be obscured by therapeutic lag, particularly when the duration of such trials is restricted to 3 years and include progressive multiple sclerosis. Further exploration of therapeutic lag and its determinants thereby depends on development of a robust method to detect when treatments attain full clinical effect.

In this study we used the two biggest multiple sclerosis registries, MSBase, the largest international observational cohort, and Observatoire Français de la Sclérose en Plaques (OFSEP), the largest national multiple sclerosis registry, to develop and externally validate an objective method to detect the onset of full clinically manifest effect of treatment on relapses and progression-of-disability events.

Materials and methods

Ethics statement

The MSBase registry (Butzkueven *et al.*, 2006) (registered with WHO ICTRP, ID ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee, and by the local ethics committees in all participating centres (or exemptions granted, according to applicable local laws and regulations). Written informed consent was obtained from enrolled patients as required. The OFSEP cohort (Vukusic *et al.*, 2020) (registered with WHO ICTRP, ID NCT02889965) was collected with approval from and in accordance with French *Commission Nationale Informatique et Libertés* and French law relative to observational research.

Patients

Longitudinal clinical and demographic data from 125 centres in 37 countries were extracted from the MSBase registry in November 2018 and from 39 French centres in the OFSEP cohort in December 2018. One additional non-MSBase non-OFSEP centre from Cambridge was included in the MSBase cohort (only patients given alemtuzumab) (Tuohy *et al.*, 2015). The following inclusion criteria were applied prior to enrolment: diagnosis of multiple sclerosis or clinically isolated syndrome as per the 2005 or 2010 McDonald criteria (Polman *et al.*, 2005, 2011), commencement of and persistence on a disease modifying therapy (DMT) for at least 12 months, minimum 3-year pre-treatment follow-up, yearly follow-up during the treatment epoch (defined below) and presence of the minimum dataset. Patients were diagnosed with clinically isolated syndrome at the time of start of their treatment, and with $\geqslant 3$ year follow-up from their first symptom. The minimum dataset consisted of patient age, sex (categorized as female and male), multiple sclerosis duration at baseline, disease phenotype (clinically isolated syndrome, relapsing-remitting, secondary progressive, primary progressive, progressive-relapsing), disability information [quantified with Expanded Disability Status Score (EDSS)] (Kurtzke, 1983) at baseline and two subsequent time points at least 6 months apart and, where applicable, date of treatment cessation.

Baseline was defined as the start of the index DMT (including a new therapy or treatment switch). The prospective follow-up period was defined as the time from the first to the last available EDSS. A treatment epoch was defined as time including 3 years prior to baseline and 1 year (for the effect on relapses) and 5 years (for the effect on disability; see below) after baseline.

All available and sufficiently represented DMTs were included in the analysis. A therapy was viewed as sufficiently represented for application of the method described below in 'Proof of principle: the method to identify therapeutic lag' section if more than 200 events (relapses or progression-of-disability events) occurred during the analysed treatment epoch. Duration of treatment effect after the last dose was estimated according to pharmacodynamics, clinical experience or previous evidence (Stellmann *et al.*, 2017), as follows [in keeping with our previous work (Kunchok *et al.*, 2020)]: 4 years after the last dose for alemtuzumab (Coles *et al.*, 2017), 14 days for dimethyl fumarate, 7 days for all interferon therapies and glatiramer acetate (Stellmann *et al.*, 2017), 30 days for fingolimod (David *et al.*, 2012), 180 days for mitoxantrone (Hartung *et al.*, 2002), 60

days for natalizumab (Sheremata *et al.*, 1999), 270 days for rituximab or ocrelizumab, and 5 years for autologous haematopoietic stem cell transplant (Sormani *et al.*, 2017). Treatment with DMTs was only allowed as a monotherapy. The two treatment epochs were merged if a period of DMT interruption, with subsequent commencement of the same therapy, was shorter than the duration of treatment effects. Treatment gaps exceeding the abovementioned periods were recorded as separate treatment epochs. In patients in whom multiple eligible baselines were identified multiple treatment epochs per patient were studied. Multiple epochs per patient were treated as independent.

All data were prospectively collected during routine clinical care predominantly from tertiary multiple sclerosis centres (Kalincik and Butzkueven, 2019; Vukusic *et al.*, 2020). Information was entered near real-time (usually at the time of a clinic visit) into the iMed patient record or online MSBase data entry system for MSBase or EDMUS patient record for OFSEP (Confavreux *et al.*, 1992). Data were subject to standardized data quality processes (Supplementary Table 1) (Kalincik *et al.*, 2017; Vukusic *et al.*, 2020).

Study outcomes

This study evaluated the time from treatment start to its full clinically manifest effect on relapses and disability progression events.

Relapses were defined as the occurrence of new symptoms or the exacerbation of existing symptoms for at least 24 h in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse (Schumacher *et al.*, 1965). In the primary analysis, relapses were analysed as recorded by the treating neurologist.

Confirmed progression of disability was defined as an increase in EDSS by 1.5 steps if baseline EDSS was 0, increase by 1 step if baseline EDSS was between 1 and 5.5 or increase in EDSS by 0.5 step if baseline EDSS was above 5.5, confirmed at least 6 months later (in the absence of a relapse within 30 days prior to the confirmatory EDSS) and sustained for the remainder of the treatment epoch (Kalincik *et al.*, 2015). The pretreatment baseline EDSS was as documented at the first recorded visit and re-baselined at the commencement of the index DMT. Progression of disability independent of relapse activity was defined as 6-month confirmed progression of disability (see above), where the increase in disability could not be attributed to a preceding relapse (Lorscheider *et al.*, 2019). This was ensured by the absence of a recorded relapse between the EDSS leading to the progression-of-disability event and the most recent preceding EDSS.

The minimum on treatment follow-up period differed according to the studied outcome. For the analysis of the time to the full effect of DMTs on relapses, patients required a minimum of 1 year on-treatment follow-up. All relapses recorded during this year were used in the analysis. For analysis of disability outcomes, patients were treated for at least 1 year and treatment epochs of 5 years post-baseline were analysed on an 'intention-to-treat' basis. This means that all disability progression events recorded during the 5-year period were analysed, irrespective of the actual treatment status. These differences in analytical approaches are motivated by the observation that the effect of DMTs on relapses are short term, whereas the effect on disability is cumulative (Brown *et al.*, 2019). This resulted in two distinct, but overlapping, cohorts for the analysis of the two studied outcomes.

Statistical analysis

All analyses were performed using R version 3.5.3. Point and interval estimates of distribution were expressed as means with 95% confidence intervals (CIs), or medians with quartiles, as appropriate. All hypotheses were tested with a two-tailed 0.05 level of significance.

Proof of principle: the method to identify therapeutic lag

The MSBase cohort was used as a discovery cohort to develop the method to identify the duration of therapeutic lag in the effect of DMTs on relapse events. Patients diagnosed with remitting relapsing multiple sclerosis or clinically isolated syndrome (i.e. patients most likely to experience relapses) were selected for this analysis. For each DMT a density curve of the relapse events during the treatment epoch (3 years before and 1 year after baseline) was produced. The Sheather-Jones criterion was applied for optimal estimation of kernel density and bandwidth selection of the density curve (Sheather and Jones, 1991).

The density curves were then used to identify the first local minimum (the minimum incidence of relapses) after commencing an index DMT, by calculating the first derivatives of the curves (Fig. 1A). This local minimum translates to the time point at which stabilization of the effect treatment on the measured outcome is reached, therapeutic lag for relapses (T_r). A 200-event minimum for study inclusion was guided by analyses showing that T_r is not identifiable for any DMT below this threshold. The estimates of T_r were recalculated by (i) non-parametric bootstrap with 10 000 repetitions; and (ii) Monte Carlo simulations using 80% of the cohort, without replacement, and 10 000 repetitions in order to model their probability distributions. No substantial differences between the two estimates of T_r were found. As the Monte Carlo method is more conservative and makes no assumption that the sample is an estimate of the true population, we chose to use the Monte Carlo method for the remainder of analyses (principles of Monte Carlo simulations are described in Supplementary Fig. 1). Gaussian mixture models were used to identify the point associated with the maximum density probability where the simulations resulted in multimodal distributions of the sought points (McLachlan and Peel, 2000). This estimate of the point was confirmed by calculation of the point from the entire available population.

The OFSEP cohort was used to perform an external validation analysis of the proposed method to detect T_r. The validation used the same inclusion criteria and methodology as the discovery analysis (see above). The differences in mean T_r between the MSBase and the OFSEP cohorts for each DMT were estimated with bootstrap analyses, including their bias corrected and accelerated 95% CIs.

To explore effects of the shape of the density curve on T_r, stability analyses were conducted. Here, the combined MSBase-OFSEP cohort was used. First, the association between the height of the peak in relapse density immediately prior to baseline (driven by relapses preceding commencement of index DMTs) and T_r was studied. Furthermore, in a series of simulations, T_r was evaluated in random samples of patients from the

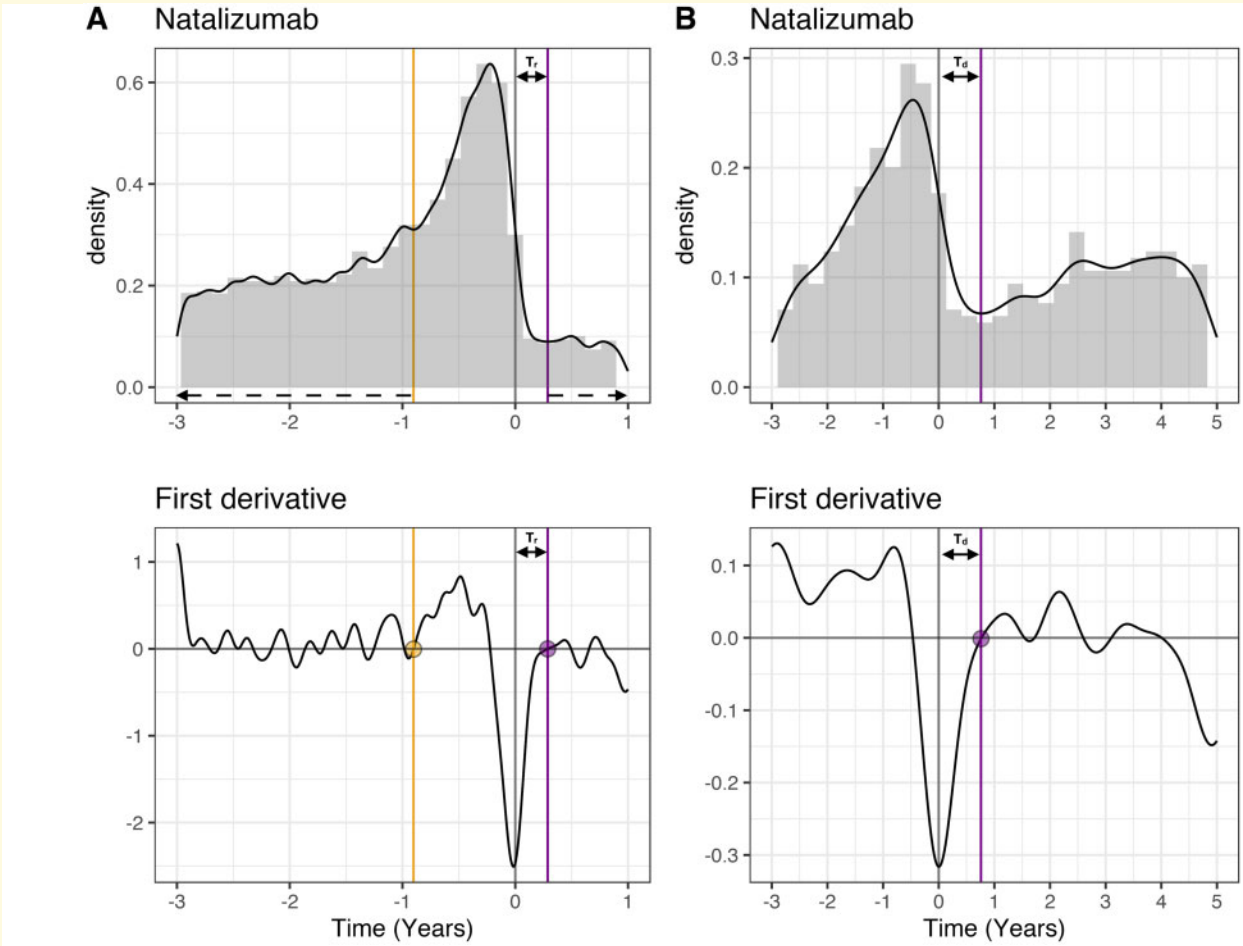

Figure 1 Density curve and first derivative of relapse (A) and 6-month confirmed disability progression (B) events prior to and after the commencement of natalizumab. Time point 0 indicates the start of index therapy. The first post-treatment local minimum of the first derivative, representing the point of stabilization of treatment effect, is indicated in purple. The duration of therapeutic lag on relapses (T_r) and disability progression (T_d) is indicated by double headed horizontal arrows. The last stable point prior to start of the index therapy, identified by the last pretreatment local minimum of the first derivative, is shown in orange. Pretreatment and on-treatment ARRs were calculated in the periods indicated by dashed arrows.

combined cohort, with sequentially increasing number of total recorded relapses in each sample.

Therapeutic lag for relapses

To estimate therapeutic lag for relapses T_r, we have used the combined MSBase-OFSEP cohort and the method established above. Monte Carlo simulations were used to estimate the 95% CIs of T_r. An additional point was identified as the point of the last 'stable' density of relapses prior to the peak of relapse incidence that prompted initiation of index DMTs (last local minimum of the first derivative before treatment start) (Fig. 1A). This point was used to calculate the pretreatment annualized relapse rates (ARRs) as the relapse density divided by the cumulative follow-up time prior to that point. The on-treatment ARR was calculated from T_r to the end of treatment epoch, dividing relapse density by the respective cumulative follow-up time. The pre- and on-treatment ARRs and their 95% bias corrected and 95% confidence interval were then visualized.

Sensitivity analyses were performed with a more stringent definition of relapses, only including events treated with corticosteroids or resulting in a change in EDSS.

Therapeutic lag for disability progression

The method described in 'Proof of principle: the method to identify therapeutic lag' was used to analyse therapeutic lag for disability progression (T_d) during the 5-year post-baseline period in patients who were treated for the minimum of 1 year from the merged MSBase-OFSEP cohort (Fig. 1B). Patients with both relapsing and progressive multiple sclerosis forms were included in this analysis. An additional analysis studied therapeutic lag for disability progression independent from relapses (T_{PIRA}).

Finally, sensitivity analyses evaluated the robustness of results for differential treatment persistence and follow-up (2, 3 and 5 years).

Table 1 Characteristics of the study population at baseline

Source	Relapse cohort		Disability progression cohort	
	MSBase[a]	OFSEP	MSBase	OFSEP
Patients (% female)	5391 (74)	3756 (76)	2339 (72)	1242 (75)
Treatment epochs	6707	4473	2682	1406
Age at treatment start, years	39.52 (9.42)	40.43 (9.71)	38.96 (9.11)	40.04 (9.49)
Disease duration, years	10.26 [6.57, 15.20]	10.58 [6.91, 15.60]	10.14 [6.54, 14.88]	10.77 [7.00, 15.93]
Disability, EDSS step	2.5 [1.5, 4.0]	2.5 [1.5, 4.0]	3.0 [2.0, 4.0]	3.5 [2.0, 5.0]
Annualized relapse rate	0.50 [0.28, 0.77]	0.43 [0.26, 0.67]	0.73 [0.43, 1.20]	0.67 [0.39, 1.06]
Disease course, treatment epochs (%)				
Clinically isolated syndrome	76 (1.1)	125 (2.8)	28 (1.1)	12 (0.9)
Remitting-relapsing	6631 (98.9)	4348 (97.2)	2275 (86.7)	1163 (82.7)
Secondary progressive	NA	NA	280 (10.7)	231 (16.4)
Primary progressive	NA	NA	41 (1.6)	0 (0.0)
Index treatment (%)				
Alemtuzumab[a]	27 (0.4)	49 (1.1)	Insufficient number of progression events for treatment inclusion	
Natalizumab	1113 (16.6)	1061 (23.7)	513 (19.1)	471 (33.5)
Mitoxantrone	89 (1.3)	43 (1.0)	141 (5.3)	57 (4.1)
Rituximab	49 (0.7)	52 (1.2)	Insufficient number of progression events for treatment inclusion	
Fingolimod	1616 (24.1)	1001 (22.4)	312 (11.6)	135 (9.6)
Dimethyl fumarate	519 (7.7)	491 (11.0)	Insufficient number of progression events for treatment inclusion	
Teriflunomide	432 (6.4)	433 (9.7)	Insufficient number of progression events for treatment inclusion	
Glatiramer acetate	818 (12.2)	461 (10.3)	468 (17.4)	225 (16.0)
Interferon beta-1b	368 (5.5)	149 (3.3)	262 (9.8)	165 (11.7)
Interferon beta-1a SC	1008 (15.0)	269 (6.0)	606 (22.6)	139 (9.9)
Interferon beta-1a IM	668 (10.0)	464 (10.4)	380 (14.2)	214 (15.2)

Values are presented as mean (standard deviation) or median [quartiles] unless otherwise stated.
Baseline refers to the start of treatment. In patients in whom multiple eligible baselines were identified multiple treatment epochs per patient were studied. Patient disposition at baseline is summarized per treatment epoch. For additional characteristics of the study population see the Supplementary material. IM = intramuscular; NA = not applicable; SC = subcutaneous.
[a]Including three patients from Cambridge.

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 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.

Results

Patients and follow-up

Of 125 421 patients (60 662 MSBase, 64 759 OFSEP) assessed for study inclusion, the numbers of patients eligible for analysis of time to full clinically manifest effect of therapy were 9147 (5391 MSBase, 3756 OFSEP) for the relapse outcome and 3581 (2339 MSBase, 1242 OFSEP) for the progression-of-disability events (Supplementary Fig. 2). The number of patients per contributing centre is shown in Supplementary Table 2 and their clinical and demographic characteristics are shown in Table 1. Apart from a longer multiple sclerosis duration, the clinicodemographic details of the included population were similar to patients who received multiple sclerosis therapies but were excluded from the study (Supplementary Table 3). Characteristics of the study population stratified by therapy are available in Supplementary Table 4.

Relapse cohort

After exclusion of insufficiently represented therapies, 11 DMTs with 11 180 treatment epochs in 9013 patients (5325 MSBase, 3688 OFSEP) were analysed (Table 1). Overall, 75% of patients were female, with a mean age at treatment initiation of 39.9 years, a median disease duration at baseline of 10.4 years and an ARR of 0.47 (0.27–0.74). The median pre-baseline follow-up duration was 6.6 years. Twenty-three per cent of patients were treatment naïve at baseline and in 57% the preceding therapy was an injectable DMT. Lack of efficacy was the most commonly reported reason for discontinuation of the preceding DMT. Population characteristics were similar between registries.

Disability progression cohort

From 3531 patients, 4088 (2682 MSBase, 1406 OFSEP) treatment epochs were obtained and seven sufficiently represented DMTs (Table 1). The median baseline EDSS was 3 (2–4.5) and 13.7% of the cohort had progressive multiple

Table 2 Duration of therapeutic lag for relapses in discovery and validation cohorts

	Discovery cohort: MSBase					Validation cohort: OFSEP					Difference between means (weeks)	
	Patients	Treatment epochs	Relapses	Duration of therapeutic lag (weeks)		Patients	Treatment epochs	Relapses	Duration of therapeutic lag (weeks)			
	n	*n*	*n*	Mean	CI	*n*	*n*	*n*	Mean	CI	Mean	CI
Natalizumab	1064	1113	3228	17.2	14.6–19.7	1011	1061	3332	12.3	10.8–13.8	5.2	–4.5–22.4
Mitoxantrone	87	89	353	23.3	19.9–26.8			–				–
Fingolimod	1594	1616	3217	14.1	11.8–16.5	989	1001	1847	Insufficient[a]		Insufficient[a]	
Dimethyl fumarate	518	519	776	27.5	25.8–29.1	486	491	525	Insufficient[a]		Insufficient[a]	
Teriflunomide	432	432	424	19.2	16.8–21.6	427	433	323	17.8	14.0–21.7	1	–5.6–10.7
Glatiramer acetate	788	818	1746	15.0	13.2–16.7	441	461	1016	Insufficient[a]		Insufficient[a]	
Interferon beta-1b	362	368	760	12.6	11.4–13.7	140	149	376	Insufficient[a]		Insufficient[a]	
Interferon beta-1a SC	954	1008	2167	13.6	9.6–17.6	265	269	668	23.1	17.1–27.1	–8.8	–20–5.2
Interferon beta-1a IM	629	668	1110	18.1	15.3–21.0	448	464	882	21.4	15.4–27.3	–2.6	–20–3.2

As illustrated in the subsequent sequential analysis (Supplementary Fig. 4) 2000 relapse events were required for consistent identification of T_r in fingolimod and glatiramer acetate in a merged MSBase–OFSEP cohort.

– = not sufficiently represented for inclusion; CI = confidence interval; IM = intramuscular; SC = subcutaneous.

[a]Insufficient number of events to detect T_r.

sclerosis. Despite the requirement of 1-year treatment persistence the index DMT was continued for a median of 4.6 years (range 2.4–5 years). Patients in the MSBase cohort had a lower median EDSS (3 versus 3.5) and a higher proportion of pre-baseline time on treatment (0.59 versus 0.37) than those in OFSEP.

Proof of principle: the method to identify therapeutic lag

In the discovery analysis, data from MSBase were used to calculate the time to full clinically manifest effect of treatment for relapses in nine adequately represented therapies (Table 2). T_r was identified in all DMTs with more than 200 relapse events and ranged between 12.6 and 27.5 weeks. In the validation analysis (data from OFSEP) T_r was identified for four of eight DMTs analysed (natalizumab, teriflunomide, interferon beta-1b, subcutaneous interferon beta-1a and intramuscular interferon beta-1a) and ranged between 12.3 and 23.1 weeks; an insufficient number of events were available to find the first local minimum of the first derivative for fingolimod, dimethyl fumarate, glatiramer acetate and interferon beta-1b. The mean T_r estimated in MSBase and OFSEP were similar. The bootstrapped mean (95% CI) differences in T_r (in weeks) between the registries were 1 (–5.6, 10.7) for teriflunomide, –8.8 (–20, 5.2) for subcutaneous interferon beta-1a, –2.6 (–20, 3.2) for intramuscular interferon beta-1a and 5.2 (–4.5, 22.4) for natalizumab.

On exploration of the effects of the shape of the density curve on T_r, no correlation between the height of the peak of the density curve and T_r was observed (Supplementary Fig. 3). Results from a sequential analysis, analysing the number of relapses required for stable estimates of T_r, are shown in Supplementary Fig. 4. The minimum number of events required to estimate a consistent and stable T_r varied in response to variation in the shape of the relapse density curves. For all DMTs, the variability of T_r estimates reduced with increasing number of relapses sampled. Whilst T_r reached stability with fewer than 1000 relapses for most therapies, a minimum of 2000 relapse events were required for stability of T_r on natalizumab, fingolimod and glatiramer acetate.

Therapeutic lag for relapses

Time to treatment effect

In the combined MSBase-OFSEP cohort of 9013 patients with 11 180 treatment epochs, 23 424 relapses were recorded. For all 11 studied therapies, an increase in relapse density preceded the initiation of the index DMT, reflecting the events leading to commencement of new treatments, and was followed by a subsequent decline in relapse occurrence (Fig. 2). Initial decline in relapse density was observed even prior to the start of index therapy; this artefact results from delay between a relapse and commencement of next therapy and the fact that all events within 30 days from a prior relapse constitute a single relapse. The calculated time to full clinically manifest treatment effect on relapses (T_r) is displayed in Table 3 and Fig. 2. Mean time to treatment effect ranged between 9.4 and 19.8 weeks for all treatments other than dimethyl fumarate, which showed T_r of 30.2 weeks (95% CI 26.6–33.7). A bimodal distribution of T_r was present for fingolimod, with 85% of estimates and the highest density probability occurring at 12.7 weeks. For all treatments, the bootstrapped T_r estimate with the highest density probability mirrored the point identified from the entire available population. There were insufficient number of relapses on rituximab (304 relapses in 101 treatment epochs) to identify T_r. Despite only 220 relapses on alemtuzumab, T_r was identified at a mean of 16 weeks (95% CI

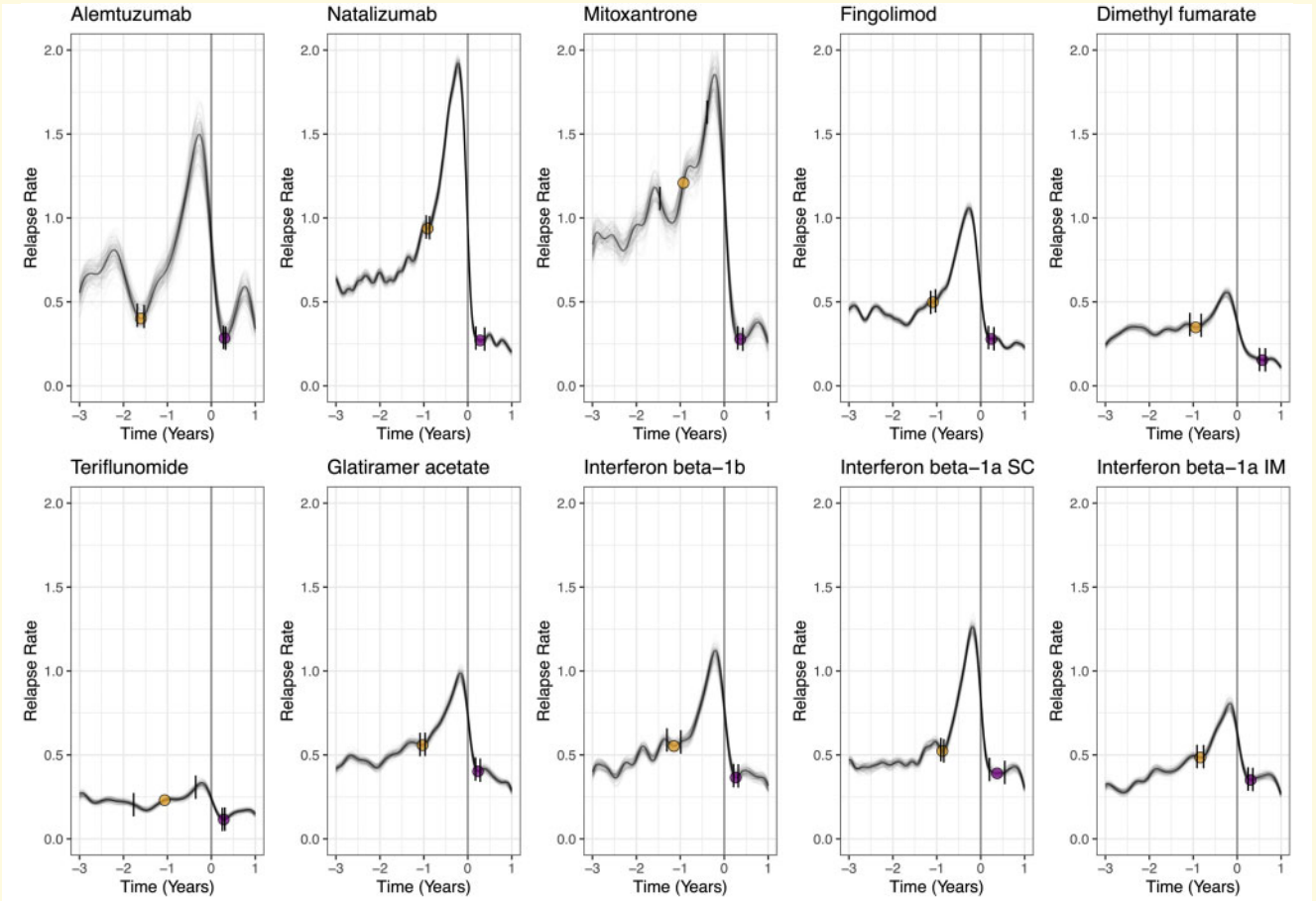

Figure 2 Duration of therapeutic lag for relapses. Density curve indicates the ARR and duration of therapeutic lag for relapses. The first post-treatment local minimum, representing the point of stabilization of treatment effect, is indicated in purple (T_r). The last stable point prior to start of the index therapy is indicated in orange. Two black lines indicate the upper and lower bounds of 95% CIs. Density curves from Monte Carlo simulations are indicated in grey.

Table 3 Duration of therapeutic lag for relapses: merged MSBase-OFSEP cohort

	Patients	Treatment epochs	Relapses	T_r (weeks)	
	n	*n*	*n*	Mean	CI
Alemtuzumab	76	76	220	16.0	14.6–17.3
Natalizumab	2075	2174	6560	15.0	9.8–20.1
Mitoxantrone	129	132	503	19.2	16.1–22.3
Rituximab	98	101	304		Insufficient[a]
Fingolimod	2583	2617	5064	12.7	9.5–15.8
Dimethyl fumarate	1004	1010	1301	30.2	26.6–33.7
Teriflunomide	859	865	747	14.9	13.4–16.4
Glatiramer acetate	1229	1279	2762	12.4	9.6–15.1
Interferon beta-1b	502	517	1136	14.0	11.4–16.7
Interferon beta-1a SC	1219	1277	2835	19.8	10.5–29.0
Interferon beta-1a IM	1077	1132	1992	16.1	13.3–18.9

IM = intramuscular; SC = subcutaneous.
[a]Insufficient number of events to detect T_r (duration of therapeutic lag on relapses)

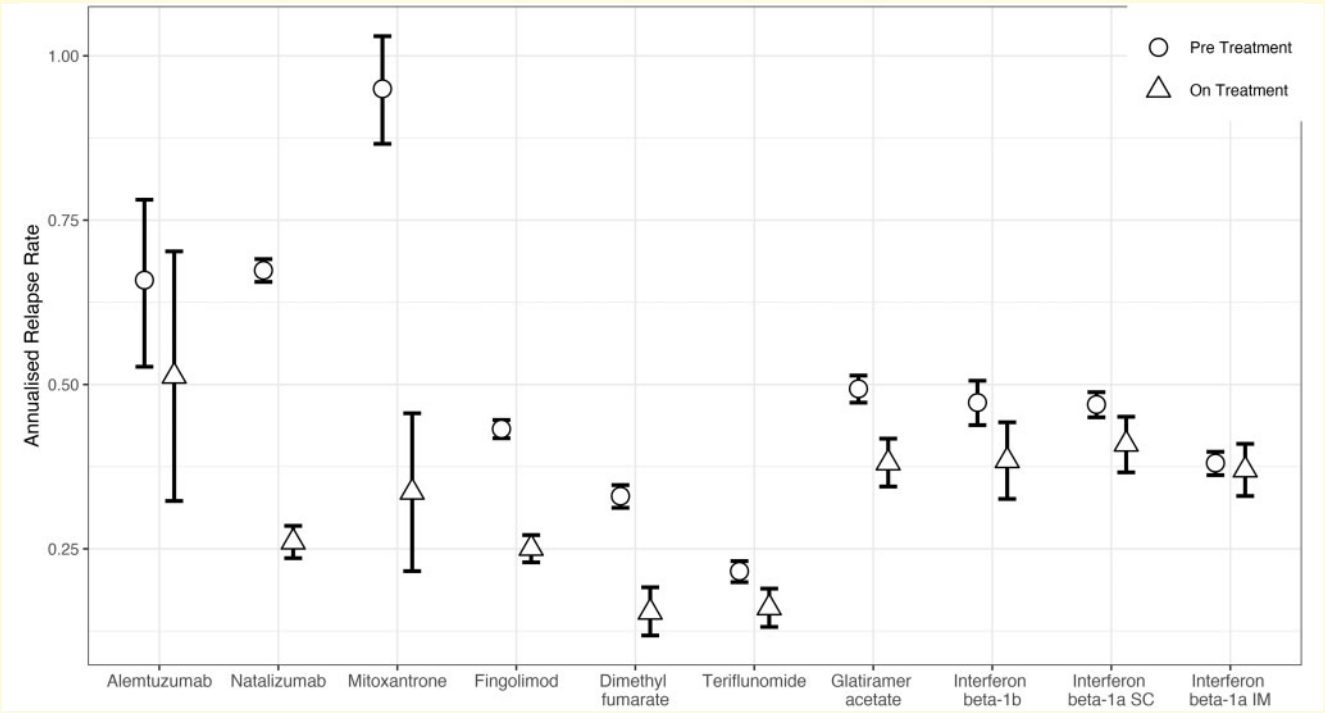

Figure 3 ARRs in the pretreatment and on-treatment periods. The pretreatment ARR was calculated from the start of the treatment epoch to the last point of stabilization prior to treatment start, dividing relapse density by the cumulative follow-up time prior to that point. The on-treatment ARR was calculated from T_r to the end of treatment epoch, dividing relapse density by the respective cumulative follow-up time.

14.6–17.3) with satisfactory stability in the sequential analysis (Supplementary Fig. 4).

A sensitivity analysis restricting relapses to those necessitating treatment with corticosteroids or resulting in a change in EDSS showed consistent results for all adequately represented DMTs (Supplementary Table 3).

Magnitude of treatment effect

For each therapy, ARRs were compared in the pre- and on-treatment periods (Fig. 3). With the exception of intramuscular interferon beta-1a, all therapies were associated with a drop-in relapse activity on-treatment versus pre-baseline. This suggests that over the short term, the chosen therapies led to the desired improved control of disease activity.

Therapeutic lag for confirmed progression-of-disability events

In the 4088 included treatment epochs from 3531 patients, 2563 disability progression events were identified across seven DMTs. On inspection of the progression-of-disability density curves, increase in the likelihood of progression-of disability preceded commencement of the index DMT (Fig. 4). Similar to relapses, progression event rates in the pre-baseline period were highest for patients commenced on higher efficacy therapies, natalizumab and mitoxantrone. The occurrence of progression-events after initial stabilization at T_d resumed to increase for most studied DMTs. However, for mitoxantrone and interferon beta-1b, the number of progression-of-disability events continued to decline throughout the 5-year follow-up period. The occurrence of relapse independent progression-of-disability events reduced for ~1–2 years after commencement of therapy and resumed to increase thereafter for most DMTs (Supplementary Fig. 5).

The calculated duration of therapeutic lag on progression-of-disability events (T_d) across therapies is shown in Table 4 and Fig. 4. T_d for the seven sufficiently represented therapies ranged between 30 and 52 weeks, with the exception of intramuscular interferon beta-1a, for which the mean T_d was estimated at 70.4 weeks (95% CI 59.8–81). An insufficient number of relapse independent progression-of-disability events (T_{PIRA}) were present to calculate the duration of therapeutic lag for any DMT.

Discussion

In this study, we have used the two largest multiple sclerosis registries to develop and externally validate a method to quantify the duration of clinical therapeutic lag of immunotherapies for multiple sclerosis. We have then applied this method to estimate therapeutic lag with respect to two principal clinical presentations of multiple sclerosis—relapses and progression-of-disability—for the most commonly used immunotherapies. Full effect of treatment on relapses is reached within 12–30 weeks after commencing therapy, whilst the full effect on disability progression is reached within 30–70 weeks.

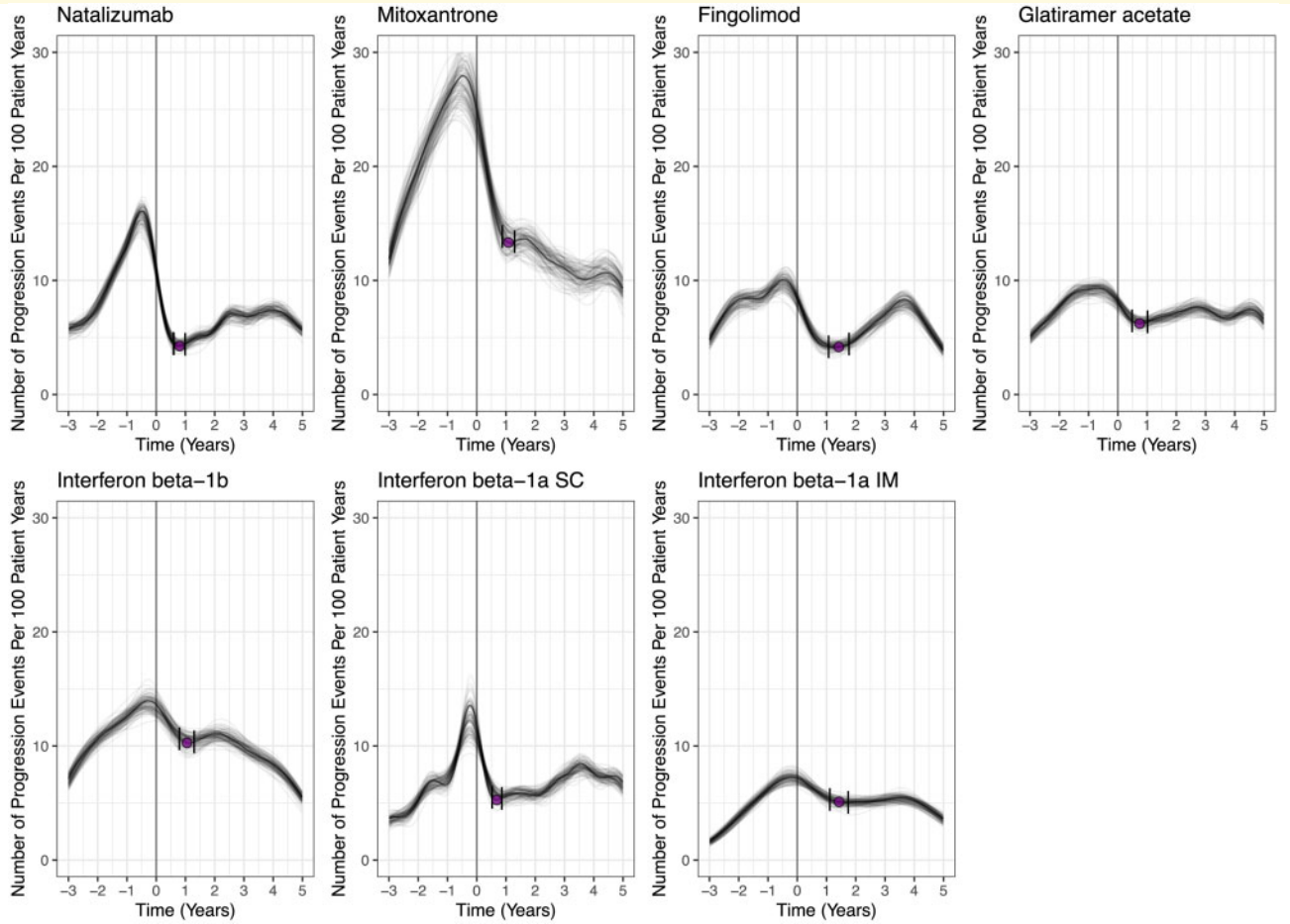

Figure 4 Duration of therapeutic lag for progression of disability. Density curve representing the number of progression events per 100 patient-years and duration of therapeutic lag for progression of disability. The first post-treatment local minimum, representing the point of stabilization of treatment effect, is indicated in purple (T_d). Two vertical black lines indicate the upper and lower bounds of 95% CIs. Density curves from Monte Carlo simulations are indicated in grey.

Table 4 Duration of therapeutic lag for disability progression: merged MSBase-OFSEP cohort

	Patients	Treatment epochs	Disability progression	T_d (weeks)	
	n	*n*	*n*	Mean	CI
Natalizumab	965	984	615	36.4	32.7–40.1
Mitoxantrone	194	198	265	52.9	47.6–58.2
Fingolimod	446	447	250	47.2	39.4–55.0
Glatiramer acetate	674	693	412	35.6	31.0–40.2
Interferon beta-1b	415	427	360	49.3	45.0–53.6
Interferon beta-1a SC	722	745	415	30.2	27.5–33.0
Interferon beta-1a IM	572	594	246	70.4	59.8–81.0

IM = intramuscular; SC = subcutaneous; T_d = duration of therapeutic lag for 6-month confirmed worsening of disability events.

Therapeutic lag: the clinical and the biological perspective

When treating multiple sclerosis, timely reduction in disease activity is required to diminish inflammation, minimize neuroaxonal loss and prevent long-term disability (Trojano *et al.*, 2009; Giovannoni *et al.*, 2016). As treatment initiation or switch is often prompted by ongoing disease activity, understanding of the time required to manifest fully and clinically the effect of therapy is essential for further therapeutic decisions. Phase III studies conventionally report the effect of therapy on clinical and radiological end points over the follow-up period in its entirety, typically spanning 2 or

more years. *Post hoc* analyses have explored the differences between treatment and comparator groups in time to first relapse; this, however, is not a pure measure of the magnitude of full clinical effect of therapy, as time to first event also reflects the onset of clinical effect of the compared interventions (Kappos *et al.*, 2013, 2015, 2016; Traboulsee *et al.*, 2018).

Unlike biological markers of treatment effect, clinical markers of the effect of multiple sclerosis therapies cannot be studied in individual patients. This is because the traditional outcomes in multiple sclerosis trials are discrete, rarely-occurring events. To identify their temporal trends, such effects require evaluation at the level of large cohorts. We have used a reproducible mathematical approach to quantifying trends in the occurrence of relapses and disability progression events and identify the time point at which the frequency of events stabilizes after a new treatment has been started (Diller *et al.*, 2006). Invariably, commencement of new DMTs tended to be preceded by a peak in the relapse density, consistent with a relapse presently being a major driver of therapeutic decisions (Montalban *et al.*, 2018). Subsequent to the relapse peak, all therapies resulted in stabilization of relapse frequency at a new, on-treatment level over the following 3–6-month period. This observation is consistent with results from *post hoc* analyses of the pivotal trials of fingolimod, dimethyl fumarate and natalizumab; the greatest reduction in ARR occurred within the first 3 months of treatment, with further reduction between months 3 and 6 and a subsequent plateau over the rest of the follow-up period (Kappos *et al.*, 2013, 2015, 2016).

The duration of therapeutic lag is often inferred from the timing of biological changes associated with treatment initiation. Absolute T- and B-cell counts reduced 3 months and reached steady state 9 months after starting dimethyl fumarate, with an association noted between higher absolute lymphocyte counts and shorter time to first relapse (Wright *et al.*, 2017). This is in keeping with our observation that the estimate of T_r for dimethyl fumarate (7.1 months), is longer than in other multiple sclerosis therapies. Comparatively, fingolimod results in a reduction, and subsequent steady state, in lymphocyte counts within 2 weeks after treatment begins (Francis *et al.*, 2014), whilst in clinical trials the proportion of patients free from relapses significantly differed from placebo after 3–6 months (Kappos *et al.*, 2016). In our analysis, a mean period of 3 months (12.7 weeks) was required for fingolimod to attain full effect on reducing relapses, suggesting that the full effect of therapies on clinical outcomes may, in some DMTs, follow the effect on biological markers with a lag. The differences between the effect of therapies on biological and clinical markers of multiple sclerosis highlight the complementary value in evaluating both aspects of treatment effect in concert.

Consistent with the increase in the incidence of relapses that leads to commencement of new DMTs, differences between pretreatment relapse frequency highlight systematic differences in the nature of the cohorts treated with different therapies. Patients with the most active disease were predominantly commenced on high-efficacy therapies, such as alemtuzumab, natalizumab, and mitoxantrone. All therapies, with the exception of intramuscular interferon beta-1a, resulted in a change in the ARR. This highlights that clinical decisions to commence new therapies have, at the group level, been successful in achieving improved control of relapse activity. The inability to detect a change in ARR for intramuscular interferon beta-1a was likely influenced by lower pre-baseline and on-treatment ARRs in this group compared to the other low-efficacy injectable DMTs, suggesting that these patients had with less active disease. Moreover, the results reflect a magnitude of change in ARR in the pre-baseline versus on-treatment period, as opposed to a comparison to placebo. Importantly, no corrections were made for differences between the cohorts starting different DMTs, one should therefore resist the temptation to compare the results among treatments.

Therapeutic lag in controlling worsening of disability

In our study DMTs resulted in a full effect on disability progression between 6 months and 1.3 years after commencement. This is in accordance with a *post hoc* analysis of the combined DEFINE and CONFIRM cohorts, where dimethyl fumarate reduced the risk of 12-week confirmed disability progression after 62 weeks (Kappos *et al.*, 2015). Time to treatment effect on disability progression is, to the authors' knowledge, infrequently reported. In our analysis the commencement of DMTs resulted in a transient attenuation in the number of progression events, but did not abolish the accumulation of disability over time. For most therapies, the frequency of confirmed disability progression events resumed to increase after ~2 years from starting a DMT. In particular, disability progressions occurring independent of relapse activity were only briefly reduced by multiple sclerosis immunotherapy. This highlights the contribution of relapse-independent disability progression to reduced capacity in patients with multiple sclerosis, and is supported by studies showing that therapies delay, but do not entirely stop, disease progression (Brown *et al.*, 2019; Lorscheider *et al.*, 2019). Clinical relapses, however, represent the tip of the iceberg of episodic inflammatory activity; 5–10 new white matter lesions are accrued for every relapse diagnosed (McDonald *et al.*, 1994). Radiologically apparent, yet clinically silent, episodic inflammatory activity may thus still contribute to progression independent of relapse activity. Progression-of-disability trends differed for patients receiving mitoxantrone and interferon beta-1b; these groups experienced continued reduction in the number of progression events over the 5-year period (Le Page *et al.*, 2008). The interferon beta-1b and mitoxantrone cohorts were enriched for patients with progressive disease and with greater EDSS scores. As the probability of experiencing a progression event reduces at higher EDSS scores (Kalincik *et al.*, 2015),

these differences cannot be entirely attributable to treatment effect, but potentially to systematic differences in the rate of transition between different EDSS steps.

Limitations

This study used data obtained from longitudinal observational registries, which may be subject to variable data quality. Data quality was, however, controlled through a previously published data verification process (Kalincik *et al.*, 2017). The use of two differing sources of data (MSBase, a global registry of self-selected predominantly academic multiple sclerosis centres, and OFSEP, a national cohort from academic multiple sclerosis centres) helps further mitigate the effects of selection and reporting biases. Second, the described method is reliant on a large number of events in order to identify a stable, reproducible estimate of the duration of therapeutic lag. We combine data from the two largest multiple sclerosis registries in order to maximize the available power. We have used objective methods to identify therapies for which the available data were sufficient, including the evaluation of the estimated T_r in relation to the number of recorded events. Where the critical mass of events was not reached, analyses were discontinued. As confirmed disability progression events are less frequent than relapses, time to treatment effect on this outcome could only be calculated for seven therapies in merged progressive and relapsing multiple sclerosis cohort. Similarly, highly effective therapies with smaller patient numbers, and newer therapies, such as the B-cell therapies or cladribine, were not sufficiently represented to qualify for inclusion. Because T_r is estimated within large groups of events, it may be subject to bias and fluctuation where the density curves are multimodal. We have therefore implemented additional measures to ensure robust estimates of the lag duration, including Monte Carlo simulations to estimate the variance, sequential analyses to ensure consistency of results and Gaussian mixture models to identify the most robustly supported T_r in multimodal curves. Importantly, the T_r estimator was developed and externally validated in two large non-overlapping registry datasets, with no significant differences in T_r between registries. As all relapses within 30 days from a prior relapse constitute a single event, this refractory period, together with regression to the mean, contributes to the decline in relapse density. Third, unmatched differences remain between the cohorts on different therapies, and any comparisons between treatments should be avoided. This includes variability in the reasons for treatment switch and the use of DMTs during the 3-year pretreatment period. These differences would most likely be associated with the height of the peak of relapses preceding treatment switch, but would not directly influence the time to treatment effect. It is therefore reassuring that the height of the relapse peak did not impact the duration of therapeutic lag. Fourth, relapses did not require confirmation with EDSS or treatment with corticosteroids; this may have inflated the number of relapse events present. A sensitivity analysis with a more stringent relapse definition was however performed, with no substantial change in the results. Fifth, the EDSS was used as a measure of disability progression. The EDSS has a number of limitations including a floor and a ceiling effect, low intra- and inter-rater reliability and at higher scores is predominantly a measure of ambulation (Hobart *et al.*, 2000). The issue of variability is partially addressed through the use of specialist neurologist EDSS raters (D'Souza *et al.*, 2017) and the use of a robust definition of disability progression. Additionally, no objective measures of disability in cognitive domain or manual dexterity were included in the analysis as they are not routinely documented in registry data. Sixth, the requirement for 3-year pretreatment follow-up and 1-year treatment persistence precludes generalizability to patients who commence treatment early after multiple sclerosis onset and those with early treatment cessation due to intolerance or treatment failure. Seventh, the duration of treatment effect after the last dose was based on rough estimates as per Kunchok *et al.* (2020). Eighth, the use of re-baselining brain MRI shortly after commencement of therapy, as per the present monitoring guidelines (Wattjes *et al.*, 2015), may have influenced the persistence on study therapy. Where MRI activity was detected, physicians may have been tempted to discontinue study medication, which would thus not fulfill the inclusion criterion of 1-year treatment persistence. This would have, in turn, led to selective exclusion of treatment epochs with early subclinical activity. On the other hand, early on-treatment MRI activity may be representative of changes immediately preceding treatment initiation or occurring before the newly commenced treatment has become fully effective, and such early MRI assessment would be requested with the aim of creating a new radiological 'baseline' rather than immediately guide continued treatment (Montalban *et al.*, 2018). The novel information generated by our study will help clinicians in choosing the optimal time for the re-baselining brain MRI after start of a new DMT. Lastly, evaluation of the time to treatment effect on MRI activity was not included in this study; an observational cohort, with semiquantitative imaging information acquired approximately at yearly intervals does not provide a reliable marker of neuroradiological onset of treatment effect. To address this, a prospective study such as the ongoing MAGNIFY-MS trial (https://ClinicalTrials.gov/show/NCT03364036), with frequent prespecified imaging time points (at least one MRI per month), would be needed.

Conclusion

Accurate expectations regarding the time required for full clinically manifest treatment effect has important implications for therapeutic decisions, particularly during the initial months after patients have commenced new multiple sclerosis immunotherapies. In this observational study, the lag to a measurable maximum effect of therapies on relapses and progression of disability was 3–7 and 7–16 months, respectively. Objectively defined periods of expected therapeutic lag

for the presently used therapies allows insights into the evaluation of treatment response in randomized clinical trials and may guide clinical decision-making in patients who experience early on-treatment disease activity. Further exploration of the influence different patient or disease characteristics have on the duration of therapeutic lag will allow personalization of care in patients who commence different therapies in various clinical scenarios.

Acknowledgements

We wish to thank all patients and their carers who have participated in this study and who have contributed data to the MSBase and OFSEP cohorts. The list of OFSEP steering committee and MSBase Study Group co-investigators and contributors are provided in Appendix 1 and full details in the Supplementary material.

Funding

This study was supported by the EDMUS Foundation, Biogen and NHMRC (1140766, 1129189, 1157717). I.R. is supported by a MSIF-ARSEP McDonald fellowship grant and a Melbourne Research Scholarship. The MSBase Foundation is a not-for-profit organization that receives support from Biogen, Novartis, Merck, Roche, Teva and Sanofi Genzyme. The Observatoire Français de la Sclérose en Plaques (OFSEP) is supported by a grant provided by the French State and handled by the 'Agence Nationale de la Recherche,' within the framework of the 'Investments for the Future' program, under the reference ANR-10-COHO-002, by the Eugène Devic EDMUS Foundation against multiple sclerosis and by the ARSEP Foundation. The study was conducted separately and apart from the guidance of the sponsors.

Competing interests

The authors have received research support, support to attend conferences, speaker honoraria and fees for participation at advisory boards from Actelion, Almirall, Bayer-Schering, Biogen, BioCSL, Celgene, EMD, Geneuro, Medday, Merck, Myalin, Novartis, Roche, Sanofi-Genzyme, Teva, WebMD Global outside the submitted work.

Supplementary material

Supplementary material is available at *Brain* online.

Appendix 1

Full details are provided in the Supplementary material.

MSBase investigators

Pierre Duquette, Francois Grand'Maison, Gerardo Iuliano, Cristina Ramo-Tello, Claudio Solaro, Jose Antonio Cabrera-Gomez, Maria Edite Rio, Ricardo Fernandez Bolaños, Vahid Shaygannejad, Celia Oreja-Guevara, Jose Luis Sanchez-Menoyo, Thor Petersen, Ayse Altintas, Michael Barnett, Shlomo Flechter, Yara Fragoso, Maria Pia Amato, Fraser Moore, Radek Ampapa, Freek Verheul, Suzanne Hodgkinson, Edgardo Cristiano, Bassem Yamout, Guy Laureys, Jose Andres Dominguez, Cees Zwanikken, Norma Deri, Eniko Dobos, Carlos Vrech, Ernest Butler, Csilla Rozsa, Tatjana Petkovska-Boskova, Rana Karabudak, Cecilia Rajda, Jabir Alkhaboori, Maria Laura Saladino, Cameron Shaw, Neil Shuey, Steve Vucic, Angel Perez Sempere, Jamie Campbell, Imre Piroska, Bruce Taylor, Anneke van der Walt, Ludwig Kappos, Etienne Roullet, Orla Gray, Magdolna Simo, Carmen-Adella Sirbu.

OFSEP steering committee and investigators

Bruno Brochet, François Cotton, Jérôme De Sèze, Armelle Dion, Pascal Douek, Francis Guillemin, David Laplaud, Christine Lebrun-Frenay,Thibault Moreau, Javier Olaiz, Jean Pelletier, Claire Rigaud-Bully, Bruno Stankoff, Romain Marignier, Marc Debouverie, Gilles Edan, Jonathan Ciron, Aurélie Ruet, Nicolas Collongues, Catherine Lubetzki, Patrick Vermersch, Pierre Labauge, Gilles Defer, Mikaël Cohen,Agnès Fromont, Sandrine Wiertlewsky, Eric Berger, Pierre Clavelou, Bertrand Audoin, Claire Giannesini, Olivier Gout, Eric Thouvenot, Olivier Heinzlef, Abdullatif Al-Khedr, Bertrand Bourre, Olivier Casez, Philippe Cabre, Alexis Montcuquet, Alain Créange, Jean-Philippe Camdessanché, Justine Faure, Aude Maurousset, Ivania Patry, Karolina Hankiewicz, Corinne Pottier, Nicolas Maubeuge, Céline Labeyrie, Chantal Nifle.

References

Brown JWL, Coles A, Horakova D, Havrdova E, Izquierdo G, Prat A, et al. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. JAMA 2019; 321: 175–87.

Butzkueven H, Chapman J, Cristiano E, Grand'Maison F, Hoffmann M, Izquierdo G, et al. MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. Mult Scler 2006; 12: 769–74.

Coles AJ, Cohen JA, Fox EJ, Giovannoni G, Hartung HP, Havrdova E, et al. Alemtuzumab CARE-MS II 5-year follow-up: efficacy and safety findings. Neurology 2017; 89: 1117–26.

Confavreux C, Compston DA, Hommes OR, McDonald WI, Thompson AJ. EDMUS, a European database for multiple sclerosis. J Neurol Neurosurg Psychiatry 1992; 55: 671–6.

D'Souza M, Yaldizli O, John R, Vogt DR, Papadopoulou A, Lucassen E, et al. Neurostatus e-Scoring improves consistency of Expanded Disability Status Scale assessments: a proof of concept study. Mult Scler 2017; 23: 597–603.

David OJ, Kovarik JM, Schmouder RL. Clinical pharmacokinetics of fingolimod. Clin Pharmacokinet 2012; 51: 15–28.

Diller GP, Uebing A, Willson K, Davies LC, Dimopoulos K, Thorne SA, et al. Analytical identification of ideal pulmonary-systemic flow balance in patients with bidirectional cavopulmonary shunt and univentricular circulation: oxygen delivery or tissue oxygenation? Circulation 2006; 114: 1243–50.

Francis G, Kappos L, O'Connor P, Collins W, Tang D, Mercier F, et al. Temporal profile of lymphocyte counts and relationship with infections with fingolimod therapy. Mult Scler 2014; 20: 471–80.

Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G, et al. Brain health: time matters in multiple sclerosis. Mult Scler Relat Disord 2016; 9 (Suppl 1): S5–48.

Giovannoni G, Cutter G, Sormani MP, Belachew S, Hyde R, Koendgen H, et al. Is multiple sclerosis a length-dependent central axonopathy? The case for therapeutic lag and the asynchronous progressive MS hypotheses. Mult Scler Relat Disord 2017; 12: 70–8.

Hartung HP, Gonsette R, Konig N, Kwiecinski H, Guseo A, Morrissey SP, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet 2002; 360: 2018–25.

Hobart J, Freeman J, Thompson A. Kurtzke scales revisited: the application of psychometric methods to clinical intuition. Brain 2000; 123: 1027–40.

Kalincik T, Butzkueven H. The MSBase registry: informing clinical practice. Mult Scler 2019; 25: 1828–34.

Kalincik T, Cutter G, Spelman T, Jokubaitis V, Havrdova E, Horakova D, et al. Defining reliable disability outcomes in multiple sclerosis. Brain 2015; 138: 3287–98.

Kalincik T, Kuhle J, Pucci E, Rojas JI, Tsolaki M, Sirbu CA, et al. Data quality evaluation for observational multiple sclerosis registries. Mult Scler 2017; 23: 647–55.

Kappos L, Giovannoni G, Gold R, Phillips JT, Arnold DL, Hotermans C, et al. Time course of clinical and neuroradiological effects of delayed-release dimethyl fumarate in multiple sclerosis. Eur J Neurol 2015; 22: 664–71.

Kappos L, O'Connor PW, Polman CH, Vermersch P, Wiendl H, Pace A, et al. Clinical effects of natalizumab on multiple sclerosis appear early in treatment course. J Neurol 2013; 260: 1388–95.

Kappos L, Radue EW, Chin P, Ritter S, Tomic D, Lublin F. Onset of clinical and MRI efficacy occurs early after fingolimod treatment initiation in relapsing multiple sclerosis. J Neurol 2016; 263: 354–60.

Kunchok A, Malpas C, Nytrova P, Havrdova EK, Alroughani R, Terzi M, et al. Clinical and therapeutic predictors of disease outcomes in AQP4-IgG+ neuromyelitis optica spectrum disorder. Mult Scler Relat Disord 2020; 38: 101868.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983; 33: 1444–52.

Le Page E, Leray E, Taurin G, Coustans M, Chaperon J, Morrissey SP, et al. Mitoxantrone as induction treatment in aggressive relapsing remitting multiple sclerosis: treatment response factors in a 5 year follow-up observational study of 100 consecutive patients. J Neurol Neurosurg Psychiatry 2008; 79: 52–6.

Lizak N, Lugaresi A, Alroughani R, Lechner-Scott J, Slee M, Havrdova E, et al. Highly active immunomodulatory therapy ameliorates accumulation of disability in moderately advanced and advanced multiple sclerosis. J Neurol Neurosurg Psychiatry 2017; 88: 196–203.

Lorscheider J, Benkert P, Schädelin S, Yaldizli O, Derfuss T, Lalive P, et al. ECTRIMS 2019—oral presentation: disability progression unrelated to relapses in relapsing-remitting multiple sclerosis: insights from the Swiss multiple sclerosis cohort study. Mult Scler J 2019; 25: 3–130.

McDonald WI, Miller DH, Thompson AJ. Are magnetic resonance findings predictive of clinical outcome in therapeutic trials in multiple sclerosis? The dilemma of interferon-beta. Ann Neurol 1994; 36: 14–8.

McLachlan G, Peel D. Finite Mixture Models. 1 edn. New York, NY: John Wiley & Sons, Inc.; 2000.

Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler 2018; 24: 96–120.

Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Ann Neurol 2011; 69: 292–302.

Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005; 58: 840–6.

Schumacher GA, Beebe G, Kibler RF, Kurland LT, Kurtzke JF, McDowell F, et al. Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. Ann N Y Acad Sci 1965; 122: 552–68.

Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS (SPECTRIMS) Study Group. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: clinical results. Neurology 2001; 56: 1496–504.

Sheather SJ, Jones MC. A reliable data-based bandwidth selection method for kernel density estimation. J R Stat Soc Ser B 1991; 53: 683–90.

Sheremata WA, Vollmer TL, Stone LA, Willmer-Hulme AJ, Koller M. A safety and pharmacokinetic study of intravenous natalizumab in patients with MS. Neurology 1999; 52: 1072–4.

Sormani MP, Giovannoni G. Therapeutic lag: is treatment effect delayed in progressive MS? Mult Scler J 2016; 22: 7–87.

Sormani MP, Muraro PA, Schiavetti I, Signori A, Laroni A, Saccardi R, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a meta-analysis. Neurology 2017; 88: 2115–22.

Stellmann JP, Krumbholz M, Friede T, Gahlen A, Borisow N, Fischer K, et al. Immunotherapies in neuromyelitis optica spectrum disorder: efficacy and predictors of response. J Neurol Neurosurg Psychiatry 2017; 88: 639–47.

Traboulsee A, Li DKB, Cascione M, Fang J, Dangond F, Miller A. Effect of interferon beta-1a subcutaneously three times weekly on clinical and radiological measures and no evidence of disease activity status in patients with relapsing-remitting multiple sclerosis at year 1. BMC Neurol 2018; 18: 143.

Tramacere I, Giovane Salanti DC, D'Amico G, Filippini R. G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev 2015; CD011381.

Trojano M, Pellegrini F, Paolicelli D, Fuiani A, Zimatore GB, Tortorella C, et al. Real-life impact of early interferon beta therapy in relapsing multiple sclerosis. Ann Neurol 2009; 66: 513–20.

Tuohy O, Costelloe L, Hill-Cawthorne G, Bjornson I, Harding K, Robertson N, et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. J Neurol Neurosurg Psychiatry 2015; 86: 208–15.

Vukusic S, Casey R, Rollot F, Brochet B, Pelletier J, Laplaud DA, et al. Observatoire Francais de la Sclerose en Plaques (OFSEP): a unique multimodal nationwide MS registry in France. Mult Scler 2020; 26: 118–22.

Wattjes MP, Rovira A, Miller D, Yousry TA, Sormani MP, de Stefano MP, et al. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis–establishing disease prognosis and monitoring patients. Nat Rev Neurol 2015; 11: 597–606.

Wolinsky JS, Narayana PA, O'Connor P, Coyle PK, Ford C, Johnson K, et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol 2007; 61: 14–24.

Wright K, Winkler MD, Newton BD, Sormani MP, Okuda DT. Patient outcomes influenced by reduced lymphocyte counts after dimethyl fumarate initiation. Neurol Neuroimmunol Neuroinflamm 2017; 4: e397.