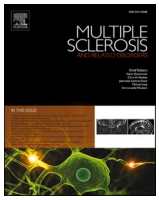
Multiple Sclerosis and Related Disorders 53 (2021) 103012

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Original article

The effectiveness of natalizumab vs fingolimod–A comparison of international registry studies

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https://doi.org/10.1016/j.msard.2021.103012

Available online 8 May 2021

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ARTICLE INFO

Keywords:
Multiple sclerosis
Natalizumab
Fingolimod
Treatment effectiveness
Head-to-head comparison

ABSTRACT

Background: Natalizumab and fingolimod were the first preparations recommended for disease breakthrough in priorly treated relapsing-remitting multiple sclerosis. Of three published head-to-head studies two showed that natalizumab is the more effective to prevent relapses and EDSS worsening.
Methods: By re-analyzing original published results from MSBase, France, and Denmark using uniform methodologies, we aimed at identifying the effects of differences in methodology, in the MS-populations, and at re-evaluating the differences in effectiveness between the two drugs.
We gained access to copies of the individual amended databases and pooled all data. We used uniform inclusion/exclusion criteria and statistical methods with Inverse Probability Treatment Weighting.
Results: The pooled analyses comprised 968 natalizumab- and 1479 fingolimod treated patients. The on-treatment natalizumab/fingolimod relapse rate ratio was 0.77 (p=0.004). The hazard ratio (HR) for a first relapse was 0.82 (p=0.030), and the HR for sustained EDSS improvement was 1.4 (p=0.009). There were modest differences between each of the original published studies and the replication study, but the conclusions of the three original studies remained unchanged: in two of them natalizumab was more effective, but in the third there was no difference between natalizumab and fingolimod.
Conclusion: The results were largely invariant to the epidemiological and statistical methods but differed between the MS populations. Generally, the advantage of natalizumab was confirmed.

1. Introduction

Evidence-based 2018 guidelines (Montalban et al., 2018) for the use of disease modifying drugs (DMDs) in multiple sclerosis (MS) suggest that in patients with relapsing-remitting MS (RRMS) the choice of DMD should be based upon patient characteristics and comorbidities, disease severity, drug safety profile and accessibility of the drug. In RRMS patients with inadequate treatment response it is recommended to switch to a drug with higher efficacy including natalizumab or fingolimod (Montalban et al., 2018).

No randomized clinical trial has assessed the comparative efficacy of natalizumab and fingolimod in RRMS patients. Observational studies have shown inconsistent results as to difference in clinical effectiveness in real life settings (Koch-Henriksen et al., 2017; Gajofatto et al., 2014; Carruthers et al., 2014; Guger et al., 2018; Braune et al., 2013; Kalincik et al., 2015; Barbin et al., 2016; Lorscheider et al., 2018; Prosperini et al., 2017) These studies varied in sources of data, sample size, inclusion and exclusion criteria, study design, outcomes, and statistical analyses as well as in the MS populations. This study is based on three published studies from The Danish Multiple Sclerosis Treatment Register (Koch-Henriksen et al., 2017), the French MS Registry (Observatoire Français de la Sclérose en Plaques) OFSEP (Kalincik et al., 2015) and MSBase (Barbin et al., 2016) which led to seemingly discordant results. We hypothesize that these differences are primarily driven by differences in the studied populations rather than the used analytical methodology. This study is the first of a series of three studies which will replicate and combine the observations from the original three analyses, then quantify the effect of clinical and demographic differences between the MS populations on the observed effects of the two DMDs with high efficacy, and, lastly in detail explore the effect of statistical methodology. The present study may by its study design adjust the outcomes of the original studies as well as the robustness and internal validity. Differences in the studied samples may influence external validity and reflect variability in reported response to treatment in different patient subgroups (Kalincik and Butzkueven, 2016).

Kalincik et al. (2015) used data from the MSBase (Butzkueven, 2017) and reported a higher effectiveness of natalizumab compared to fingolimod in reducing the annualized relapse rate (ARR) and sustained disability improvement in RRMS. Barbin et al. (2016), using the French Multiple Sclerosis Registry (OFSEP) (Vukusic et al., 2018), supported the

Table 1
Differences in methods for the original studies and the present replication study and pooled study.

	MSBase 2015 (7)	OFSEP 2016 (8)	DMSTR 2016 (2)	Present replicationstudy and pooled study
Number of centers	66	27	14	174
Design	Cohort, longitudinal data.	Cohort, longitudinal data.	Cohort, longitudinal data.	Cohort, longitudinal data.
Inclusion/ exclusion	Relapse or disability worsening within 6 months before start; No previous participation in randomized trials	RRMS. Age 18 to 65. EDSS $\leq$ 5.5	RRMS $\geq$1 relapse within 12 months before start or, if treatment naïve, else $\geq$2 relapses with residual symptoms	RRMS; >= 90 days of DMD first-line treatment prior to study medication; >= 3 months of study treatment; no previous participation in randomized trials;
Propensity score: Matching or weighting	Matched by propensity score based on age; sex; number of relapses in 6 or 12 months EDSS; Disease activity under previous treatment (relapses, EDSS-worsening or both). MRI data available from a proportion of patients, multiple imputation used.	Weighted by inverse probability of treatment (IPTW) based on sex; number of relapses in previous year; EDSS; hospital; Gd-enhancing lesions on MRI.	Matched by propensity score based on sex; age; being treatment naïve; ARR during previous treatment; MSSS (derived from EDSS) with ignoring unmatchable cases. No MRI data available for matching.	Weighted by stabilized inverse probability of treatment (IPTW) based on sex; age; MS duration; EDSS; #relapses in 12 months; disease activity in 12 months (relapses, EDSS-worsening or both).
Statistical analyses	Adjusted paired proportional hazards models and weighted negative binomial model	t test; Wilcoxon test; chi-square.	Generalized linear models assuming negative binominal distribution; Kaplan-Meyer analysis; Mann Whitney U test; Pearson chi-square.	Negative binominal model; Cox proportional Hazards; Anderson-Gill model
Follow-up	December 2013	July 2014	October 2015	-
Clinical study endpoints	Freedom from clinical relapses. ARR. Disability worsening. Disability improvement.	Proportion of patients with at least one on-study relapse in the first year and at two years.	ARR; proportion of patients remaining free of relapses; time to 1st relapse; proportion with worsening or improving EDSS.	ARR; relapse rate ratio; time to 1st relapse; increase in EDSS sustained for 6 months; improvement of EDSS sustained for 6 months

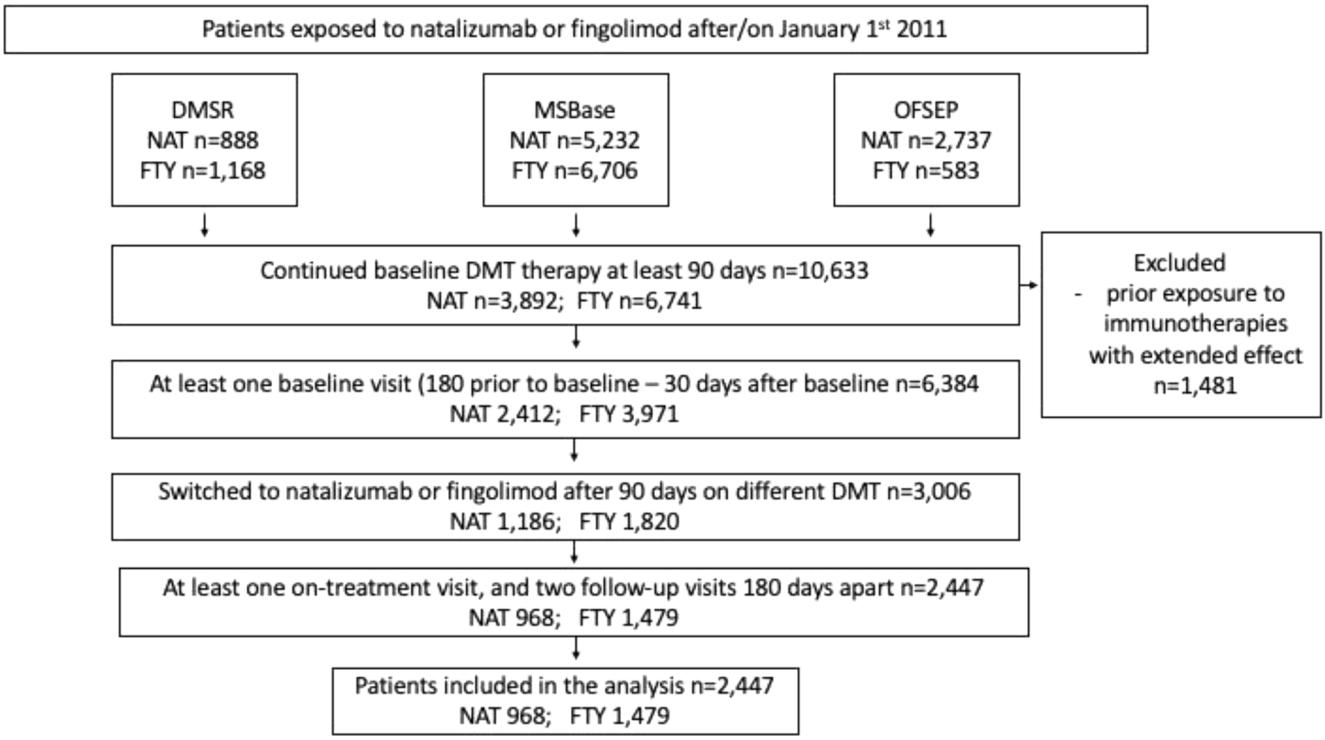

Fig. 1. Flowchart presentation of the included patients in the pooled cohort.

finding of higher effectiveness of natalizumab compared to fingolimod on reducing the proportion of relapse-free patients. Conversely, Koch--Henriksen et al. (2017) analysed data from the nationwide Danish Multiple Sclerosis Treatment Register and found no significant differences when comparing the effectiveness of natalizumab and fingolimod in any of the clinical endpoints.

The three original head-to-head studies represented different MS populations, and they differed to some extent in inclusion/exclusion criteria, and there may have been local differences in how clinicians prescribed the two preparations.

The purpose of this study was to compare disease activity after switch from first-line therapy to natalizumab or fingolimod using pooled and extended data from the three databases and to replicate their differences when using uniform methodology.

2. Material and methods

2.1. Study design

This study is a historical cohort study of prospectively collected data, recorded in three large MS registries, OFSEP, DMSR and MSBase (Koch-Henriksen et al., 2017; Kalincik et al., 2015; Barbin et al., 2016).

The study consists of two parts: 1) the replication *study* in which the same data were subjected to new and uniform selection criteria, definition of endpoints, and statistical analyses, and 2) the *pooled study* in which data from the three cohorts were pooled and subjected to the same methods and analyses as used for the replication study (see below).

Data in MSBase and DMSR had been updated with more patients and longer follow-up presented in this study, whereas the data provided from OFSEP for this study was the same as used in the original study. Table 1 shows the differences in the inclusion/exclusion criteria, statistical methods and clinical endpoints used in the three original studies and in the pooled study.

2.2. Data sources

The MSBase Registry is a large international collaboration database with patient records from 129 participating MS centres located in 34 different countries (Butzkueven, 2017). The MSBase longitudinally collects data most from tertiary MS centres. The inclusion criteria for the MSBase is a diagnosis of MS or clinically isolated syndromes based on the 2005 or 2010 revised McDonald Criteria. The MSBase protocol stipulates update on the minimum data set at least annually, although this was not a required inclusion criterion. The median inter-visit interval is 5 months. The data entry portal was either iMed MS patient record system or the MSBase online data system. An operationalised data quality procedure was applied (Kalincik et al., 2017).

The Danish Multiple Sclerosis Registry (DMSR) (Koch-Henriksen et al., 2015) was founded in 1956. It comprises data on all patients diagnosed with - or suspected of having - MS by a neurologist. The diagnostic criteria applied before 2005 were the Poser criteria (Poser et al., 1983) and thereafter the current version of the McDonald criteria (Polman et al., 2005). Since 1996, acquisition of relapses and Expanded Disability Status Scale (EDSS) scores and of the clinical characteristics has been performed in all DMD-treated patients at baseline, after 3 months and thereafter every 6 months during the clinical follow-up with mandatory notification of the DMSR due to reimbursement. Only departments of neurology in public hospitals are authorized to prescribe and dispense the DMDs to the patients, and the treating neurologists are joined in a network enabling use of uniform guidelines. All 14 Danish MS centres contribute, and data collection is done through an online data collection platform, which enables continuous completion of data improving its completeness and validity.

The Observatoire Français de la Sclérose en Plaques (OFSEP) (Vukusic, 2018) collects information from 40 MS expert centres throughout France, representing more than one half of the French MS population. Clinical data are collected during routine follow-up visits, usually at least once a year, retrospectively at the first visit and prospectively thereafter. Minimum standardized datasets are recorded through the EDMUS database and synchronised with the OFSEP database at 6-month

Table 2
Baseline characteristics of the pooled cohort and the three individual cohorts contributing to it before and after stabilized inverse probability of treatment weighting (sIPTW).

	Before sIPTW			After sIPTW		
	Natalizumab	Fingolimod		Natalizumab	Fingolimod	
MSBase (international)	N = 410	N = 792	SMD*			SMD*
Female %	73.2	72.9	0.071	72.1	72.8	0.018
Mean age at baseline,years (sd)	36.2 (10.3)	38.1 (9.6)	0.183	37.6 (11.1)	37.6 (9.5)	0.004
Mean MS duration, years (sd)	8.1 (6.6)	9.2 (7.2)	0.151	9.1 (7.9)	8.9 (7.0)	0.025
Mean EDSS at baseline, (sd)	2.9 (1.52)	2.28 (1.51)	0.411	2.66 (1.42)	2.49 (1.58)	0.114
Mean nr of relapses 12 months prior to baseline	1.35 (0.96)	0.94 (0.84)	0.447	1.14 (0.88)	1.07 (0.90)	0.079
Mean nr of previous DMDs, (sd)	1.59 (0.80)	1.67 (0.88)	0.106	1.67 (0.88)	1.67 (0.87)	0.008
Disease activity 12 months prior to baseline%						
None	13.66	27.02	0.337	18.92	22.86	0.097
Worsening	3.90	5.56	0.078	4.36	5.25	0.042
Relapse	51.95	45.2	0.135	49.06	46.16	0.058
Relapse and worsening	30.49	22.22	0.188	27.66	25.73	0.044
DMSR (Denmark)	N = 399	N = 581				
Female %	70.9	65.1	0.126	67.3	67.4	0.017
Mean age at baseline (sd)	39.2 (9.5)	40.4 (9.2)	0.131	39.9 (9.5)	39.9 (9.3)	0.001
Mean MS duration, years (sd)	8.8 (7.4)	8.9 (6.7)	0.025	8.8 (7.6)	8.8 (6.6)	0.003
Mean EDSS at baseline	2.90 (1.59)	2.63 (1.46)	0.171	2.73 (1.56)	2.74 (1.50)	0.005
Mean nr of relapses 12 months prior to baseline	0.76 (0.84)	0.71 (0.75)	0.072	0.73 (0.80)	0.73 (0.78)	0.001
Mean nr of previous DMDs	1.61 (0.95)	1.51 (0.76)	0.117	1.56 (0.87)	1.55 (0.79)	0.005
Disease activity 12 months prior to baseline%						
None	25.81	30.98	0.115	28.99	28.97	0.001
Worsening	18.30	13.77	0.124	15.36	15.41	0.002
Relapse	28.32	30.98	0.058	30.10	30.02	0.002
Relapse and worsening	27.57	24.27	0.075	25.55	25.60	0.001
OFSEP (France)	N = 159	N = 106				
Female %	76.7	73.6	0.073	74.9	76.7	0.042
Mean age at baseline (sd)	37.1(10.2)	39.1 (9.2)	0.198	37.9(10.4)	37.8 (9.5)	0.023
Mean MS duration (years)	8.0 (5.4)	9.8 (6.9)	0.297	8.7 (5.8)	8.6 (6.3)	0.015
Mean EDSS at baseline	2.82 (1.58)	2.61 (1.67)	0.131	2.77 (1.54)	2.85 (1.66)	0.049
Mean nr of relapses 12 months prior to baseline	1.62 (1.07)	0.99 (0.93)	0.623	1.38 (1.06)	1.41 (1.1)	0.029
Mean nr of previous DMDs	1.69 (0.89)	1.58 (0.87)	0.114	1.66 (0.89)	1.68 (0.9)	0.024
Disease activity 12 months prior to baseline%						
None	6.92	25.47	0.520	14.09	14.03	0.002
Worsening	3.77	7.55	0.164	5.12	5.10	0.001
Relapse	45.91	44.34	0.032	45.29	44.31	0.019
Relapse and worsening	43.4	22.64	0.453	35.49	36.56	0.022
Pooled cohort (MSBase+DMSR+OFSEP)	N = 968	N = 1479				
Female %	72.8	69.8	0.066	70.3	71.0	0.015
Mean age at baseline (sd)	37.6 (10.0)	39.1 (9.5)	0.150	38.8 (10.5)	38.6 (9.5)	0.022
Mean MS duration, years (sd)	8.4 (6.8)	9.1 (6.9)	0.110	9.0 (7.8)	8.9 (6.8)	0.026
Mean EDSS at baseline	2.89(1.56)	2.44 (1.51)	0.289	2.71 (1.50)	2.65 (1.57)	0.036
Mean nr of relapses 12 months prior to baseline	1.15 (0.99)	0.85 (0.82)	0.327	0.99 (0.91)	0.98 (0.91)	0.017
Mean nr of previous DMDs	1.61 (0.88)	1.6 (0.84)	0.011	1.61 (0.84)	1.62 (0.84)	0.004
Disease activity 12 months prior to baseline%						
None	17.56	28.47	0.261	23.12	24.29	0.028
Worsening	9.81	8.92	0.031	8.97	9.41	0.015
Relapse	41.22	39.55	0.034	40.64	39.51	0.023
Relapse and worsening	31.40	23.06	0.188	27.27	26.79	0.011

* Standardized mean difference (difference as fraction of the pooled standard deviation)

intervals. OFSEP has implemented a strategy to improve the quality of its data and samples. The EDMUS software has an integrated data verification tool to identify missing or incoherent data. Twice a year, a quality report is sent to all centres, with queries on incoherent data entries. Information documents, data quality indicators, training sessions and audits are displayed.

2.3. Inclusion criteria for the replication study and the pooled study

The inclusion criteria and statistical methods used in the replication study and the pooled study were agreed upon by the three registries. They were: 1) RRMS at commencing study treatment; 2) patients have commenced treatment with either natalizumab or fingolimod for the first time on or after 1st of January 2011 (to ensure accessibility of both drugs in Europe and Australia); 3) continuous treatment with either natalizumab or fingolimod for ≥3 months; 4) no prior exposure to immunotherapies with extended effect (mitoxantrone, alemtuzumab, ocrelizumab, daclizumab, rituximab, cyclophosphamide, or cladribine); 5) no prior participation in any interventional randomised controlled trials; 6) exposure to DMD treatment for more than 90 consecutive days within the 12 months immediately prior to commencing natalizumab or fingolimod; 7) sufficient EDSS follow-up (consisting of EDSS recorded 6 months to +1 months of baseline; more than one EDSS assessment recorded on study therapy and more than one EDSS assessment recorded ≥ 6 months later (irrespective of the treatment status at that time)). EDSS scores recorded <= 30 days after a prior relapse were ignored. Baseline was defined as the day of initiation of natalizumab or fingolimod. Patients' follow-up was censored at discontinuation of the study therapy or the last recorded follow-up. The numbers of eligible patients are presented in Fig. 1 and Table 2. All three registries used equivalent definitions of the EDSS score as derived from functional score systems described by Kurtzke (Kurtzke, 1984). Relapses were defined as occurrence of new or worsening neurological symptoms persisting for at least 24 hours in the absence of fever and infection (Polman et al., 2005) and onset year as the year of first experienced symptom of MS. MSBase and OFSEP had the date and year of onset registered, whereas only year of

Table 3
Results of replication analyses based on weighted (IPTW) data in the pooled cohort and the three individual cohorts contributing to it.

		Pooled cohortN=2447	MSBaseN=1202	DMSRN=980	OFSEPN=265
Annualized relapse rate	Natalizumab	0.14	0.09	0.18	0.18
	[95% CI]	[0.12; 0.16]	[0.06; 0.12]	[0.14 0.22]	[0.14; 0.23]
	Fingolimod	0.17	0.14	0.15	0.39
	[95% CI]	[0.14; 0.19]	[0.12; 0.17]	[0.12; 0.18]	[0.21; 0.57]
Difference of means (FTY minus NAT)					
	[95% CI]	0.026	0.053	-0.027	0.204
		[-0.004; 0.06]	[0.02; 0.09]	[0.07; -0.02]	[0.02, 0.39]
Relapse rate atio*§		0.77	0.62	1.12	0.47
	[95% CI]	[0.64; 0.93]	[0.45-0.84]	[0.87; 1.44]	[0.28; 0.76]
	p-value	0.004	0.0013	0.397	0.002
Hazard Ratio* for a first relapse		0.82	0.61	1.12	0.66
	[95% CI]	[0.68; 0.98]	[0.44; 0.85]	[0.88; 1.43]	[0.40; 1.10]
	p value	0.030	0.0032	0.359	0.111
Hazard Ratio* for a first sustained EDSS-worsening		1.13	1.08	0.97	0.77
	[95% CI]	[0.83; 1.53]	[0.63; 1.85]	[0.63; 1.51]	[0.26; 2.30]
	p value	0.438	0.767	0.910	0.645
Hazard Ratio* for a first sustained EDSS-improvement		1.40	1.89	1.11	1.57
	[95% CI]	[1.08; 1.80]	[1.24; 2.88]	[0.79; 1.57]	[0.62; 3.96]
	p value	0.009	0.003	0.539	0.342
Ratio* of cumulative hazards of multiple events of EDSS-worsening		1.10	1.06	0.94	0.79
	[95% CI]	[0.82; 1.46]	[0.64; 1.75]	[0.62; 1.41]	[0.26; 2.34]
	p value	0.528	0.814	0.745	0.669
Ratio* of cumulative hazards of multiple events of EDSS-improvement		1.37	1.89	1.09	1.69
	[95% CI]	[1.08; 1.76]	[1.25; 2.86]	[0.78; 1.51]	[0.68; 4.20]
	p value	0.011	0.002	0.624	0.259

*with Fingolimod as reference
§calculated as the adjusted exponentiated regression coefficient of count of relapses with logarithmic transformed observation time as offset.

onset was recorded for some patients in the DMSR (if missing, date was set to 15/6 in the recorded year of onset).

2.4. Study endpoints of the replication study and the pooled study

ARR was calculated at the individual level as the number of relapses divided by annualized observed person-time from baseline to treatment discontinuation or censor date in years.

Time to first relapse was calculated as the time from baseline to the date of start of a first relapse.

Worsening of EDSS was defined as an increase by $\geq$ 1.5 step sustained for 6 months if EDSS at baseline was 0; or $\geq$ 1 step if EDSS at baseline was $\geq$ 1 and $\leq$ 5.5; and $\geq$ 0.5 step if EDSS at baseline was $\geq$ 6. Improvement of EDSS was defined as a decrease by $\geq$ 1 EDSS step if EDSS at baseline was $\leq$ 6 and $\geq$ 1.5; $\geq$ 0.5 step if EDSS at baseline was $>$ 6; and 1.5 step if EDSS at baseline was 1.5, of which all should be confirmed by EDSS scores recorded over $\geq$ 6 months.

2.5. Statistical analyses

2.5.1. The replication study

2.5.1.1. Estimation of propensity scores. To control for treatment indication bias, we used stabilized inverse probability of treatment weighting (sIPTW) calculated from propensity scores. The propensity score is a balanced score representing the probability of being treated with natalizumab (relative to fingolimod) given the patients' baseline clinical and demographic characteristics. In the replication analyses, it was computed separately for each database using a multivariable logistic regression based on sex, age, MS duration, EDSS at baseline, number of relapses in the 12 months prior to baseline, disease activity 12 months prior to baseline (classified as relapse or EDSS progression, or both), and the number of previously DMDs commenced prior to baseline. In the pooled analysis we computed sIPTW based on the pooled data. For the MSBase cohort and the pooled cohort, the models of sIPTW included country as a random effect.

Using the propensity scores, we calculated sIPTW (Austin and Stuart, 2015). Each patient who fulfilled the inclusion criteria was assigned a weight. The weight was proportional to the inverse of the probability of receiving the treatment that the subject actually received (Austin, 2011) given the individual patient's baseline characteristics, e.g. a patient treated with natalizumab with a low probability of being treated with natalizumab was assigned a high weight.

2.5.1.2. Comparison of treatment effectiveness. Demographic and clinical characteristics of patients from either treatment group within each registry as well as the pooled cohort at baseline are reported, including their standardized differences. A difference of $\leq$ 10% was considered acceptable (Austin and Stuart, 2015). The propensity score distributions in the two groups were assessed for the degree of overlap, also named the common support.

ARR for natalizumab and fingolimod were reported. The counts of relapses between natalizumab and fingolimod in the treated periods were compared using generalized linear models with weighted negative binomial distribution model and with logarithmic transformed length of treatment period as offset. The regression coefficients were exponentiated to obtain the ratio of relapse rates. Weighted Cox proportional hazards models were used to evaluate the cumulative hazard of 1st relapse as well as 1st EDSS improvement and 1st EDSS worsening. The weighted Andersen-Gill proportional hazards model was used to evaluate the cumulative hazards of multiple events of EDSS worsening and improvement. Robust estimation of variance was used.

Analyses were performed per protocol using the R-software (R 3.4.0).

3. Results

3.1. The replication analyses

Table 2 shows the baseline characteristics for the cases from the three databases, before and after stabilized inverse probability weighting (sIPTW). The weighting improved the balance between the natalizumab and the fingolimod treated groups which is demonstrated by the reduced standardized mean differences (SMD).

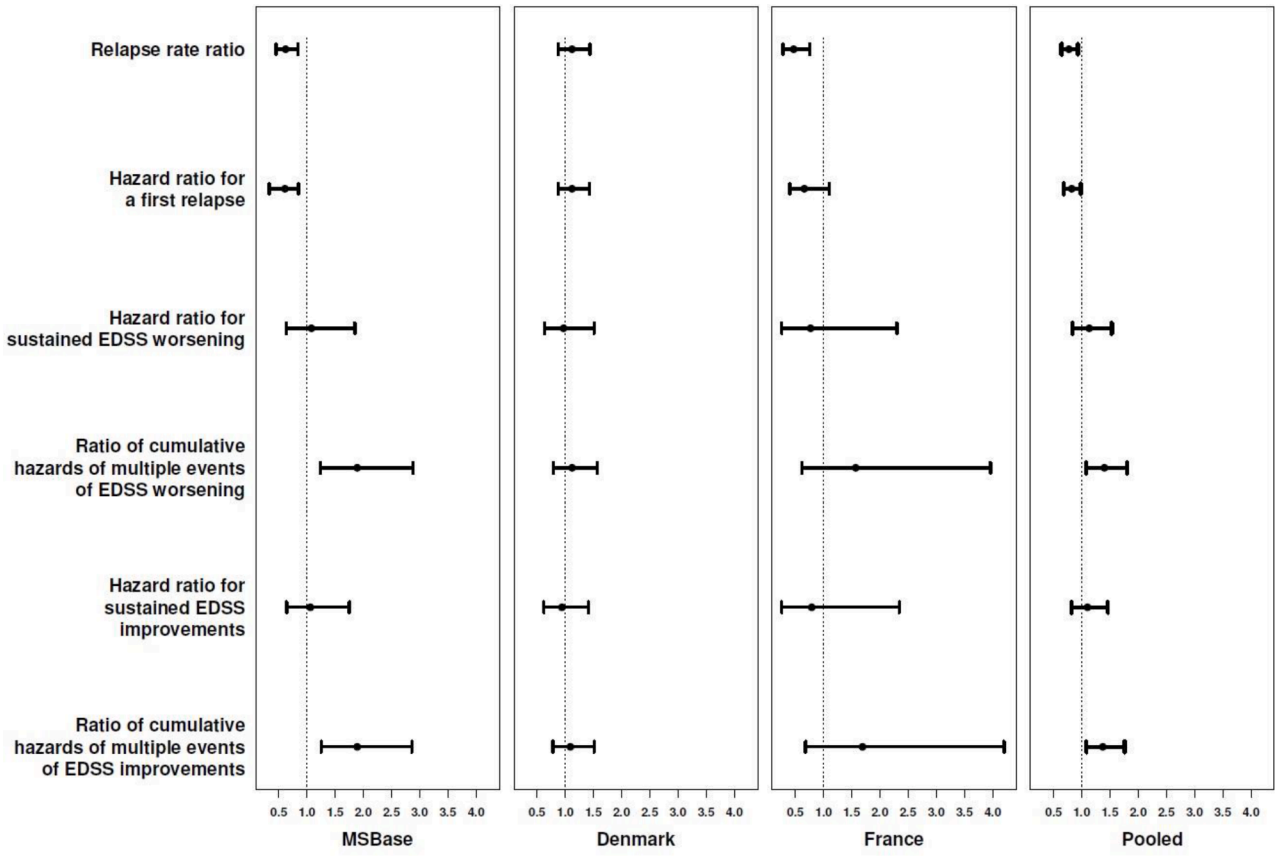

Fig. 2. Comparative presentation of study outcomes. Fingolimod is the reference drug in all comparisons.

3.2. The MSBase

This part of the study included 1202 patients, 410 treated with natalizumab and 792 treated with fingolimod. The detailed demographic and clinical baseline characteristics are shown in Table 2 before and after sIPTW. The results of the replication analysis from the MSBase using unified methodology showed an ARR of 0.091 for natalizumab and 0.144 for fingolimod. With fingolimod as reference, the weighted ratio of the ARRs was 0.619; $p = 0.0013$. The hazard ratio (HR) for a first relapse was 0.61 ($p = 0.003$). HR for the first sustained EDSS-worsening was close to unity: 1.08 ($p = 0.767$), but the Cox regression analysis of a first sustained EDSS-improvement indicated that natalizumab was associated with a greater chance of decrease in EDSS than fingolimod: HR = 1.89 ($p = 0.003$). The estimates and confidence intervals are shown in Table 3.

3.3. The DMSR cohort

This cohort included 980 patients, 399 treated with natalizumab and 581 with fingolimod. Demographic and clinical baseline characteristics before and after sIPTW are presented in Table 2. In the replication analyses the results were comparable between the treatment groups: ARR was 0.178 for natalizumab and 0.151 for fingolimod. With fingolimod as reference the weighted ratio of the ARRs was 1.115 ($p = 0.397$). HR for a first relapse was 1.12 ($p = 0.359$), for a first sustained EDSS-worsening: 0.97 ($p = 0.91$), and for a first sustained EDSS-improvement: 1.11 ($p = 0.539$). For the full results and confidence intervals see Table 3.

3.4. The OFSEP cohort

This part of the study included 265 patients, 159 treated with natalizumab and 106 with fingolimod. Table 2 presents detailed demographic and clinical baseline characteristics before and after sIPTW. The replication analysis of the OFSEP data showed that the ARR was 0.183 on natalizumab and 0.387 on fingolimod. Treatment with fingolimod as reference the weighted ratio of the ARRs was 0.466 ($p = 0.002$). For the other outcomes there were no statistically significant differences between the treatment groups. HR for a first relapse was 0.66 ($p=0.111$), for a first sustained EDSS worsening: 0.77 ($p=0.645$), and for a first sustained EDSS-improvement: 1.57 ($p=0.342$). For full results of the analysis and confidence intervals see Table 3.

In summary, with some differences, the results of the present replication analyses for each database were roughly the same as those published in the three individual original studies (Koch-Henriksen et al., 2017; Kalincik et al., 2015; Barbin et al., 2016), when using the uniform design and statistical analyses, with a larger cohort and longer follow-up times for two of the study populations.

3.5. The pooled analysis

The pooled cohort from the three databases consisted of 2447 patients, 968 treated with natalizumab and 1479 treated with fingolimod. In patients treated with natalizumab the ARR was 0.138, compared with the ARR of 0.165 in patients treated with fingolimod. With fingolimod as reference the weighted ratio of the ARRs was 0.771 ($p = 0.004$), and HR for a first relapse was 0.82; ($p=0.030$). We found no difference in hazards for a first sustained EDSS-worsening: HR 1.13 ($p = 0.438$), but sustained EDSS improvement was in the favour of natalizumab with a HR of 1.40 ($p=0.009$), and for multiple EDSS-improvement events of 1.37 ($p = 0.011$). A visual presentation of the results is presented in Fig. 2. Table 3 shows full results with confidence intervals. Analyses with interaction terms for registry x treatment confirmed the differences in comparative effectiveness presented in the replication analyses above (data not shown).

4. Discussion

Using unified design and methodology, this study reanalysed original and extended clinical data from three different published studies that compared effectiveness of natalizumab and fingolimod in RRMS. The analyses of the pooled cohort confirmed an advantage of natalizumab over fingolimod in reducing the risk of relapses by 23% and facilitating early recovery from neurological disability by 40%. These results were largely driven by MSBase and OFSEP. However, similar to the original studies, the pooled study found no difference in the risk of EDSS worsening between the two disease modifying therapies.

Also, the original studies from OFSEP and MSBase (Kalincik et al., 2015; Barbin et al., 2016) showed that natalizumab was associated with lower risk of relapses than fingolimod. The study in the MSBase cohort also suggested that natalizumab was associated with a higher probability of recovery from disability. On the other hand, there was a certain degree of heterogeneity as the study from DMSR (Koch-Henriksen et al., 2017) showed no significant differences between the effects of the two drugs.

When we replicated the results from the three contributing databases with the uniform present inclusion criteria and methodology, the results were roughly the same as in the original studies.

The heterogeneity between the results of MSBase, OFSEP, and, on the other hand, DMSR can best be explained by differences in the clinical and demographic characteristics of the study populations (Kalincik and Butzkueven, 2016): For example, the OFSEP and the MSBase cohorts were enriched for younger patients with higher prior relapse activity (mean ARR 1.38-1.41 and 1.07-1.14, respectively) and greater exposure to DMDs prior to their treatment with natalizumab or fingolimod than the DMSR in the original studies (mean ARR 0.73). In 12 months prior to treatment switch more of the DMSR patients had experienced worsening compared with patients from MSBase and OFSEP, but fewer of them had recorded relapses in this period. This could also explain some of the differences between the main results from the three databases. In fact, the difference in the effect on relapses between natalizumab and fingolimod was greatest in the cohort with the highest disease activity (OFSEP). This suggests that a 'floor effect' exists when one compares effectiveness among highly potent DMDs, and the differences between fingolimod and natalizumab become apparent in patients with highly active disease. The overall frequency of relapses was higher in the OFSEP dataset than in the DMSR dataset, and the magnitudes of treatment effectiveness were similar or greater in the MSBase and OFSEP datasets than in the combined dataset. We cannot rule out that these differences may be partly driven by differences in reporting methods among the three registries.

Confounding by variables that influence the choice of treatment as well as short-term disease outcomes is a major concern when comparing treatment arms in non-randomized open-label studies. The three original studies had dealt with this issue using different statistical methods. The present study used a uniform analytical methodology, based on a consensus among the investigators, and we used the sIPTW to successfully reduce treatment indication bias. This is reflected by the very close balance of baseline variables between the two treatment arms after weighting. To account for possible heterogeneity, we have included the country of data origin in the estimation of sIPTW in the pooled alalyses.

The reported findings were mainly driven by the MSBase and the DMSR cohorts which constitute 49% and 40% of the data in the pooled cohort, respectively. The size of the treatment groups in the individual cohorts (with the exception of the fingolimod group in MSBase) decreased as a result of more rigorous inclusion criteria in the unified analyses. However, our inclusion of data from 183 MS-centers across 36 counties strengthens the generalizability of our pooled data in a real-world setting.

The results of our pooled study are in keeping with a growing body of studies showing the advantage of natalizumab over fingolimod in terms of treatment effectiveness (Lorscheider et al., 2018, Prosperini et al., 2017, Carruthers et al., 2014).

4.1. Limitations

The inclusion only of patients with sufficient follow-up EDSS is a limitation of this study as this inclusion criterion, which aimed at including a population of patients who became established on their new therapy and with sufficient on-treatment disability information available for the analysis, would limit generalization of the observations for the subset of patients who discontinued their therapy early after only a brief time on treatment.

Furthermore, the lack of magnetic resonance imaging (MRI) data, either as a baseline or as an endpoint parameter is a limitation of this study. A recently published guideline (Montalban et al., 2018) emphasises the advantage of using MRI activity as short- and long-term predictors of disability worsening in RRMS patients. However, two of the original analyses had used (OFSEP) or imputed (MSBase) MRI information in their analyses, without any noticeable effect on the magnitude of the reported difference in the latter. Small numbers in some of the cohorts could have a negative impact on the power of the specific replication analyses, and their results should be interpreted with some caution. Reassuringly, these results confirmed the results of the original studies. Finally, this study did not compare incidence of adverse events, as this information was not available from all combined registries.

In conclusion: This study, conducted in a large combined cohort from three MS registries, reconciles the results of several previous analyses, and shows that natalizumab, after controlling for indication bias, is associated with a better control of relapse activity and improved chance of early recovery from disability among patients with active RRMS. The different results between the registries are primarily attributable to clinical and demographic differences between the studied cohorts. (Bovis et al., 2019). These characteristics warrant further research as they hold the promise of guiding personalised approach to choosing between different treatment options.

Data availability

DMSR: Anonymized data will be shared on request from any qualified researcher under approval from the Danish Data Protection Agency.

OFSEP: The individual data from the present study can be obtained upon request and after validation from the OFSEP scientific committee (see website: http://www.ofsep.org/fr/http://www.ofsep.org/en/data-access)

MSBase: MSBase is a data processor, and warehouses data from individual principal investigators who agree to share their datasets on a project-by-project basis. Each principal investigator will need to be approached individually for permission to access the datasets. Author contribution, see Appendix 1

Standard protocol approvals, registrations, and patient consents

The MSBase registry was approved by the Melbourne Health Human Research Ethics Committee and the local ethics committees at participating centres. Enrolled patients provided written informed consent as required. OFSEP was conducted in accordance with the French law relative to clinical noninterventional research according to the French law on Bioethics. Data confidentiality and safety are ensured according to the recommendations of the French Commission Nationale Informatique et Libertés (CNIL). OFSEP has received approval for storing clinical, biological and imaging data for research purpose. Patients gave informed consent for their data to be stored in the database and used for research, in France and abroad (www.ofsep.org/en/cohort/ofsep-consent). The cohort has been registered to clinicaltrials.gov under the number NCT02889965. The Danish study was conducted according to the Danish laws. Non-interventional register-based studies do not require ethical approval in Denmark. Required approvals were obtained

with the Center for Data Review applications (j. nr. 2012-58-0004/VD-2018-121 I-suite 6361).

Declaration of Competing Interest

J.B. Andersen received travel grant and congress participation support from Merck.

N. Koch-Henriksen received support for participation in congresses and symposia by Biogen, Merck, Novartis, and Teva.

F. Sellebjerg served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria, or received research support for his laboratory from Biogen, Merck, Novartis, Roche, Sanofi Genzyme and Teva.

P. S. Sørensen received personal compensation for serving on scientific advisory boards, steering committees, independent data monitoring committees or have received speaker honoraria for Merck, Novartis, TEVA, GlaxoSmithKline, MedDay Pharmaceuticals, SanofiAventis/Genzyme, and Celgene.

C. Hilt received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Genzyme, Biogen, Roche, Novartis, and Merck

P.V. Rasmussen received speaker honoraria from TEVA, Biogen, Roche and Novartis, support for congress participation from Merck, Roche, Sanofi and TEVA, fees for serving on advisory boards from Merck, Roche, Novartis, Biogen, and Sanofi.

M.B. Jensen served on scientific advisory boards, served as a consultant, received support for congress participation or received speaker honoraria from Biogen, Merck, Novartis, Roche, Sanofi Genzyme, and Teva.

J. Frederiksen recieved no funding to support the presented work. She has served on scientific advisory boards for and received funding for travel related to these activities as well as honoraria from Biogen Idec, Merck Serono, Sanofi-Aventis, Teva, Novartis, Roche and Almirall. She has received speaker honoraria from Biogen Idec, Teva, Roche and Novartis

S. Bramow received one speaking honorary from Biogen Idec (Denmark) and reimbursement for congress participation from Biogen, Roche, Merck and Sanofi Genzyme.

Received restricted hospital-administered research grant form Roche Denmark for research in pathological correlates of progressive multiple sclerosis.

H.K. Mathiesen received funding for congress participation from Teva, Merch Serono, Bayer Schering, Biogen Idec and Sanofi.

K.I. Schreiber served on scientific advisory boards, been onthe steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria from Biogen, Merck, Novartis, Roche, Sanofi Genzyme and Teva

M. Magyari served on scientific advisory board for Biogen, Sanofi, Teva, Roche, Novartis, Merck, has received honoraria for lecturing from Biogen, Merck, Novartis, Sanofi, Genzyme, has received research support and support for congress participation from Biogen, Genzyme, Teva, Roche, Merck, Novartis.

S. Sharmin did not disclose any conflict of interests.

D. Horakova received speaker honoraria and consulting fees from Biogen, Merck, Teva, Roche, Sanofi Genzyme, and Novartis, as well as support for research activities from Biogen and Czech Minsitry of Education [project Progres Q27/LF1].

E.K. Havrdova received speaker honoraria and consultant fees from Actelion, Biogen, Celgene, Merck, Novartis, Roche, Sanofi and Teva, and support for research activities from Czech Ministry of Education [project Progres Q27/LF1].

R. Alroughani received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme.

G. Izquierdo received speaking honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall and Teva.

S. Eichau did not declare any competing interests.

S. Ozakbas did not declare any competing interests.

F. Patti received speaker honoraria or advisory board fees from Almirall, Bayer, Biogen, Celgene, Merck, Myalin, Novartis, Roche, Sanofi-Genzyme and TEVA. He received research funding from Ministero Italiano della Universite della Ricerca Scientifica, Fondazione Italiana Sclerosi Multipla, Biogen and Merck.

M. Onofrj did not declare any competing interests.

A. Lugaresi served as a Bayer, Biogen, Merck, Novartis, Roche, Sanofi/ Genzyme and Teva Advisory Board Member. She received congress and travel/accommodation expense compensations and speaker honoraria from Bayer, Biogen, Merck, Novartis, Sanofi/Genzyme, Teva and Fondazione Italiana Sclerosi Multipla (FISM). Her institutions received research grants from Novartis.

M. Terzi received travel grants from Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.

P. Grammond is a Merck, Novartis, Teva-neuroscience, Biogen and Genzyme advisory board member, consultant for Merck, received payments for lectures by Merck, Teva-Neuroscience and Canadian Multiple sclerosis society, and received grants for travel from Teva-Neuroscience and Novartis.

F. Grand'Maison received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, Mitsubishi and ONO Pharmaceuticals.

B. Yamout did not declare any competing interests.

A. Prat did not declare any competing interests.

M. Girard received consulting fees from Teva Canada Innovation, Biogen, Novartis and Genzyme Sanofi; lecture payments from Teva Canada Innovation, Novartis and EMD. He has also received a research grant from Canadian Institutes of Health Research.

P. Duquette served on editorial boards and has been supported to attend meetings by EMD, Biogen, Novartis, Genzyme, and TEVA Neuroscience. He holds grants from the CIHR and the MS Society of Canada and has received funding for investigator-initiated trials from Biogen, Novartis, and Genzyme.

C. Boz received conference travel support from Biogen, Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.

M. Trojano received speaker honoraria from Biogen-Idec, Bayer-Schering, Sanofi Aventis, Merck, Teva, Novartis and Almirall; has received research grants for her Institution from Biogen-Idec, Merck, and Novartis.

P. McCombe did not declare any competing interests.

M. Slee has participated in, but not received honoraria for, advisory board activity for Biogen, Merck, Bayer Schering, Sanofi Aventis and Novartis.

J. Lechner-Scott accepted travel compensation from Novartis, Biogen and Merck. Her institution receives the honoraria for talks and advisory board commitment from Bayer Health Care, Biogen, Genzyme Sanofi, Merck, Novartis and Teva, has been involved in clinical trials with Biogen, Novartis and Teva.

R. Turkoglu did not declare any competing interests.

P. Sola served on scientific advisory boards for Biogen Idec and TEVA, she has received funding for travel and speaker honoraria from

Biogen Idec, Merck, Teva, Sanofi Genzyme, Novartis and Bayer and research grants for her Institution from Bayer, Biogen, Merck, Novartis, Sanofi, Teva.

D. Ferraro received travel grants and/or speaker honoraria from Merck, TEVA, Novartis, Biogen and Sanofi-Genzyme.

F. Granella received an institutional research grant from Biogen and Sanofi Genzyme, served on scientific advisory boards for Biogen, Novartis, Merck, Sanofi Genzyme and Roche, received funding for travel and speaker honoraria from Biogen, Merck, and Sanofi-Aventis.

V. Shaygannejad did not declare any competing interests.

J. Prevost accepted travel compensation from Novartis, Biogen, Genzyme, Teva, and speaking honoraria from Biogen, Novartis, Genzyme and Teva.

O. Skibina did not declare any competing interests.

C. Solaro served on scientific advisory boards for Merck, Genzyme, Almirall, and Biogen; received honoraria and travel grants from Sanofi Aventis, Novartis, Biogen, Merck, Genzyme and Teva.

R. Karabudak did not declare any competing interests.

B.V. Wijmeersch received research and rravel grants, honoraria for MS-Expert advisor and Speaker fees from Bayer-Schering, Biogen, Sanofi Genzyme, Merck, Novartis, Roche and Teva.

T. Csepany received speaker honoraria/ conference travel support from Bayer Schering, Biogen, Merck, Novartis, Roche, Sanofi-Aventis and Teva.

D. Spitaleri received honoraria as a consultant on scientific advisory boards by Bayer-Schering, Novartis and Sanofi-Aventis and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva and Merck.

S. Vucic did not declare any competing interests.

H. Butzkueven served on scientific advisory boards for Biogen, Novartis and Sanofi-Aventis and has received conference travel support from Novartis, Biogen and Sanofi Aventis. He serves on steering committees for trials conducted by Biogen and Novartis, and has received research support from Merck, Novartis and Biogen.

T. Kalincik served on scientific advisory boards for Celgene, Roche, Sanofi-Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi-Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Roche, Genzyme-Sanofi, Teva, BioCSL and Merck and received research support from Biogen.

M. Lefort reported travel grants from Roche SAS. This work was part of Mathilde Lefort's Ph.D., which was funded through an unconditional donation from Roche SAS, without any link to the scientific contents of the work.

R. Casey has nothing to disclose.

M. Debouverie has nothing to disclose.

G. Edan received consultancy and lecturing fees from Bayer-Schering, Biogen, LFB, Merck, Novartis, Roche, Sanofi; research grants from Bayer, Biogen, Genzyme, Mercks, Novartis, Roche, Teva, and the ARSEP.

J. Ciron received consulting and lecturing fees, travel grants from Biogen, Novartis, Merck, Teva, Genzyme and Roche.

A. Ruet received consultancy fees, speaker fees, research grants (non personal), or honoraria approved by the institutions from Novartis, Biogen Idec, Genzyme, Medday, Roche, Teva and Merck.

J.D. Sèze received consulting and lecturing fees, travel grants and unconditional research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, Sanofi Aventis and Teva Pharma.

E. Maillart received consulting and lecturing fees from Biogen, Novartis, Genzyme, Teva Pharmaceuticals, Merck Serono, Roche and Ad Scientiam and research support from Novartis and Roche.

H. Zephir hreceived consulting or lectures, and invitations for national and international congresses from Biogen, Merck, Teva, Sanofi-Genzyme, Novartis and Bayer, as well as research support from Teva and Roche and academic research grants from Académie de Médecine, LFSEP, FHU Imminent and ARSEP Foundation.

P. Labauge received consulting and lecturing fees, travel grants and unconditional research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, and Teva Pharma.

G. Defer received consulting and lecturing fees for Biogen, Novartis, Genzyme, Merck-Serono, Roche and Teva and funding for travel from Merck Serono, Biogen, Sanofi-Genzyme, Novartis and Teva. Institution granted for research supporting from Merck Serono, Biogen, Genzyme and Novartis.

C. Lebrun received fees for consulting or lectures from Novartis, Genzyme, Roche.

T. Moreau received fees as scientific adviser from Biogen, Medday, Novartis, Genzyme, Sanofi.

E. Berger received honoraria and consulting fees from Novartis, Sanofi Aventis, Biogen, Genzyme, Roche and Teva Pharma.

P. Clavelou received consulting and lecturing fees, travel grants and unconditional research support from Actelion, Biogen, Genzyme, Novartis, Medday, Merck Serono, Roche, and Teva Pharma.

J. Pelletier received fees as scientific adviser and travel grants from Biogen, Merck-Serono, Novartis,from Biogen, Medday, Novartis, Genzyme, Roche, Sanofi, Teva and unconditional research support from Merck-Serono and Roche.

B. Stankoff received consulting and lecturing fees, travel grants from Biogen Idec, Merck-Serono, Novartis, Genzyme, and unconditional research support from Merck-Serono, Genzyme, and Roche.

O. Gout has nothing to disclose.

E. Thouvenot received consulting and lecturing fees, travel grants or unconditional research support from the following pharmaceutical companies: Actelion, Biogen, Genzyme, Merck Serono, Novartis, Roche, Teva pharma; has a patent pending for biomarkers of neurodegeneration and neuroregeneration and a patent pending for a diagnosis method of multiple sclerosis (EP18305630.8) ; and received academic research support from PHRC and ARSEP Foundation.

O. Heinzlef received consulting and lecturing fees from Bayer Schering, Merck, Teva, Genzyme, Novartis, Almirall and BiogenIdec, travel grants from Novartis, Teva, Genzyme, Merck Serono and Biogen Idec and research support from Roche, Merck and Novartis.

A. Al-Khedr has nothing to disclose.

B. Bourre received served on scientific advisory board for Biogen, Genzyme, Merck Serono, Novartis, Roche and received funding for travel and honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Roche and Teva.

O. Casez received funding for travel and honoraria from Biogen, Merck Serono, Novartis, Sanofi-Genzyme and Roche.

P. Cabre has nothing to disclose.

A. Montcuquet received honoria and travel grants from Merck Serono, Teva, Novartis, Sanofi-Genzyme and Biogen.

A. Wahab received expert testimony from Roche and travel grants from Biogen.

J.P. Camdessanché received consulting and lecturing fees from Akcea, Alnylam, Biogen, CSL-Behring, Genzyme, Grifols, Laboratoire Français des Biotechnologies, Natus, Novartis, Pfizer, Pharmalliance, Teva, SNF-Floerger; travel grants from Biogen, CSL-Behring, Genzyme, Laboratoire Français des Biotechnologies, Merck-Serono, Novartis, Pfizer, Teva.

A. Marousset received funding for travel from Merck Serono, Teva, Novartis, Sanofi-Genzyme, Biogen and Roche. Served on scientific advisory board for Roche. Received honoria from Biogen, Novartis, and

Roche.

I. Patry received honoraria and consulting fees from Novartis, Genzyme and Roche, research supports from Biogen and Novartis and travel grants from Genzyme, Novartis and Roche.

K. Hankiewicz has nothing to disclose.

C. Pottier has nothing to disclose

N. Maubeuge received speaker fees and invitations for national and international congresses from Biogen, Merck, Sanofi-Genzyme, Novartis and Roche.

C. Labeyrie received consulting and lecturing fees from Biogen, Novartis and Genzyme.

C. Nifle has nothing to disclose.

E. Leray served on scientific advisory boards for Roche, Sanofi, Novartis, MedDay, Merck and Biogen, received conference travel support and/or speaker honorario from Novartis, Roche and Merck and received research support from Fondation ARSEP and Agence Nationale de la Sécurité du Médicament (ANSM).

DA. Laplaud served on scientific advisory boards for Roche, Sanofi, Novartis, MedDay, Merck and Biogen, received conference travel support and/or speaker honoraria from Novartis, Biogen, Roche, Sanofi, Celgene and Merck and received research support from Fondation ARSEP and Agence Nationale de la Recherche.

S. Vukusic received grants, personal fees and non-financial support from Biogen, grants and personal fees from Geneuro, grants, personal fees and non-financial support from Genzyme, grants and personal fees from Medday, grants, personal fees and non-financial support from Merck-Serono, grants, personal fees and non-financial support from Novartis, grants, personal fees and non-financial support from Roche, grants, personal fees and nonfinancial support from Sanofi, personal fees from Teva.

Funding

The MSBase Foundation is a not-for-profit organization that receives support from Biogen, Novartis, Merck, Roche, Teva and Sanofi Genzyme. The study was conducted separately and apart from the guidance of the sponsors. CORe received funding from NHMRC [1140766, 1129789, 1157717] to support studies of comparative effectiveness of MS therapies.

OFSEP was 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.

DMSR did not receive any funding to collaborate in this study.

Acknowledgement

DMSR would like to thank the following DMSR investigators who participated in data acquisition:

Alex Heick, Lars Kristian Storr, Mads Ravnborg, Matthias Kant, Nasrin Asgari, Jens Arentsen, Thor Petersen, Bjarne Sivertsen, Helle Hvilsted Nielsen, Georgi Sirakov, Allan Pedersen, and Mette Kirstine Christensen for providing clinical information and notification of The Danish Multiple Sclerosis Treatment Register. They also thank the secretariat of the Clinical Quality Databases under Danish Regions for allowing them to use data from the Danish Multiple Sclerosis Treatment Register for this study.

OFSEP would like to thank the following OFSEP investigators who participated in data acquisition:

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CORe would like to thank the following MSBase investigators who participated in data acquisition:

From Centro Internacional de Restauracion Neurologica, Havana, Cuba, Dr Jose Antonio Cabrera-Gomez. From MS Clinic, Hopital Tenon, Paris, France, Dr Etienne Roullet. From University Hospital Nijmegen, Nijmegen, Netherlands, Dr Cees Zwanikken. From Francicus Ziekenhuis, Roosendaal, Netherlands, Dr Leontien Den braber-Moerland. From INEBA - Institute of Neuroscience Buenos Aires, Buenos Aires, Argentina, Dr Maria Laura Saladino. From Sanatorio Allende, Cordoba, Argentina, Dr Carlos Vrech. From Brain and Mind Centre, Sydney, Australia, Dr Michael Barnett. From University of Melbourne, Melbourne, Australia, Dr Tomas Kalincik, Dr Mark Marriott, Dr Trevor Kilpatrick, Dr John King, Dr Katherine Buzzard, Dr Ai-Lan Nguyen, Dr Chris Dwyer, Dr Mastura Monif, Dr Izanne Roos, Ms Lisa Taylor, Ms Josephine Baker. From John Hunter Hospital, Newcastle, Australia, Dr Jeannette Lechner-Scott. From Liverpool Hospital, Sydney, Australia, Dr Suzanne Hodgkinson. From Westmead Hospital, Sydney, Australia, Dr Steve Vucic. From Flinders University, Adelaide, Australia, Dr Mark Slee. From University of Queensland, Brisbane, Australia, Dr Pamela McCombe. From Townsville Hospital, Townsville, Australia, Dr Mike Boggild. From Royal Hobart Hospital, Hobart, Australia, Dr Bruce Taylor.

From Monash University, Melbourne, Australia, Dr Olga Skibina. From Austin Health, Melbourne, Australia, Dr Richard Macdonell. From Concord Repatriation General Hospital, Sydney, Australia, Dr Todd Hardy. From Royal Brisbane and Women's Hospital, Brisbane, Australia, Dr Pamela McCombe. From Cliniques Universitaires Saint-Luc, Brussels, Belgium, Dr Vincent Van Pesch.

From Rehabilitation and MS-Centre Overpelt and Hasselt University, Hasselt, Belgium, Dr Bart Van Wijmeersch. From Universidade Metropolitana de Santos, Santos, Brazil, Dr Yara Fragoso.

From CSSS Saint-JÈrÙme, Saint-Jerome, Canada, Dr Julie Prevost. From Jewish General Hospital, Montreal, Canada, Dr Fraser Moore. From CHUM MS Center and Universite de Montreal, Montreal, Canada, Dr Alexandre Prat, Dr Marc Girard, Dr Pierre Duquette, Dr C. Larochelle. From CISSS ChaudiËre-Appalache, Levis, Canada, Dr Pierre Grammond. From Neuro Rive-Sud, Quebec, Canada, Dr Francois Grand'Maison. From Nemocnice Jihlava, Jihlava, Czech Republic, Dr Radek Ampapa. From Kommunehospitalet, Arhus C, Denmark, Dr Thor Petersen. From Hospital Universitario Virgen de Valme, Seville, Spain, Dr Ricardo Fernandez BolaÒos. From Hospital Universitario Donostia, San Sebasti•n, Spain, Dr Javier Olascoaga. From Hospital Clinico San Carlos, Madrid, Spain, Dr Celia Oreja-Guevara. From Hospital de Galdakao-Usansolo, Galdakao, Spain, Dr Jose Luis Sanchez-Menoyo. From Hospital Germans Trias i Pujol, Badalona, Spain, Dr Cristina Ramo-Tello. From Hospital Universitario de la Ribera, Alzira, Spain, Dr Jose Andres Dominguez.From Cordoba, Spain, Dr Eduardo Aguera-Morales. From South East Trust, Belfast, United Kingdom, Dr Orla Gray. From VeszprÈm Megyei Csolnoky Ferenc KÛrh•z zrt., Veszprem, Hungary, Dr Imre Piroska. From Jahn Ferenc Teaching Hospital, Budapest, Hungary, Dr Csilla Rozsa, Dr Krisztian Kasa. From Semmelweis University Budapest, Budapest, Hungary, Dr Magdolna Simo. From BAZ County Hospital, Miskolc, Hungary, Dr Attila Sas. From Szent Imre Hospital, Budapest, Hungary, Dr Eniko Dobos. From University of Szeged, Szeged, Hungary, Dr Cecilia Rajda. From Azienda Sanitaria Unica Regionale Marche - AV3, Macerata, Italy, Dr Elisabetta Cartechini, Dr Matteo Diamanti. From University of Florence, Florence, Italy, Dr Maria Pia Amato. From IRCCS Mondino Foundation, Pavia, Italy, Dr Roberto Bergamaschi. From Ospedali Riuniti di Salerno, Salerno, Italy, Dr Gerardo Iuliano. From Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino, Italy, Dr Daniele Spitaleri. From ASL3 Genovese, Genova, Italy, Dr Claudio Solaro. From Garibaldi Hospital, Catania, Italy, Dr Davide Maimone. From Amiri Hospital, Sharq, Kuwait, Dr Raed Alroughani. From American University of Beirut Medical Center, Beirut, Lebanon, Dr Bassem Yamout. From Zuyderland Ziekenhuis, Sittard, Netherlands, Dr Raymond Hupperts. From Groene Hart Ziekenhuis, Gouda, Netherlands, Dr Freek Verheul. From Royal Hospital, Muscat, Oman, Dr Jabir Alkhaboori. From Hospital S.,o Jo.,o, Porto, Portugal, Dr Maria Edite Rio. From Hospital de Sao Joao, Porto, Portugal, Dr Maria Josa Sa. From Razi Hospital, Manouba, Tunisia, Dr Youssef Sidhom, Dr Riadh Gouider. From KTU Medical Faculty Farabi Hospital, Trabzon, Turkey, Dr Cavit Boz. From Hacettepe University, Ankara, Turkey, Dr Rana Karabudak. From Koc University, Istanbul, Turkey, Dr Ayse Altintas. From Bakirkoy Education and Research Hospital for Psychiatric and Neurological Diseases, Istanbul, Turkey, Dr Aysun Soysal. From Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey, Dr Recai Turkoglu. From University of Catania, Catania, Italy, Dr Clara Chisari, Dr Emanuele D'Amico, Dr Lo Fermo Salvatore. From University "G. d'Annunzio", Chieti, Italy, Dr Giovanna De Luca, Dr Valeria Di Tommaso, Dr Daniela Travaglini, Dr Erika Pietrolongo, Dr Maria di Ioia, Dr Deborah Farina, Dr Luca Mancinelli. From Azienda Ospedaliera Universitaria, Modena, Italy, Dr Francesca Vitetta, Dr Anna Maria Simone. From University of Parma, Parma, Italy, Dr Erica Curti, Dr Elena Tsantes. From Monash University, Melbourne, Australia, Dr Anneke van der Walt.

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