RESEARCH PAPER

Comparison of fingolimod, dimethyl fumarate and teriflunomide for multiple sclerosis

Tomas Kalincik,[1,2] Eva Kubala Havrdova,[3] Dana Horakova,[3] Guillermo Izquierdo,[4] Alexandre Prat,[5,6] Marc Girard,[5,6] Pierre Duquette,[5,6] Pierre Grammond,[7] Marco Onofrj,[8] Alessandra Lugaresi,[9,10] Serkan Ozakbas,[11] Ludwig Kappos,[12] Jens Kuhle,[12] Murat Terzi,[13] Jeannette Lechner-Scott,[14,15] Cavit Boz,[16] Francois Grand'Maison,[17] Julie Prevost,[18] Patrizia Sola,[19] Diana Ferraro,[19] Franco Granella,[20,21] Maria Trojano,[22] Roberto Bergamaschi,[23] Eugenio Pucci,[24] Recai Turkoglu,[25] Pamela A McCombe,[26] Vincent Van Pesch,[27] Bart Van Wijmeersch,[28] Claudio Solaro,[29] Cristina Ramo-Tello,[30] Mark Slee,[31] Raed Alroughani,[32] Bassem Yamout,[33] Vahid Shaygannejad,[34] Daniele Spitaleri,[35] José Luis Sánchez-Menoyo,[36] Radek Ampapa,[37] Suzanne Hodgkinson,[38] Rana Karabudak,[39] Ernest Butler,[40] Steve Vucic,[41] Vilija Jokubaitis,[42] Tim Spelman,[42] Helmut Butzkueven[42,43,44]

For numbered affiliations see end of article.

Correspondence to
A/Prof Tomas Kalincik, CORe, Department of Medicine, University of Melbourne, Melbourne, VIC 3050, Australia; tomas.kalincik@unimelb.edu.au

Received 15 October 2018
Revised 7 December 2018
Accepted 14 December 2018
Published Online First 13 January 2019

To cite: Kalincik T, Kubala Havrdova E, Horakova D, *et al*. *J Neurol Neurosurg Psychiatry* 2019;**90**:458–468.

ABSTRACT

Objective Oral immunotherapies have become a standard treatment in relapsing-remitting multiple sclerosis. Direct comparison of their effect on relapse and disability is needed.

Methods We identified all patients with relapsing-remitting multiple sclerosis treated with teriflunomide, dimethyl fumarate or fingolimod, with minimum 3-month treatment persistence and disability follow-up in the global MSBase cohort study. Patients were matched using propensity scores. Three pairwise analyses compared annualised relapse rates and hazards of disability accumulation, disability improvement and treatment discontinuation (analysed with negative binomial models and weighted conditional survival models, with pairwise censoring).

Results The eligible cohorts consisted of 614 (teriflunomide), 782 (dimethyl fumarate) or 2332 (fingolimod) patients, followed over the median of 2.5 years. Annualised relapse rates were lower on fingolimod compared with teriflunomide (0.18 vs 0.24; p=0.05) and dimethyl fumarate (0.20 vs 0.26; p=0.01) and similar on dimethyl fumarate and teriflunomide (0.19 vs 0.22; p=0.55). No differences in disability accumulation (p≥0.59) or improvement (p≥0.14) were found between the therapies. In patients with ≥3-month treatment persistence, subsequent discontinuations were less likely on fingolimod than teriflunomide and dimethyl fumarate (p<0.001). Discontinuation rates on teriflunomide and dimethyl fumarate were similar (p=0.68).

Conclusion The effect of fingolimod on relapse frequency was superior to teriflunomide and dimethyl fumarate. The effect of the three oral therapies on disability outcomes was similar during the initial 2.5 years on treatment. Persistence on fingolimod was superior to the two comparator drugs.

INTRODUCTION

Oral immunotherapies have changed the standard of managing relapsing-remitting multiple sclerosis (MS) and prescription practices globally.[1] Their availability as a first-line treatment has led to their use as a default initial therapy in several countries. While oral immunotherapies are highly effective modulators of MS activity,[2–4] they have not been directly compared in randomised settings.[5] The recently published post hoc comparisons combining data from the pivotal placebo-controlled trials[6–9] and observational cohorts[10 11] suggested that fingolimod and dimethyl fumarate are comparable in suppressing episodic inflammatory activity. However, results of these studies varied, most probably due to variability in patients' underlying disease activity. For instance, while the proportions of patients with no evidence of disease activity were similar in those treated with fingolimod or dimethyl fumarate as their first treatment choice, fingolimod was superior to dimethyl fumarate among patients who switched to oral agents from injectable therapies.[11]

Direct comparisons of relapse and disability data are needed to inform evidence-based choices of first oral therapy, switching between oral agents due to the lack of tolerance, or treatment escalation with oral agents in the setting of prior treatment failure. Where postmarketing trials are failing to provide this much needed information,[5] several observational cohorts have demonstrated capacity to generate valuable evidence for comparative effectiveness of various therapies, highly concordant with pivotal trials.[12–16] In this study, we compared relapse activity, disability accumulation, disability improvement and persistence on therapy among patients treated with three of the four currently available oral MS immunotherapies: teriflunomide, dimethyl fumarate and fingolimod.

PATIENTS AND METHODS

Database and study population

MSBase, an international observational MS cohort study,[17] was approved by the Melbourne Health Human Research Ethics Committee. Patients have provided written informed consent, as required. The list of study contributors is given in online supplementary table 1.

The inclusion criteria for this study consisted of: definite relapse-onset MS,[18 19] continuous exposure to one of the study therapies for ≥3 months, no prior treatment with alemtuzumab or haematopoietic stem cell transplantation, a minimum data set (including sex, age, date of first MS symptom, dates of clinical relapses, disease course and disability score at treatment start (recorded within 6 months before and 1 month after the start of therapy)) and minimum recorded follow-up (5 months before treatment start and two disability scores recorded after commencing study therapy, ≥6 months apart with ≥1 score recorded while on the study therapy).

Procedures

Patients were treated with one of the oral therapies: teriflunomide (14 mg daily), dimethyl fumarate (240 mg twice daily) or fingolimod (0.5 mg daily). Study baseline was defined as the first commencement of an index therapy and patients were censored at treatment discontinuation or the last recorded disability score.

The data were recorded as part of standard clinical practice, mostly at tertiary MS centres, with data entry at the time of clinical visits, as governed by the MSBase Observational Plan. Data entry portals were iMed or the MSBase online data entry system. MRI information was reported by treating neurologists based on the local MRI protocols and reporting standards. A cerebral MRI acquired within 12 months prior to and 1 week after the commencement of study therapy was considered as baseline MRI. Missing MRI data were handled through multiple imputation.[20]

An automated quality assurance procedure was applied (online supplementary table 2), quantifying erroneous data entry, data density and generalisability as described elsewhere.[21]

Study endpoints

The primary study outcomes were annualised relapse rate (ARR), cumulative hazards of relapses, disability accumulation events and disability improvement events while on study therapy, and cumulative hazard of treatment discontinuation.

A relapse was defined as new symptoms or exacerbation of existing symptoms persisting for ≥24 hours, in the absence of concurrent illness/fever, and occurring ≥30 days after a previous relapse. Confirmation of relapses by disability score was not required. Individual ARRs between baseline and censoring were calculated.

Disability was quantified using the Expanded Disability Status Scale (EDSS), which was typically derived from clinical exam. Neurostatus certification was required at the participating centres. Scores obtained <30 days after a relapse were excluded. Disability accumulation was defined as an on-treatment increase in EDSS by 1 step (1.5 steps if baseline EDSS was 0 and 0.5 steps if baseline EDSS was >5.5) confirmed by subsequent EDSS scores over ≥6 months (irrespective of treatment status at confirmation). Disability improvement was defined as a decrease in EDSS by 1 step (1.5 steps if baseline EDSS was 1.5 and 0.5 steps if baseline EDSS was >6) confirmed over ≥6 months.[22] Treatment discontinuation events and their main reasons were recorded; these reasons did not use unified definitions the reasons for treatment discontinuation were reported as per treating neurologists.

Matching and statistical analysis

Matching and statistical analyses were conducted using R (V.3.4.1) in three separate matched analyses of dimethyl fumarate versus teriflunomide, fingolimod versus teriflunomide or fingolimod versus dimethyl fumarate. Individual patients were matched on their propensity of receiving either of the compared therapies.[23 24] Individual propensity scores were calculated using a multivariable logistic regression model of treatment allocation that used sex, age, time from first symptom, EDSS at baseline, number of relapses in the prior 1 year, disease activity recorded in the prior 1 year (relapses/progression of disability/relapses and progression of disability/no activity), presence/absence of contrast-enhancing lesion on cerebral MRI at baseline, number of hyperintense T2 lesions on cerebral MRI at baseline (categorised as 1–2, 3–8 or ≥9 lesions), number of prior MS therapies, the most effective previously used therapy (as per ranking based on a network meta-analysis of randomised trials)[25] and country.

Where information about baseline cerebral MRI at treatment start was not available, multiple imputation with an expectation maximisation with bootstrapping algorithm was used to impute the missing values (generating 17 imputed data sets).[20 26 27] The imputation was based on patient ID, sex, age at baseline, baseline date, MS duration at baseline, treatment group, baseline EDSS, prebaseline MS activity, the last prebaseline therapy, time from the previous therapy and the duration of the prebaseline follow-up. A sensitivity analysis was carried out after loosening the missingness-not-at-random assumption. The analysis used normalised weights to approximate the inferences in the data with MRI missing not at random.[28] The associations between the clinical and demographic variables and missingness of the MRI data were evaluated with multivariable logistic regression. The δ was chosen based on a published algorithm.[29]

Patients were matched without replacement in a variable 2:1 (dimethyl fumarate:teriflunomide), 4:1 (fingolimod:teriflunomide) or 5:1 (fingolimod:dimethyl fumarate) ratio using nearest neighbour matching within a calliper of 0.15 SDs of the propensity score.[30] All subsequent analyses were paired with weighting to adjust for the variable matching ratio. Pairwise censoring was used to determine common on-treatment follow-up time to mitigate attrition bias and the effect of differential treatment persistence.[12]

Tests of statistical inference were carried out at $\alpha=0.05$. ARRs were compared with a marginal weighted negative binomial model with a cluster term for matched patient sets. Cumulative hazards of relapses, and disability accumulation and improvement events were analysed with weighted conditional proportional hazards models (Andersen-Gill). Models of disability outcomes were adjusted for visit frequency. Cumulative hazard of discontinuing therapy was evaluated with weighted conditional proportional hazards models (Cox) in cohorts that were not pairwise censored. Where the proportionality of hazards assumption was violated (as per Schoenfeld's global test), an interaction term for treatment and time was included.

Robustness of the statistically significant differences to unidentified confounders was quantified with Rosenbaum sensitivity test for Hodges-Lehmann Γ. Γ estimates the minimum magnitude of an unmeasured confounder that would change the conclusion of an analysis.[31] Where no statistically significant differences were observed, analytical power was quantified as the minimum detectable effect at $1-\beta=0.8$ using 200 simulations.

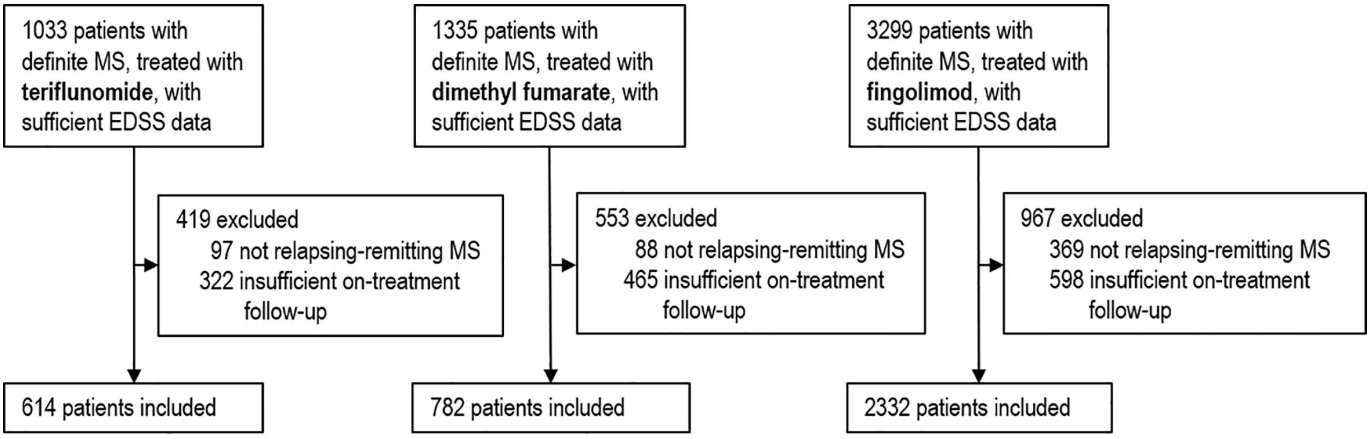

Figure 1 Patient disposition. EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

Sensitivity analyses

Eight sensitivity analyses were completed to evaluate the robustness of the results to potential confounders: (1) excluding MRI from the estimation of propensity score (to eliminate a potential effect of multiple imputation); (2) matching on relapses during the prior 2 years (to evaluate the influence of the assessment of prebaseline disease activity); (3) matching in a fixed 1:1 ratio (to evaluate the effect of matching ratio); (4) only including patients who were exposed to other immunotherapies and experienced relapses during the 1 year prebaseline; (5) only including patients from countries where fingolimod is second-line therapy; (6) only including patients from countries where fingolimod is first-line therapy; (7) complete case analysis of patients with baseline cerebral MRI available; and (8) analysis of all information recorded after the start of study therapy irrespective of treatment status and duration—the 'intention to treat' paradigm (to eliminate potential effect of early treatment discontinuation, informed censoring and enable evaluation of delayed changes in disability).

RESULTS

Study population

A total of 614 (teriflunomide), 782 (dimethyl fumarate) and 2332 (fingolimod) patients who fulfilled the inclusion criteria and were treated between 12 December 2006 and 20 September 2017 (figure 1;online supplementary tables 3 and 4) were included in the study. Of the patients who commenced the study medication, 109 (5.2%) on teriflunomide, 275 (10.1%) on dimethyl fumarate and 221 (3.4%) on fingolimod discontinued therapy during the initial 3 months from treatment start and were excluded from the analysis (reported under the insufficient on-treatment follow-up category). The reported reasons for treatment discontinuation among these excluded early discontinuations are shown in online supplementary table 5.

As expected, the three included treatment groups differed in their baseline characteristics before matching (online supplementary table 6). Logistic regression models were used to calculate the propensity scores—the probability of exposure to either of the compared treatment pairs (online supplementary table 7). These models showed that before matching, patients treated with teriflunomide tended to be older, with longer time from disease onset, less relapses and MRI activity during the previous year and with lower EDSS relative to the other two study therapies. In addition, patients treated with fingolimod tended to have higher EDSS and more relapses during the prior year in comparison to those treated with dimethyl fumarate. The characteristics of the patients excluded by the matching procedure are shown in online supplementary table 8.

The numbers of patients retained in the matched cohorts for all three pairwise primary analyses are shown in table 1. The matching procedure significantly decreased the between-group differences in propensity scores from 0.20–0.40 to 0.004–0.030, corresponding to a 90.9%–98.2% improvement in balance between the matched groups (online supplementary table 9). The close match on individual characteristics between the groups is demonstrated in table 1 (standardised differences ≤20% for most variables and 26% for prior relapse activity for fingolimod vs teriflunomide). Among those with cerebral MRI information available, the proportions of the patients with contrast-enhancing lesions and with high and low lesion counts were balanced. As a result of pairwise censoring, on-treatment follow-up was identical in the matched groups. The numbers of matched patients followed for ≥2.5 years were 147 vs 111 for dimethyl fumarate versus teriflunomide, 501 vs 98 for fingolimod versus teriflunomide and 1056 vs 155 for fingolimod versus dimethyl fumarate, respectively.

Effectiveness

Dimethyl fumarate versus teriflunomide

The mean ARR did not differ between patients treated with dimethyl fumarate (0.19, 95% CI 0.15 to 0.23) and teriflunomide (0.22, 95% CI 0.18 to 0.26, p=0.55, figure 2A). This observation was confirmed by similar cumulative hazards of relapses in the two treatment groups (HR 0.86, 95% CI 0.64 to 1.14, p=0.29; figure 2C). No differences were observed for confirmed disability accumulation (HR 1.02, 95% CI 0.60 to 1.76, p=0.92) and improvement (HR 1.26, 95% CI 0.58 to 2.74, p=0.55; figure 2B,D,E). These results were fully replicated with imputation of missing MRI data under missing-not-at-random assumption. The analysis was sufficiently powered to identify differences of 0.18 relapses per year (ARR), 58% difference in cumulative hazards of relapses and 3% and 21% differences in cumulative hazards of disability accumulation and improvement, respectively (online supplementary table 12).

Fingolimod versus teriflunomide

The mean ARR was lower in fingolimod-treated patients (0.18, 95% CI 0.16 to 0.21) than in those treated with teriflunomide (0.24, 95% CI 0.21 to 0.27, p=0.05, figure 3A). The difference

Table 1 Demographic, clinical and paraclinical characteristics of the matched patients

	Dimethyl fumarate (n=470)	Teriflunomide (n=355)	Cohen's d	Fingolimod (n=910)	Teriflunomide (n=403)	Cohen's d	Fingolimod (n=1825)	Dimethyl fumarate (n=672)	Cohen's d
Female patients (%)	352 (75)	266 (75)		673 (74)	294 (73)		1332 (73)	504 (75)	
Age (years), mean±SD	41±11	42±10	0.06	40±10	42±10	0.11	39±10	40±11	0.03
Disease duration (years), median (quartiles)	9.2 (4.6–15.2)	9.7 (5–16.1)	0.07	8.9 (4.9–14.6)	9.4 (4.7–15.8)	0.08	8.7 (4.7–14.4)	8.4 (3.8–14.3)	0.04
Disability (EDSS), median (quartiles)	2 (1–3.5)	2 (1–3)	0.05	2 (1.5–3.5)	2 (1–3)	0.16	2.5 (1.5–3.5)	2 (1.5–3.5)	0.22
Relapses 12 months prebaseline, mean±SD	0.6±0.8	0.4±0.7	0.16	0.7±0.8	0.5±0.7	0.26	0.9±0.9	0.8±0.9	0.11
Prior disease activity, patients									
Relapses (%)	126 (27)	72 (20)		313 (34)	90 (22)		757 (41)	233 (35)	
Progression (%)	0 (0)	0 (0)		0 (0)	0 (0)		6 (0)	3 (0)	
Relapses and progression (%)	75 (16)	53 (15)		153 (17)	59 (15)		355 (19)	126 (19)	
None (%)	269 (57)	230 (65)		444 (49)	254 (63)		707 (39)	310 (46)	
MRI information available, patients (%)	87 (18)	82 (23)		255 (28)	108 (27)		489 (27)	136 (20)	
MRI, number of T2 lesions, patients									
T2 lesion count available (%)	38 (8)	52 (15)		159 (17)	62 (15)		316 (17)	39 (6)	
1–2 (%)	1 (3)	1 (2)		1 (1)	1 (2)		3 (1)	0 (0)	
3–8 (%)	6 (16)	9 (17)		17 (11)	9 (15)		27 (9)	2 (5)	
≥9 (%)	31 (82)	42 (81)		141 (89)	52 (84)		286 (91)	37 (95)	
MRI, contrast-enhancing lesions, patients									
MRI with contrast available (%)	61 (13)	49 (14)		152 (17)	71 (18)		323 (18)	113 (17)	
Contrast-enhancing lesions present (%)	13 (21)	9 (18)		20 (13)	9 (13)		103 (32)	37 (33)	
CSF, oligoclonal bands, patients									
CSF with oligoclonal bands available (%)	253 (54)	175 (49)		458 (50)	193 (48)		990 (54)	394 (59)	
Oligoclonal bands present (%)	221 (87)	157 (90)		400 (87)	173 (90)		887 (90)	341 (87)	
Pairwise-censored follow-up on study therapy (years), median (quartiles)	1.3 (1.0–1.9)	1.3 (1.0–1.9)	0.00	1.4 (1.0–2.0)	1.4 (1.0–2.0)	0.00	1.3 (1.0–2.0)	1.3 (1.0–2.0)	0.00
Visit interval (months), median (quartiles)	5 (3–8)	5 (3–8)	0.02	4 (3–7)	4 (3–7)	0.04	4 (3–6)	4 (3–7)	0.00
Previous therapies (n), median (quartiles)	1 (1–2)	1 (1–2)	0.05	1 (1–2)	1 (1–2)	0.08	2 (1–2)	1 (1–2)	0.10
Most active previous therapy, patients									
Interferon β/ glatiramer acetate (%)	350 (74)	275 (77)		689 (76)	320 (79)		1279 (70)	512 (76)	
Teriflunomide (%)	0 (0)	0 (0)		0 (0)	0 (0)		29 (2)	14 (2)	
Fingolimod (%)	34 (7)	23 (6)		0 (0)	0 (0)		0 (0)	0 (0)	
Natalizumab (%)	37 (8)	16 (5)		95 (10)	21 (5)		335 (18)	74 (11)	
Mitoxantrone (%)	4 (1)	4 (1)		19 (2)	4 (1)		49 (3)	9 (1)	
None (%)	45 (10)	37 (10)		84 (9)	45 (11)		133 (7)	63 (9)	

Most effective previous therapy is shown in the ascending order as per a previous network meta-analysis of multiple sclerosis therapies.[25]
Low-efficacy therapy: interferon β, glatiramer acetate, teriflunomide.
CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale.

was resistant to unmeasured confounders with relative magnitude of 20% of the reported treatment effect. Consistent with the above, cumulative hazard of relapses was lower in the fingolimod cohort when compared with the teriflunomide cohort (HR 0.77, 95% CI 0.63 to 0.95, p=0.03; figure 3C). No differences in the rate of confirmed disability accumulation (HR 1.01, 95% CI 0.64 to 1.59, p=0.97) and improvement (HR 1.57, 95% CI 0.87 to 2.86, p=0.14) events were found (figure 3B,D,E). The results were replicated with imputation of MRI values missing not at random. The analysis was sufficiently powered to detect 1% and 36% differences in the cumulative hazards of disability accumulation and improvement, respectively.

Fingolimod versus dimethyl fumarate

The mean ARR was lower among the patients treated with fingolimod (0.20, 95% CI 0.19 to 0.22) matched to the patients treated with dimethyl fumarate (0.26, 95% CI 0.24 to 0.28, p=0.01; figure 4A), consistent with the comparison of the cumulative hazard of relapses (HR 0.78, 95% CI 0.68 to 0.90, p=0.0005; figure 4C). These results were resistant to unmeasured confounders with relative magnitude of 20% of the reported treatment effect. Cumulative hazards of confirmed disability accumulation (HR 1.10, 95% CI 0.78 to 1.56, p=0.59) and improvement (HR 0.83, 95% CI 0.62 to 1.11, p=0.20) were similar in the fingolimod and dimethyl fumarate cohorts (figure 4B,D,E). The analysis of MRI values missing not and random confirmed the above results in full. This analysis was sufficiently powered to demonstrate 9% and 14% differences in the cumulative hazards of disability accumulation and improvement, respectively.

Persistence

The likelihood of discontinuing therapy was similar in the dimethyl fumarate and teriflunomide cohorts (24% during the initial 2 years; HR 0.95, 95% CI 0.74 to 1.20, p=0.68; figure 2F). As the reason for discontinuation, adverse event was reported at a similar rate in the two treatments (in 8% and 7% of the matched patients, respectively), whereas lack of efficacy (as per neurologist) was relatively more commonly reported in teriflunomide (15%) than dimethyl fumarate (8%, online supplementary table 10).

Patients were less likely to discontinue fingolimod than teriflunomide (HR 0.56, 95% CI 0.44 to 0.71, p=10^{-6}; 10% vs 26% at 2 years, respectively; figure 3F). Lack of efficacy as a

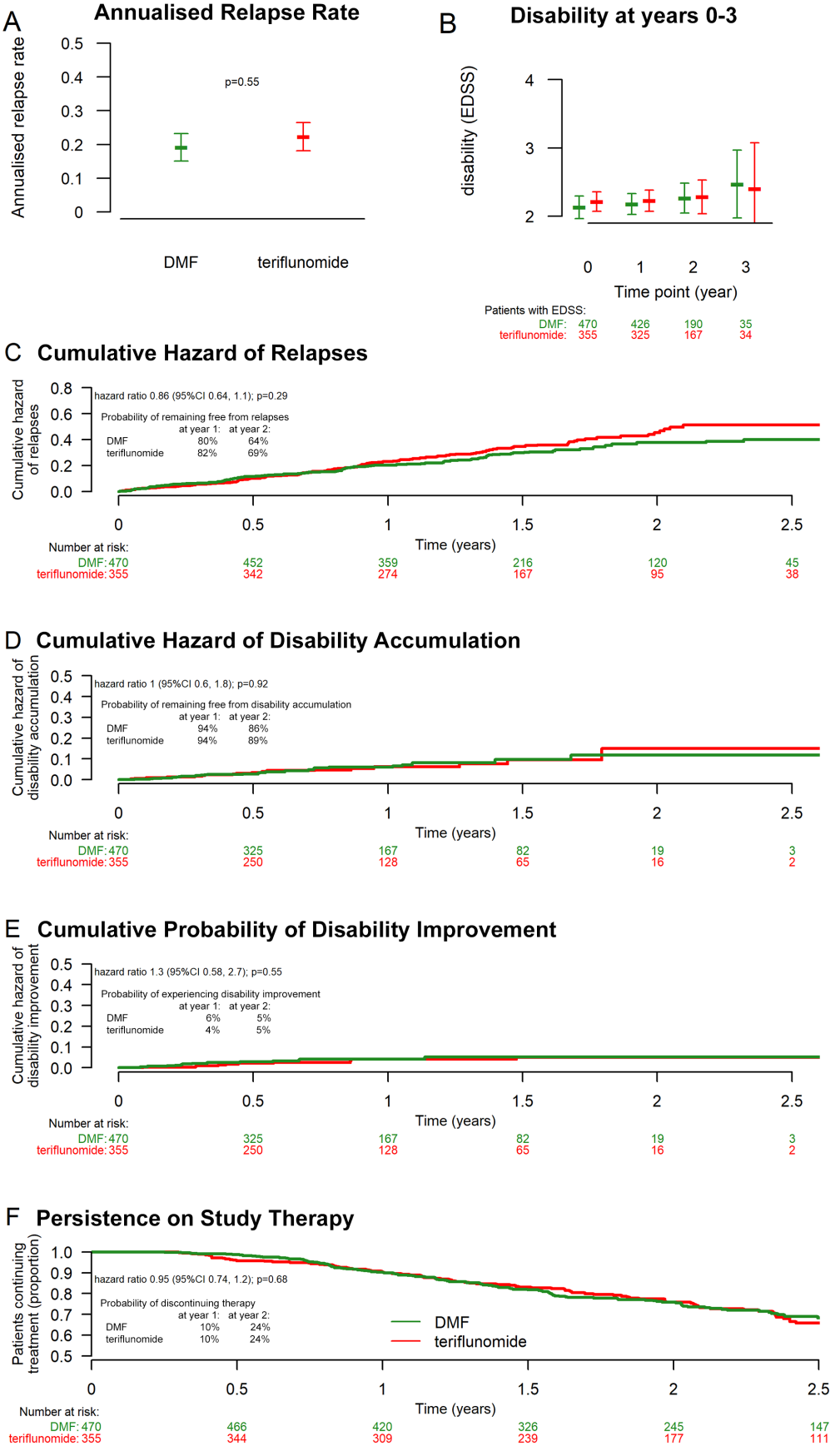

Figure 2 Comparison of the treatment outcomes for dimethyl fumarate versus teriflunomide. Bar graphs show mean±95% CIs. Mean EDSS scores in panel B are calculated from scores available at a given year post-treatment. DMF, dimethyl fumarate; EDSS, Expanded Disability Status Scale.

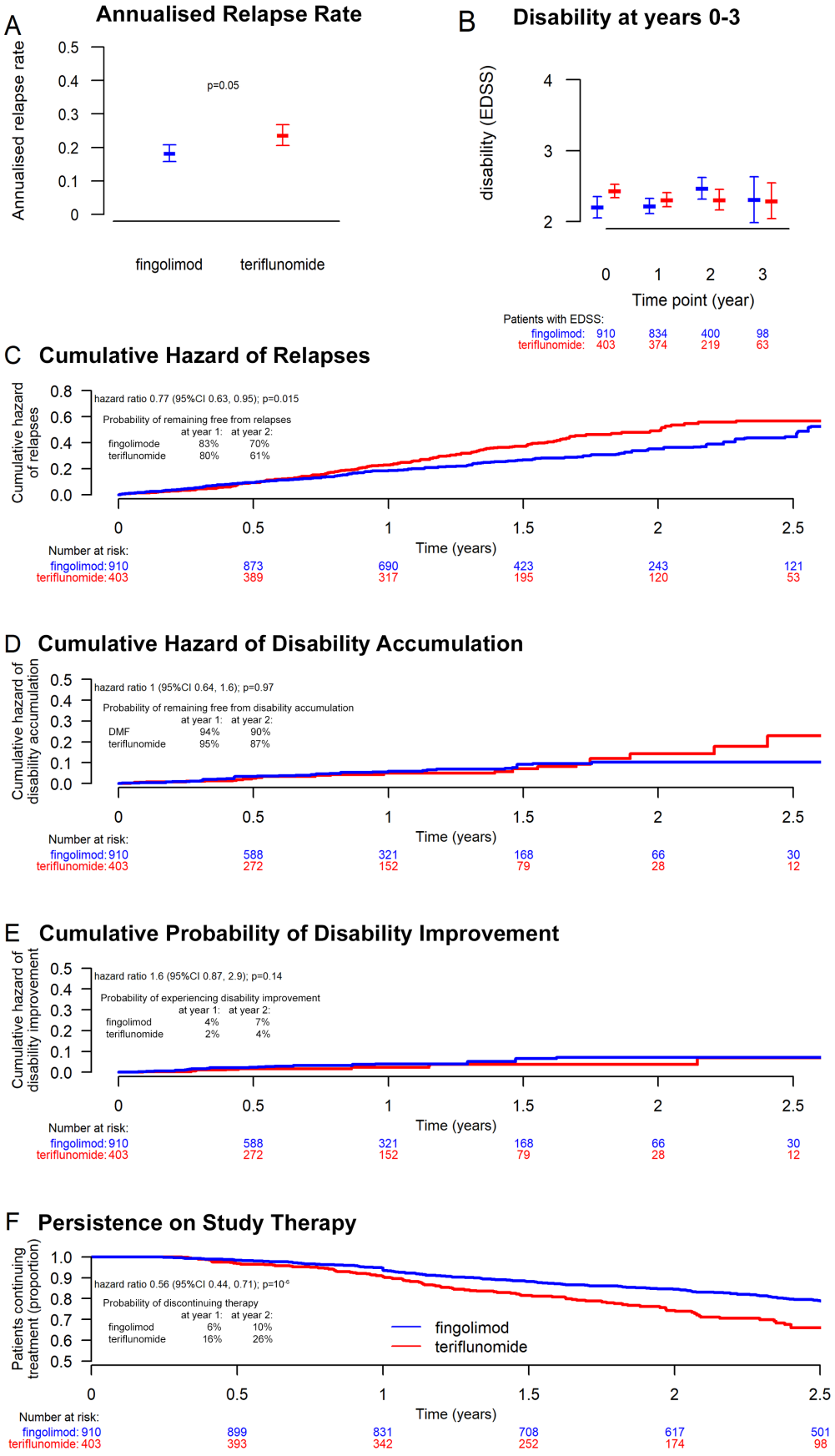

Figure 3 Comparison of the treatment outcomes for fingolimod versus teriflunomide. Bar graphs show mean±95% CIs. Mean EDSS scores in panel B are calculated from scores available at a given year post-treatment. EDSS, Expanded Disability Status Scale.

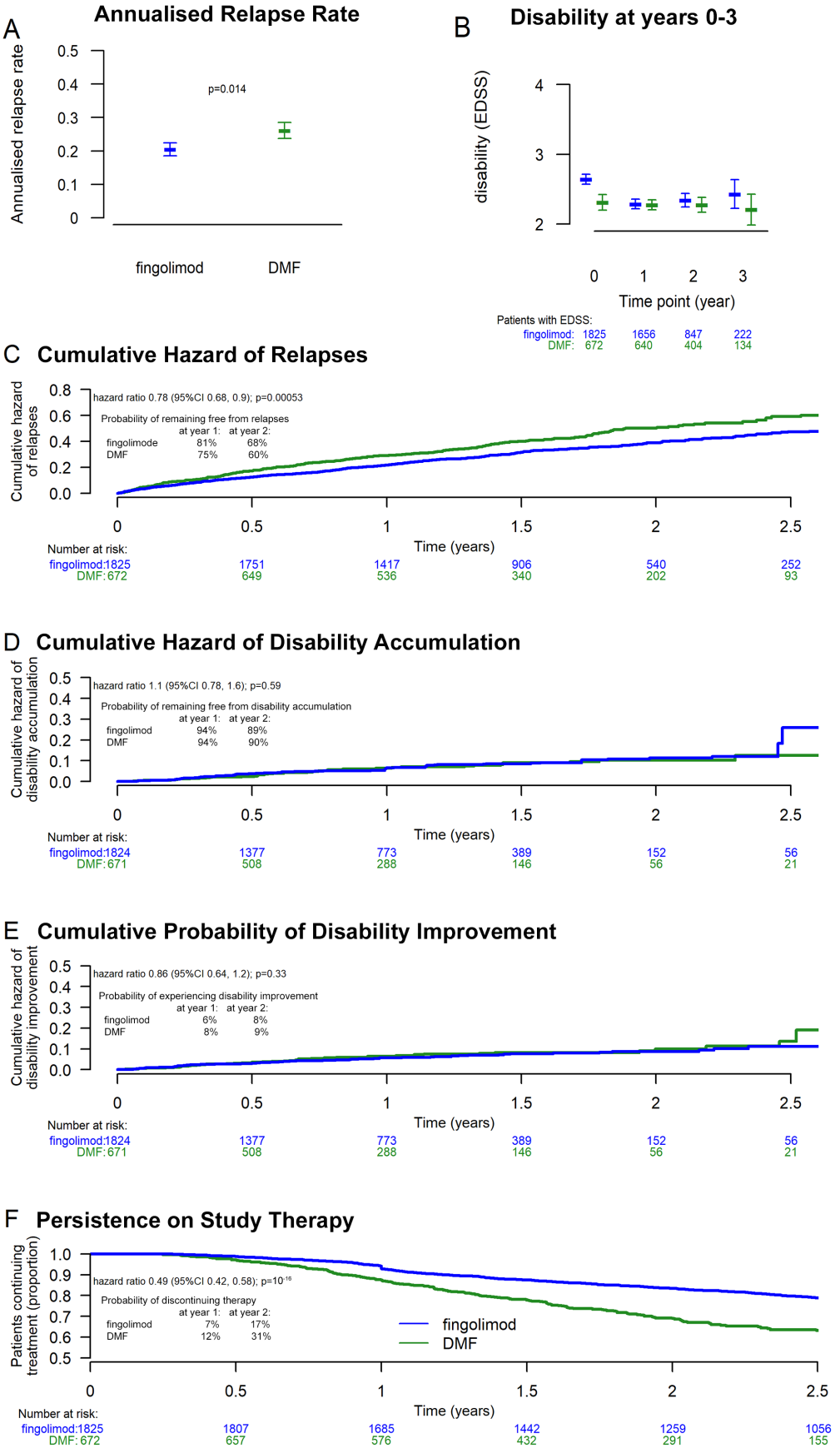

Figure 4 Comparison of the treatment outcomes for fingolimod versus dimethyl fumarate. Bar graphs show mean±95% CIs. Mean EDSS scores in panel B are calculated from scores available at a given year post-treatment. DMF, dimethyl fumarate; EDSS, Expanded Disability Status Scale.

reason for discontinuation was reported similarly in both treatments (5% fingolimod vs 5% teriflunomide), with adverse events being less commonly reported in fingolimod (7% vs 13%, respectively; online supplementary table 10).

Patients were less likely to discontinue fingolimod than dimethyl fumarate (HR 0.49, 95% CI 0.42 to 0.58, $p=10^{-16}$; 17% vs 31% at 2 years, respectively; figure 4F). The proportions of patients with lack of efficacy being the reported reason for discontinuation were similar in fingolimod (9%) and dimethyl fumarate (8%). Discontinuation due to reported adverse events was more common in dimethyl fumarate (10%) than fingolimod (4%; online supplementary table 10).

Sensitivity analyses

For the comparison of dimethyl fumarate and teriflunomide, sensitivity analyses largely confirmed the results of the primary analysis (online supplementary table 11). Interestingly, the frequency of relapses trended to be marginally lower on dimethyl fumarate than teriflunomide in the analysis of complete cases with baseline MRI and the intention-to-treat analysis. In addition, the intention-to-treat analysis suggested a trend towards a more frequent recovery from disability on dimethyl fumarate when compared with teriflunomide.

The results of the primary analysis comparing fingolimod and teriflunomide were replicated by most of the sensitivity analyses. The exceptions were the comparisons of ARRs in patients matched on relapse incidence during the 2 years preceding the study therapy and two relatively less powered subcohorts—complete case analysis of patients with baseline cerebral MRI and in countries where fingolimod is first-line therapy.

Similarly, the results of the primary analysis of fingolimod versus dimethyl fumarate were replicated by most of the sensitivity analyses, with a small number of exceptions, in which the trends were consistent with the primary analysis.

DISCUSSION

In this propensity score-matched analysis of the global observational MSBase cohort, we have studied patients with relapsing-remitting MS exposed to one of three oral immunotherapies for MS, most of whom had not experienced relapses within a year prior to commencing study therapy, with ≥9 cerebral lesions and previously exposed to other immunotherapies, in particular interferon β and glatiramer acetate. The effect of fingolimod on relapse activity was superior to dimethyl fumarate and teriflunomide. During the initial 2.5 years, the three therapies had comparable effects on disability accumulation and disability improvement. Dimethyl fumarate and teriflunomide were more likely to be discontinued than fingolimod.

A limited number of studies compared treatment effectiveness between pairs of oral preparations for relapsing-remitting MS. A propensity score-matched, pairwise-censored analysis of observational data from 550 patients from seven centres in Italy suggested that the proportions of patients with no evidence of disease activity or relapses over 18 months were similar in those treated with fingolimod or dimethyl fumarate.[11] However, among patients who switched to their study therapy from another immunotherapy (similar to the majority of patients in our study), those treated with fingolimod were more likely to remain free from evidence of disease activity, relapses and confirmed worsening of disability than those treated with dimethyl fumarate. A single-centre propensity score-weighted study among 659 patients did not find a statistically significant difference in the rate of relapses between patients treated with fingolimod or dimethyl fumarate over 2 years. In that study, 0.20–0.21 on-treatment relapses per patient and year were reported, but the mean time to the first relapse was markedly longer in fingolimod (7.56 months) than dimethyl fumarate (3.83 months).[10] A network meta-analysis of two pooled post hoc analyses of placebo-controlled trials reported non-significant trends favouring fingolimod over dimethyl fumarate in relapse frequency and 3-month confirmed disability progression in highly active MS.[7]

Another network meta-analysis reported no differences in relapse and disability outcomes between fingolimod and dimethyl fumarate, but showed a relatively lower effect of teriflunomide on relapse frequency.[8] A matching-adjusted indirect comparison of patient data from the randomised trials of dimethyl fumarate with aggregate data from the randomised trials of fingolimod did not find differences in relapse and 3-month confirmed disability outcomes at 2 years.[6] Another indirect analysis of trial data suggested that relapse rate ratio favours dimethyl fumarate over teriflunomide.[32] In contrast, a comparison of randomised trials showed that the numbers of treated patients needed to prevent a relapse and confirmed disability worsening were similar for dimethyl fumarate and teriflunomide but marginally lower for fingolimod.[9] An analysis of health insurance claims suggested that the relapse-related claims were similar for dimethyl fumarate and fingolimod and less frequent than the claims for teriflunomide.[33] However, health claims represent only an approximation for relapse incidence, and disability information is typically unavailable. Finally, a single-centre propensity score-weighted and matched analysis found a lower treatment discontinuation rate among patients treated with fingolimod when compared with dimethyl fumarate.[34] It is apparent that the results of studies comparing oral therapies show substantial variability, which can be attributed to the variability in the source data and methodology.[12] These differences are also probably co-determined by the amount of underlying inflammatory activity, with more pronounced differences between agents observed in patients with more active disease.[12]

Our present study directly compared the effects of the three oral immunotherapies in relapsing-remitting MS, including relapse frequency, 6-month confirmed disability worsening and improvement and the rate and reasons for treatment discontinuation. The main strengths of this study are the direct comparison of the three oral therapies from a single international registry with prospectively defined observational plan and an objective quality control procedure, and high density of disability assessments (every 4–5 months). The observational data from a relatively large number of patients are representative of day-to-day clinical practice. We have used MRI information where available at the start of study therapy, in combination with multiple imputation—under both missing at random and not at random assumptions—to mitigate an effect of any systematic differences in subclinical disease activity between the two treated cohorts. The results of multiple sensitivity analyses were consistent with the primary analysis. It is worth noting that while the primary analysis did not find a statistically significant difference in relapse frequency between dimethyl fumarate and teriflunomide, a trend favouring dimethyl fumarate was suggested by two sensitivity analyses—of cases with complete MRI data and the intention-to-treat analysis. This may imply that the effect of dimethyl fumarate on preventing relapses may be marginally superior to teriflunomide when informed censoring and subclinical inflammatory activity detectable by cerebral MRI are fully accounted for.[35]

Our conclusions are limited to an on-treatment follow-up of 2.5 years, which is only marginally longer than a follow-up in

most pivotal randomised clinical trials in relapsing-remitting MS. As discussed above, information about recent prebaseline brain MRI activity was only available for a limited cohort. We have therefore used a multiple imputation procedure to impute the missing values, including a sensitivity analysis under missing-not-at-random conditions. In order to mitigate confounding of imminent relapse activity by subclinical inflammation,[36] we have conducted a sensitivity analysis among patients with MRI data available with matching on MRI activity.

We chose propensity score matching as the strategy to control indication bias; this method allows quantification of improvement in the propensity score match and is also suitable for pairwise censoring in order to mitigate attrition bias, an important confounder in observational studies.[11 20] The importance of the context of treatment administration is exemplified by the diminished difference in relapse rates between fingolimod and the other two oral preparations when analysed in countries where fingolimod is only available as a second-line therapy. Propensity score matching decreased the overall imbalance between the compared cohorts by 90.9%–98.2%. In order to adjust the analyses for the mild residual imbalances in prebaseline relapse rates (such as imbalance due to the Will Rogers phenomenon,[37] which would be attributed to the use of different diagnostic criteria in patients diagnosed before and after 2010) and prior use of natalizumab, we conducted sensitivity analyses in a subgroup with prior on-treatment relapses or matched on 2-year relapse rate, which largely confirmed the results of the primary analyses. The effect of treatment epoch may also contribute to bias due to informed censoring; where in patients treated earlier, the tolerance for on-treatment disease activity would have been greater, while the concept of 'no evidence of disease activity' as a treatment target has only been introduced recently.[38] Thus, in more recently introduced therapies (dimethyl fumarate and teriflunomide), on-treatment disease activity could be under-reported as a result of informative censoring. Whilst in the primary analysis we were unable to mitigate this bias, if present, it would deflate rather than inflate the observed differences between fingolimod and the other two oral agents. In order to mitigate detection bias (due to differential on-treatment follow-up or differing expectations of disease activity)[22] we have adjusted the relevant models for visit frequency and have conducted a sensitivity analysis using an intention-to-treat approach (analysing the post-treatment follow-up irrespective of treatment discontinuation status), which has largely confirmed the results of the primary analysis. Propensity score-based comparative analyses mitigate the effect of measured confounders but are vulnerable to potential unmeasured confounders. As estimated by Hodges-Lehmann Γ, the present analyses were robust to unmeasured confounders of a magnitude of 20% of the treatment effects. Finally, regarding robustness of the negative results reported, we performed post hoc power analyses, which showed that our primary analysis was sufficiently powered to uncover clinically relevant treatment differences.

In this study, we have compared effectiveness of and persistence on oral immunotherapies for relapsing-remitting MS. Fingolimod is associated with a lower incidence of relapses and discontinuation rate than dimethyl fumarate and teriflunomide. The magnitude of this difference was relatively small (one relapse every 11–17 patient-years). The choice of MS therapy is determined by a multitude of factors, including treatment safety, family planning or convenience of administration. Very rare but severe adverse events, such as progressive multifocal encephalopathy, may be an important factor in the treatment decision process.[39] This is particularly relevant to fingolimod, which, among the compared oral disease-modifying therapies, is associated with the greatest risk of this potentially life-threatening complication.[40] Choosing a therapy in individual patients remains a complex task that requires thorough and individualised evaluation of disease prognosis and the corresponding risks and benefits of the increasing number of available therapies.

Author affiliations
[1]CORe, Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia
[2]Department of Neurology, Royal Melbourne Hospital, Melbourne, Victoria, Australia
[3]Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic
[4]Hospital Universitario Virgen Macarena, Sevilla, Spain
[5]Montreal, Quebec, Hopital Notre-Dame, Canada
[6]CHUM and Universite de Montreal, Montreal, Quebec, Canada
[7]CISSS de Chaudière-Appalaches, Levis, Quebec, Canada
[8]Department of Neuroscience, Imaging, and Clinical Sciences, University G d'Annunzio, Chieti, Italy
[9]Bologna, IRCCS Istituto delle Scienze Neurologiche di Bologna, Italy
[10]Department of Biomedical and Neuromotor Science, University of Bologna, Bologna, Italy
[11]Dokuz Eylul University, Izmir, Turkey
[12]Neurologic Clinic and Policlinic, Departments of Medicine and Clinical Research, University Hospital and University of Basel, Basel, Switzerland
[13]Medical Faculty, 19 Mayis University, Samsun, Turkey
[14]School of Medicine and Public Health, University Newcastle, Newcastle, New South Wales, Australia
[15]Department of Neurology, John Hunter Hospital, Hunter New England Health, Newcastle, New South Wales, Australia
[16]KTU Medical Faculty Farabi Hospital, Trabzon, Turkey
[17]Neuro Rive-Sud, Quebec City, Quebec, Canada
[18]CSSS Saint-Jérôme, Saint-Jerome, Quebec, Canada
[19]Department of Neuroscience, Azienda Ospedaliera Universitaria, Modena, Italy
[20]Department of Medicine and Surgery, University of Parma, Parma, Italy
[21]Department of Emergency and General Medicine, Parma University Hospital, Parma, Italy
[22]Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari, Bari, Italy
[23]IRCCS Mondino Foundation, Pavia, Italy
[24]UOC Neurologia, Azienda Sanitaria Unica Regionale Marche–AV3, Macerata, Italy
[25]Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey
[26]Royal Brisbane and Women's Hospital, University of Queensland, Brisbane, Queensland, Australia
[27]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
[28]Rehabilitation and MS-Centre Overpelt and Hasselt University, Hasselt, Belgium
[29]Department of Neurology, ASL3 Genovese, and Department of Rehabilitation, ML Novarese Hospital Moncrivello, Genova, Italy
[30]Hospital Germans Trias i Pujol, Badalona, Spain
[31]Flinders University, Adelaide, South Australia, Australia
[32]Division of Neurology, Department of Medicine, Amiri Hospital, Sharq, Kuwait
[33]Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Beirut, Lebanon
[34]Isfahan University of Medical Sciences, Isfahan, Iran
[35]Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino, Italy
[36]Hospital de Galdakao-Usansolo, Galdakao, Spain
[37]Nemocnice Jihlava, Jihlava, Czech Republic
[38]Liverpool Hospital, Liverpool, New South Wales, Australia
[39]Hacettepe University, Ankara, Turkey
[40]Monash Medical Centre, Melbourne, Victoria, Australia
[41]Westmead Hospital, Sydney, New South Wales, Australia
[42]Central Clinical School, Monash University, Melbourne, Victoria, Australia
[43]Department of Neurology, The Alfred Hospital, Melbourne, Victoria, Australia
[44]Department of Neurology, Box Hill Hospital, Monash University, Melbourne, Victoria, Australia

Acknowledgements We thank the patients who have agreed to participate in the global MSBase cohort study. The list of MSBase Study Group coinvestigators and contributors is given in online supplementary table 1.

Contributors Conception and design of the study: TK, TS, HB. Acquisition and analysis of data: TK, EKH, DH, GI, AP, MG, PD, PG, MO, AL, SO, LK, JK, MT, JLS, CB, FGM, JP, PS, DF, FG, MT, RB, EP, RT, PAMC, VVP, BVW, CS, CRT, MS, RA, BY, VS, DLS,

JLSM, RA, SH, RK, EB, SV, VJ, TS, HB. Drafting a significant portion of the manuscript or figures: TK.

Funding This study was financially supported by the National Health and Medical Research Council of Australia (1129189, 1140766, 1080518). The MSBase Foundation is a not-for-profit organisation that receives support from Roche, Merck, Biogen, Novartis, Bayer Schering, Sanofi Genzyme and Teva. The study was conducted separately and apart from the guidance of the sponsors.

Competing interests TK served on scientific advisory boards for Roche, Genzyme-Sanofi, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Genzyme-Sanofi, Teva, BioCSL and Merck and received research support from Biogen. EKH 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). DH 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 Ministry of Education (project PROGRES Q27/LF1). GI received speaking honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall and Teva. MG 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. PD 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. PG 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. AL 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. LK received research support from Acorda, Actelion, Allozyne, BaroFold, Bayer Health Care, Bayer Schering, Bayhill Therapeutics, Biogen, Elan, European Union, Genmab, Gianni Rubatto Foundation, GlaxoSmithKline, Glenmark, MediciNova, Merck, Novartis, Novartis Research Foundation, Roche, Roche Research Foundation, Sanofi-Aventis, Santhera, Swiss MS Society, Swiss National Research Foundation, Teva Neuroscience, UCB and Wyeth. JK received consulting fees from Novartis, Protagen; speaker fees from the Swiss MS Society, Biogen, Novartis, Roche, Genzyme; travel expenses from Merck Serono, Novartis; grants from ECTRIMS Research Fellowship Programme, University of Basel, Swiss MS Society, Swiss National Research Foundation, Bayer (Schweiz), Genzyme and Novartis. MT received travel grants from Novartis, Bayer Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis. JLS 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. CB received conference travel support from Biogen, Novartis, Bayer Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis. FGM received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, Mitsubishi and ONO Pharmaceuticals. JP accepted travel compensation from Novartis, Biogen, Genzyme and Teva and speaking honoraria from Biogen, Novartis, Genzyme and Teva. PS 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 and Teva. DF received travel grants and/or speaker honoraria from Merck, TEVA, Novartis, Biogen and Sanofi Genzyme. FG 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. MT 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. RB received speaker honoraria from Bayer Schering, Biogen, Genzyme, Merck, Novartis, Sanofi-Aventis and Teva; research grants from Bayer Schering, Biogen, Merck, Novartis, Sanofi-Aventis and Teva; congress and travel/accommodation expense compensations by Almirall, Bayer Schering, Biogen, Genzyme, Merck, Novartis, Sanofi-Aventis and Teva. EP served on scientific advisory boards for Merck, Genzyme and Biogen; he has received honoraria and travel grants from Sanofi Aventis, Novartis, Biogen, Merck, Genzyme and Teva; he has received travel grants and equipment from 'Associazione Marchigiana Sclerosi Multipla e altre malattie neurologiche'. VVP received travel grants from Biogen, Bayer Schering, Genzyme, Merck, Teva and Novartis Pharma. His institution receives honoraria for consultancy and lectures from Biogen, Bayer Schering, Genzyme, Merck, Roche, Teva and Novartis Pharma as well as research grants from Novartis Pharma and Bayer Schering. BVW received research and travel grants, honoraria for MS-Expert advisor and speaker fees from Bayer Schering, Biogen, Sanofi Genzyme, Merck, Novartis, Roche and Teva. CS 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. CRT received research funding, compensation for travel or speaker honoraria from Biogen, Novartis, Genzyme and Almirall. MS has participated in, but not received honoraria for, advisory board activity for Biogen, Merck, Bayer Schering, Sanofi Aventis and Novartis. RA received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi Genzyme. DLS 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. JLSM accepted travel compensation from Novartis and Biogen, speaking honoraria from Biogen, Novartis, Sanofi, Merck, Almirall, Bayer and Teva and has participated in a clinical trial by Biogen. RA received conference travel support from Novartis, Teva, Biogen, Bayer and Merck and has participated in a clinical trial by Biogen, Novartis, Teva and Actelion. SH received honoraria and consulting fees from Merck, Novartis, Bayer Schering and Sanofi, and travel grants from Novartis, Biogen Idec and Bayer Schering. Ricardo Fernandez Bolaños received speaking honoraria from Biogen, Novartis, Merck and Teva. VJ received conference travel support from Teva, Novartis and Merck, and speaker honoraria from Biogen. TS received honoraria for consultancy, funding for travel and compensation for serving on scientific advisory boards from Biogen and speaker honoraria from Novartis. HB 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.

Patient consent for publication Not required.

Ethics approval Melbourne Health Human Research Ethics Committee

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Warrender-Sparkes M, Spelman T, Izquierdo G, *et al*. The effect of oral immunomodulatory therapy on treatment uptake and persistence in multiple sclerosis. *Mult Scler* 2016;22:520–32.
2. Kappos L, Radue EW, O'Connor P, *et al*. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010;362:387–401.
3. O'Connor P, Wolinsky JS, Confavreux C, *et al*. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011;365:1293–303.
4. Gold R, Kappos L, Arnold DL, *et al*. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012;367:1098–107.
5. Gerardi C, Bertele' V, Rossi S, *et al*. Preapproval and postapproval evidence on drugs for multiple sclerosis. *Neurology* 2018;90:964–73.
6. Fox RJ, Chan A, Zhang A, *et al*. Comparative effectiveness using a matching-adjusted indirect comparison between delayed-release dimethyl fumarate and fingolimod for the treatment of multiple sclerosis. *Curr Med Res Opin* 2017;33:175–83.
7. Huisman E, Papadimitropoulou K, Jarrett J, *et al*. Systematic literature review and network meta-analysis in highly active relapsing-remitting multiple sclerosis and rapidly evolving severe multiple sclerosis. *BMJ Open* 2017;7:e013430.
8. Fogarty E, Schmitz S, Tubridy N, *et al*. Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: systematic review and network meta-analysis. *Mult Scler Relat Disord* 2016;9:23–30.
9. Freedman MS, Montalban X, Miller AE, *et al*. Comparing outcomes from clinical studies of oral disease-modifying therapies (dimethyl fumarate, fingolimod, and teriflunomide) in relapsing MS: assessing absolute differences using a number needed to treat analysis. *Mult Scler Relat Disord* 2016;10:204–12.
10. Hersh CM, Love TE, Bandyopadhyay A, *et al*. Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 24-month follow-up. *Multiple Sclerosis Journal – Experimental, Translational and Clinical* 2017;3:205521731771548.
11. Prosperini L, Lucchini M, Haggiag S, *et al*. Fingolimod vs dimethyl fumarate in multiple sclerosis: a real-world propensity score-matched study. *Neurology* 2018;91:e153–e61.
12. Kalincik T, Butzkueven H. Observational data: Understanding the real MS world. *Mult Scler* 2016;22:1642–8.
13. He A, Spelman T, Jokubaitis V, *et al*. Comparison of switch to fingolimod or interferon beta/glatiramer acetate in active multiple sclerosis. *JAMA Neurol* 2015;72:405–13.
14. Trojano M, Pellegrini F, Paolicelli D, *et al*. Real-life impact of early interferon beta therapy in relapsing multiple sclerosis. *Ann Neurol* 2009;66:513–20.
15. Iaffaldano P, Lucisano G, Pozzilli C, *et al*. Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis. *Brain* 2015;138:3275–86.
16. Barbin L, Rousseau C, Jousset N, *et al*. Comparative efficacy of fingolimod vs natalizumab: a French multicenter observational study. *Neurology* 2016;86:771–8.
17. Butzkueven H, Chapman J, Cristiano E, *et al*. MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. *Mult Scler* 2006;12:769–74.
18. Polman CH, Reingold SC, Edan G, *et al*. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005;58:840–6.

19. Polman CH, Reingold SC, Banwell B, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69:292–302.
20. Kalincik T, Horakova D, Spelman T, *et al*. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. *Ann Neurol* 2015;77:425–35.
21. Kalincik T, Kuhle J, Pucci E, *et al*. Data quality evaluation for observational multiple sclerosis registries. *Mult Scler* 2017;23:647–55.
22. Kalincik T, Cutter G, Spelman T, *et al*. Defining reliable disability outcomes in multiple sclerosis. *Brain* 2015;138:3287–98.
23. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc* 1984;79:516–24.
24. Kalincik T, Brown JWL, Robertson N. Comparison of alemtuzumab with natalizumab, fingolimod, and interferon beta for multiple sclerosis: a longitudinal study. *Lancet Neurol* 2017;16:271–81.
25. Tramacere I, Del Giovane C, Salanti G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev* 2015;9:Cd011381.
26. Chua AS, Egorova S, Anderson MC, *et al*. Using multiple imputation to efficiently correct cerebral MRI whole brain lesion and atrophy data in patients with multiple sclerosis. *Neuroimage* 2015;119:81–8.
27. Ferro MA. Missing data in longitudinal studies: cross-sectional multiple imputation provides similar estimates to full-information maximum likelihood. *Ann Epidemiol* 2014;24:75–7.
28. Carpenter JR, Kenward MG, White IR. Sensitivity analysis after multiple imputation under missing at random: a weighting approach. *Stat Methods Med Res* 2007;16:259–75.
29. Héraud-Bousquet V, Larsen C, Carpenter J, *et al*. Practical considerations for sensitivity analysis after multiple imputation applied to epidemiological studies with incomplete data. *BMC Med Res Methodol* 2012;12:73.
30. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011;10:150–61.
31. Rosenbaum PR. *Observational studies*. 2nd edn. New York: Springer-Verlag, 2002.
32. Hutchinson M, Fox RJ, Havrdova E, *et al*. Efficacy and safety of BG-12 (dimethyl fumarate) and other disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis: a systematic review and mixed treatment comparison. *Curr Med Res Opin* 2014;30:613–27.
33. Boster A, Nicholas J, Wu N, *et al*. Comparative effectiveness research of disease-modifying therapies for the management of multiple sclerosis: analysis of a large health insurance claims database. *Neurol Ther* 2017;6:91–102.
34. Vollmer B, Nair KV, Sillau SH, *et al*. Comparison of fingolimod and dimethyl fumarate in the treatment of multiple sclerosis: Two-year experience. *Multiple Sclerosis Journal – Experimental, Translational and Clinical* 2017;3:205521731772510.
35. Sormani MP, Gasperini C, Romeo M, *et al*. Assessing response to interferon-β in a multicenter dataset of patients with MS. *Neurology* 2016;87:134–40.
36. Kalincik T, Vaneckova M, Tyblova M, *et al*. Volumetric MRI markers and predictors of disease activity in early multiple sclerosis: a longitudinal cohort study. *PLoS One* 2012;7:e50101.
37. Sormani MP, Bruzzi P. Can we measure long-term treatment effects in multiple sclerosis? *Nat Rev Neurol* 2015;11:176–82.
38. Havrdova E, Galetta S, Stefoski D, *et al*. Freedom from disease activity in multiple sclerosis. *Neurology* 2010;74–S3–7.
39. Berger JR, Cree BA, Greenberg B, *et al*. Progressive multifocal leukoencephalopathy after fingolimod treatment. *Neurology* 2018;90:e1815–e1821.
40. Oshima Y, Tanimoto T, Yuji K, *et al*. Drug-associated progressive multifocal leukoencephalopathy in multiple sclerosis patients. *Mult Scler* 2018:135245851878607.