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Comparative analysis of fingolimod versus teriflunomide in relapsing–remitting multiple sclerosis

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ABSTRACT

Background: Fingolimod and teriflunomide are commonly used in the treatment of relapsing-remitting multiple sclerosis (RRMS). These have not been compared in controlled trials, but only in observational studies, with inconclusive results. Comparison of their effect on relapse and disability in a real-world setting is therefore needed.

Objectives: The objective of this study was to compare the efficacy of fingolimod and teriflunomide in reducing disease activity in RRMS.

Methods: This multicenter, retrospective observational study was carried out with prospectively collected data from 15 centers. All consecutive RRMS patients treated with teriflunomide or fingolimod were included. Data for relapses, Expanded Disability Status Scale (EDSS) scores and brain magnetic resonance imaging (MRI) scans were collected. Patients were matched using propensity scores.

Annualized relapse rates (ARR), disability accumulation, percentage of patients with active MRI and treatment discontinuation over a median 2.5-year follow-up period were compared.

Results: Propensity score matching retained 349 out of 1388 patients in the fingolimod group and 349 out 678 in the teriflunomide group for final analyses. Mean ARR decreased markedly from baseline after 1 and 2 years of treatment in both the fingolimod (0.58–0.17 after 1 year and 0.11 after 2 years, $p < 0.001$) and teriflunomide (0.56–0.29 after 1 year and 0.31 after 2 years, $p < 0.001$) groups. Mean ARR was lower in fingolimod-treated patients than in those treated with teriflunomide at years 1 ($p = 0.02$) and 2 ($p = 0.004$). Compared to teriflunomide, the fingolimod group exhibited a higher percentage of relapse-free patients and a lower percentage of MRI-active patients after 2.5-year follow-up. Disability worsening was similar between the two groups. Patients were less likely to discontinue fingolimod than teriflunomide ($p < 0.001$).

Conclusion: Fingolimod was associated with a better relapse control and lower discontinuation rate than teriflunomide. The two oral therapies exhibited similar effects on disability outcomes.

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1. Introduction

Oral agents (fingolimod, teriflunomide and dimethyl fumarate) are becoming increasingly widely used in relapsing-remitting multiple sclerosis (RRMS), either as first-line therapies or as a switch from other disease-modifying therapies.

They have been approved for RRMS on the basis of large phase III randomized clinical trials showing superior efficacy in reducing relapse rates, disability worsening, and MRI activity compared to placebo (Kappos et al., 2010; O'Connor et al., 2011).

Three phase III clinical trials have demonstrated the efficacy of fingolimod in achieving more favorable effects compared with placebo or intramuscular interferon beta-1a (Calabresi et al., 2014; Kappos et al., 2015, 2010). Fingolimod reduced the annualized relapse rate (ARR) from 0.40 in placebo-treated patients to 0.18 (FREEDOMS) and from 0.33 in patients treated with intramuscular interferon β1a to 0.16 (TRANSFORMS).

In the TEMSO and TOWER phase III trials, daily 14 mg teriflunomide reduced relapse rates compared to placebo and produced a reduction in ARR from 0.54 to 0.37 and from 0.50 to 0.32, respectively (Confavreux et al., 2014; O'Connor et al., 2011). Teriflunomide exhibited a similar efficacy and safety profile to subcutaneous IFNβ−1a 44 mg over 2 years in a randomized controlled study (TENERE) (Vermersch et al., 2014).

Our review of the literature revealed no randomized studies comparing the efficacy of oral agents. Unfortunately, differences among their placebo groups in their pivotal trials do not allow direct comparison of the efficacy of these drugs. However, although a randomized controlled trial is the best way of producing evidence on drug efficacy, trials are not usually feasible due to extensive costs. Moreover, trials have strict inclusion criteria, and therefore may not be reflective of the general treated MS population. For these reasons, observational studies may provide complementary information to that yielded by pivotal studies.

Limited real-world studies have addressed the comparison of oral drugs (Braune et al., 2018; Conde et al., 2018; D'Amico et al., 2018; Kalincik et al., 2019; Ontaneda et al., 2018; Prosperini et al., 2018). One retrospective claims analysis described fingolimod as more effective than teriflunomide (Boster et al., 2017). Recent indirect-treatment-comparison studies of oral drugs also suggest that fingolimod has a greater effect than teriflunomide in reducing relapses (Fox et al., 2017; Huisman et al., 2017).

In Turkey, fingolimod has been available as a treatment for RRMS since its approval by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in May 2012. A teriflunomide dosage of 14 mg was approved in May 2014. Both drugs can be prescribed as first- or second-line therapies for relapsing MS patients with an Expanded Disability Status Scale (EDSS) score less than 6. Fingolimod is generally prescribed to RRMS patients who have either experienced a suboptimal response or poor tolerability with previous injection therapies, or to treatment-naïve patients with highly active RRMS and an EDSS score less than 6. Teriflunomide is prescribed as a first- or second-line therapy for relapsing MS with an EDSS score less than 6.

While the efficacy and safety profiles of fingolimod and teriflunomide have been established in clinical trials and real-world settings, limited data are available comparing the effectiveness of these two medications.

This study aimed to compare the effectiveness of fingolimod and teriflunomide in a real-world setting with Turkish patients with RRMS. Dimethyl fumarate was excluded from this study due to its late availability in Turkey and shorter follow-up time.

2. Patients and methods

This research was performed as an independent, multicenter, real-world observational study. Each center received local regulation and local ethical committee approval for registry use for all MS patients. The observational plan and multicenter design of this study protocol was approved by the Karadeniz Technical University (KTU) Medical Faculty Ethical Committee on behalf of all participating centers. Written informed consent was required from all participating patients at each center. Data from all RRMS patients treated with fingolimod or teriflunomide for the first time who regularly attended multiple sclerosis (MS) outpatient clinics were included retrospectively. The treatment choice between fingolimod and teriflunomide was made by the treating neurologist.

Demographic, clinical and MRI data were prospectively recorded as part of routine clinical practice at 15 tertiary MS centers. The data entry portal was “IMED software,” and quality assurance procedures were followed (Supplementary Table 1) (Kalincik et al., 2017). The studied data was recorded mainly at academic MS centers. Centers that contributed more than 10 records to the database were included in the study. Centers with low quality data were excluded. ‘Low quality data’ centers were classified as centers that annual EDSS scores recorded less than 50% of patients. A series of automated procedures were applied to identify any invalid or erroneous data entries.

The usual data entry practice was real-time or a close approximation of real-time at the time of clinical visits. Data for patients treated with fingolimod or teriflunomide were extracted in the form of an Excel file from each center and were then combined for analyses.

The inclusion criteria for analyses consisted of diagnosis with RRMS according to the 2005 or 2010 Revised McDonald criteria, and continuous exposure to one of the study therapies for ≥ 3 months. The following variables were required for all patients included: sex, age, date of first MS symptom, dates of clinical relapses, and disability score assessed by EDSS at commencement of treatment and at least two disability scores recorded after commencement of one of the study therapies. EDSS scores within 3 months prior to or 1 month after commencement of the study therapy was regarded as patients' baseline EDSS.

Patients aged < 18 years, treated with fingolimod, teriflunomide or with immunosuppressants (mitoxantrone or cyclophosphamide) within the previous year, or with a progressive MS course were excluded from the study.

The study follow-up time was defined as time between start of therapy and the last available EDSS entry visit. Disability was assessed using EDSS by Neurostatus-certified MS specialists. Any EDSS score recorded within 30 days of a previous relapse was excluded.

Available MRI information reported by treating neurologists was also collected. MRI of the brain acquired within 3 months prior to the initiation of the study therapy was regarded as baseline MRI. MRIs acquired at the 12th and 24th months after the initiation of therapy (± 45 days) were defined as year 1 and year 2 MRIs, respectively.

To minimize unstandardized MRI results, included centers had to have had availability of yearly MRI data in ≥25% of patients. Categorized baseline T2 and Gd-enhancing (Gd+) lesion numbers (unavailable, 1–2, 3–8, ≥9 T2 lesions and absent or ≥1 Gd+ lesion) were analyzed. MRI parameters were excluded from the estimation of propensity scores to eliminate the potential effect of multiple imputation.

3. Study endpoints

The primary study outcomes were annualized relapse rate (ARR), time to first relapse and time to disability progression. The secondary endpoints were cerebral MRI activity and adherence to therapy.

A relapse was defined as any new neurological symptom or exacerbation of existing symptoms persisting for at least 24 h in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse (Havrdova et al., 2010). Disability progression was defined as a 1.5-point increase (if the baseline EDSS score was 0), a 1.0-point increase (if the baseline EDSS score was < 5.5), or a 0.5-point

increase (if the baseline EDSS score was ≥5.5) confirmed at 6 month intervals (Kalincik et al., 2015).

Radiological activity was defined as the occurrence of gadolinium Gd+ lesion on T1-weighted images or new hyperintense lesions on T2/FLAIR brain images. Percentages of patients with brain MRI activity (defined as the presence of ⩾1 new/enlarging T2 lesion with respect to previous brain MRI and/or the presence of ⩾1 Gd+ lesion) at years 1 and 2 were also calculated.

4. Statistical analyses

Matching and statistical analyses were conducted using R (version 3.5) and SPSS IBM v. 23 software. No formal sample size was pre-calculated since we used data already available in the database. A sample size of 349 patients in each treatment group provided 89% power for detecting an ARR difference between fingolimod and teriflunomide with an effect size of $d = 0.24$ at a significance level of $\alpha = 0.05$. Statistical power for relapse rate in year 1 was 95%, with an effect size of $d = 0.14$ and in year 2 was 97%, with an effect size of $d = 0.18$.

The included patients were matched in terms of their propensity for fingolimod treated versus teriflunomide treated groups using the MatchIt package (Zhang, 2017). The propensity score was based on a multivariable logistic regression model. Independent variables consisted of age, age at onset, gender, disease duration, baseline EDSS, number of previous DMTs, and number of relapses in the year before treatment. The output of the logistic model used to determine the propensity scores are shown in the Supplementary Table 2. Patients were then matched in a 1:1 ratio using nearest neighbor matching within a caliper of 0.1 standard deviations of the propensity score. The distribution of propensity scores in fingolimod and teriflunomide cohort both before and after matching are shown in the Supplementary Figure 1. Patients who switched or discontinued treatment were censored.

Only matched pairs were included in this analysis. Patients' baseline characteristics were evaluated to identify possible statistical differences between the two treatment groups. For continuous variables mean, standard deviation, median, min, max or interquartile range (IQR) were reported, depending on the statistical distribution. Pairwise censoring was applied to the analyses of disease outcomes (with the exception of the comparison of treatment persistence) to determine common on-treatment follow-up times in order to mitigate attrition bias and the effect of differential treatment persistence (Kalincik and Butzkueven, 2016).

In order to investigate statistical relevance, the unpaired *t*-test was used for continuous normally distributed variables and the χ^2 test for categorical data in the unmatched cohort and paired *t*-test in the matched cohort. Mann Whitney U or Wilcoxon test was used for non-parametric variables. The proportion of patients without relapse or without EDSS increase was evaluated with the Cox marginal proportional hazards model. The proportional hazards assumption was examined visually and by testing Schoenfeld's residuals. Drug persistence was compared using Kaplan–Meier survival estimates curves (log rank test). Significance was set at $p < 0.05$.

5. Results

5.1. Study population

One thousand three hundred eighty-eight fingolimod and 678 teriflunomide patients were included in the study (Fig. 1, Supplementary Table 3).

Baseline demographic and clinical characteristics of all subjects and

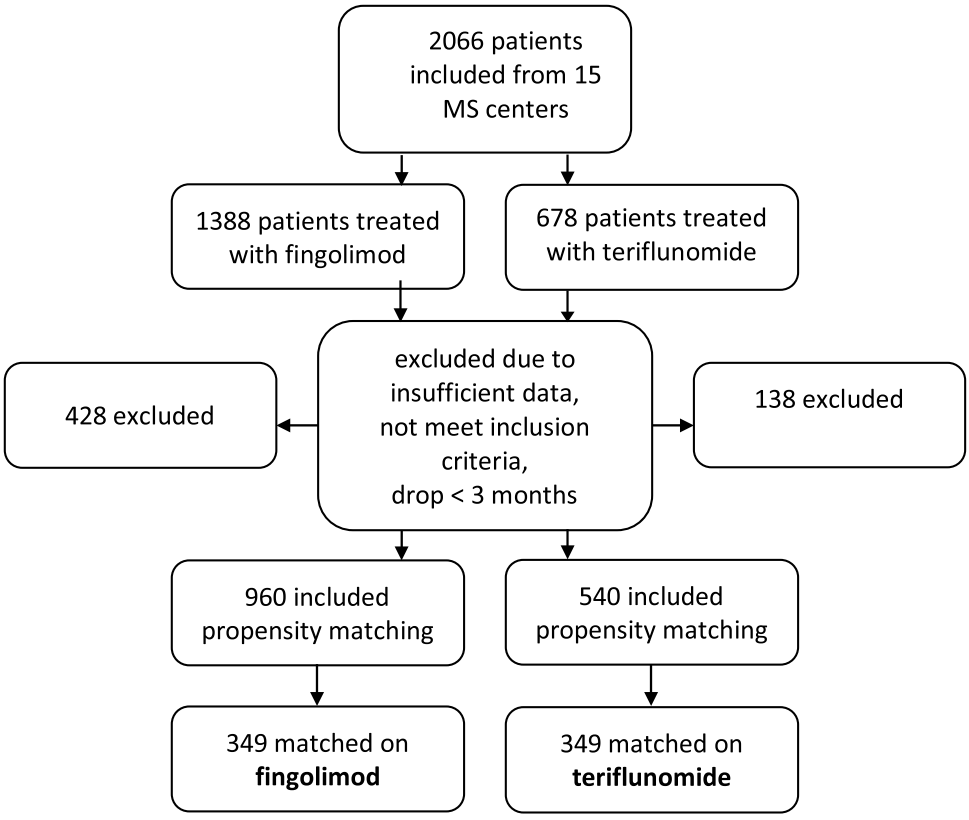

Fig. 1. Patient disposition flowchart.

Table 1
Baseline demographic and clinical characteristics of the unmatched and matched patients.

Baseline characteristics	All patients				Matched groups			
	Fingolimod (n = 1388)	Teriflunomide (n = 678)	Cohen d	p	Fingolimod (n = 349)	Teriflunomide (n = 349)	Cohen d	p
Patients female/male	926/462	454/224		0.64	236/113	235/114		0.93
Age, years, mean ± SD	38.9 ± 9.6	41.8 ± 11	0.28	0.001	41.8 ± 9.5	41.5 ± 10.4	0.03	0.60
Age at onset, years, mean ± SD	26.4 ± 8.3	29.9 ± 9.7	0.38	0.001	29.5 ± 8.6	29.2 ± 8.9	0.03	0.50
Disease duration, years, mean ± SD	12.2 ± 9	12.8 ± 8	0.07	0.16	12.4 ± 5.7	12.7 ± 9.2	0.04	0.59
Disability, EDSS, median (quartiles)	2 (1.5–4)	2 (1.5–4)	0.22	0.001	2 (1–3.5)	2 (1–3.5)	0.02	0.54
Relapses 12 months pre-baseline, mean ± SD	0.79 ± 0.92	0.53 ± 0.71	0.31	0.001	0.58 ± 0.70	0.56 ± 0.68	0.03	0.65
Previous therapies, nr, median (quartiles)	1 (1–2)	1 (1–2)	0.16	0.06	1 (1–2)	1 (1–2)	0.02	0.38
Follow up, median, months (IQR)	20.5 (11.2–32.6)	16.5(10.1–24.7)		0.01	25.7(18.2–25.6)	25.7(18.2–25.6)		ns
MRI								
Availability	711 (51%)	381 (56%)			227 (65%)	237 (68%)		
1–2	10 (1%)	13 (3%)			4 (2%)	10 (4%)		
3–8	27 (4%)	75 (20%)			12 (5%)	38 (16%)		
≥9	674 (95%)	293 (77%)			211 (93%)	189 (80%)		
≥1 Gd +	310 (43%)	128 (34%)			88 (39%)	94 (40%)		
Last therapy								
IFNβ/GA	1030 (74%)	396 (58%)			298 (85%)	297 (85%)		
Natalizumab	20 (1%)	13 (2%)			4 (1%)	3 (1%)		
Other	263 (19%)	56 (8%)			0 (0%)	0 (0%)		
Naïve	75 (5%)	213 (31%)			47 (13%)	49 (14%)		

MRI: Magnetic resonance imaging, IFNβ: interferon beta, GA: Glatiramer acetate. d: Cohen's d.
Continuous data are presented as the mean ± standard deviation or median, interquartile range (IQR) and percentage depending on the distribution.

of matched patients are shown in Table 1.

Patients treated with fingolimod were younger than those treated with teriflunomide (38.9 ± 9.6 vs.41.8 ± 11, respectively, $p < 001$), and had higher baseline ARR (0.79 ± 0.92 vs 0.53 ± 0.71, $p < 0.001$) and higher baseline EDSS (mean ± SD, 2.7 ± 1.8 vs. 2.3 ± 1.7, $p < 0.001$).

The propensity score matching procedure for the primary analysis retained 349 (25%) patients in the fingolimod group and 349 (51%) in the teriflunomide group. After matching, patients treated with fingolimod were similar in age (41.8 ± 9.5 vs. 41.5 ± 10.4, $p = 0.60$) and had similar baseline ARR (0.58 ± 0.70 vs. 0.56 ± 0.68, $p = 0.65$) and baseline EDSS (2.37 ± 1.6 vs. 2.31 ± 1.7, $p = 0.70$) to patients treated with teriflunomide.

ARRs (mean and standard error of the mean) of fingolimod and teriflunomide in the year before treatment initiation, and in the first year and second years are shown in Fig. 2. Mean ARR decreased markedly after 1 and 2 years of treatment in both the fingolimod group (0.58–0.17 after 1 year and to 0.11 after 2 years, $p < 0.001$) and teriflunomide group (0.56–0.29 after 1 year and to 0.31 after 2 years, $p < 0.001$). The mean ARR was lower in fingolimod-treated patients than in those treated with teriflunomide at year 1 ($p = 0.02$) and year 2 ($p = 0.004$).

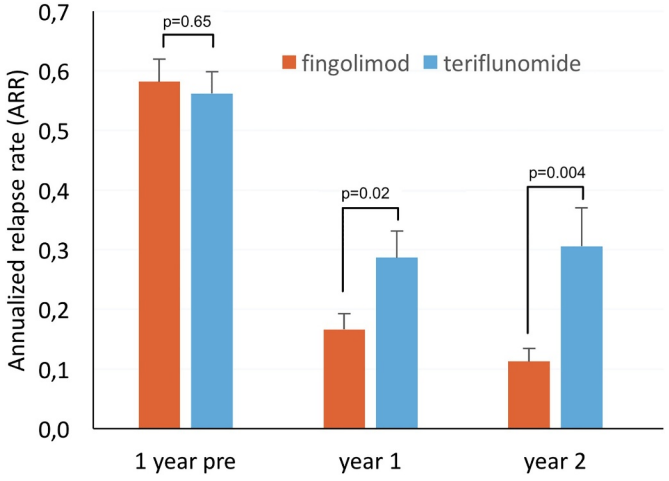

Fig. 2. Annualized relapse rates (mean and standard error of the mean) for fingolimod and teriflunomide in the year before start of treatment, and in the first and in second years of treatment.

The proportion of relapse-free patients was higher among patients treated with fingolimod than those in the teriflunomide group (hazard ratio (HR) 0.53, 95% confidence interval (95% CI) 0.38–0.73, $p < 0.001$; Fig. 3).

No differences were observed in the rate of confirmed disability accumulation (HR 0.83, 95%CI 0.53–1.27, $p = 0.12$) were found (Fig. 4).

MRI-related secondary end-point analyses revealed a higher percentage of patients free from new or enlarging lesions in the fingolimod group compared to the teriflunomide group at years 1 (72% vs 63%, $p = 0.034$) and 2 (74% vs 63%, $p = 0.04$) (Fig. 5a). Consistently, a higher percentage of fingolimod patients were free from Gd-enhancing lesions at year 1 (77% vs 68%, $p = 0.021$) and year 2 (79% vs 69%, $p = 0.042$) (Fig. 5b).

Fig. 6 shows Kaplan Meier survival analyses for drug persistence. Patients treated with fingolimod were less likely to discontinue medications than those receiving teriflunomide ($p = 0.001$).

Reported reasons for treatment discontinuation are summarized in Supplementary Table 3.

6. Discussion

This propensity score-matching analysis compared the efficacy of fingolimod and teriflunomide in RRMS patients. Patients were mostly switchers from injections. Before matching, some baseline characteristics differed between the two groups, the fingolimod group being more active than the teriflunomide group. In the matched population, both fingolimod and teriflunomide significantly reduced relapse activity. However, the effect of fingolimod was greater than that of teriflunomide in terms of relapse, MRI activity and adherence to therapy in RRMS. Both therapies exhibited comparable effects on disability accumulation during the initial 2.5 years.

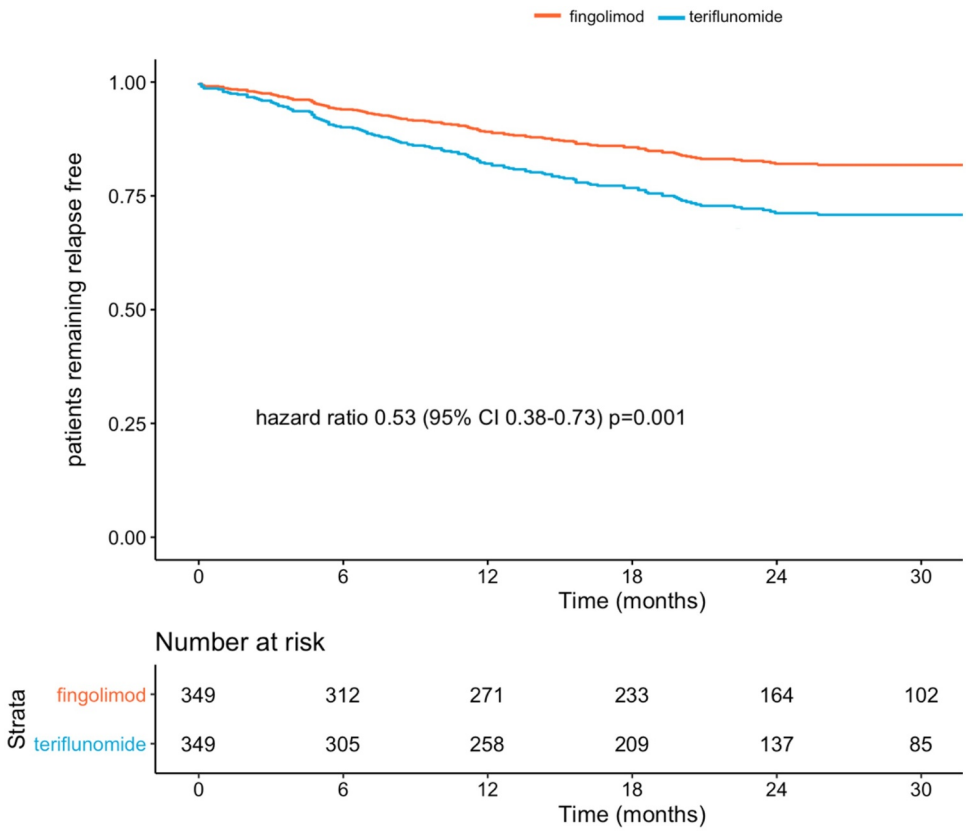

Fig. 3. Proportions of patients free from relapses.

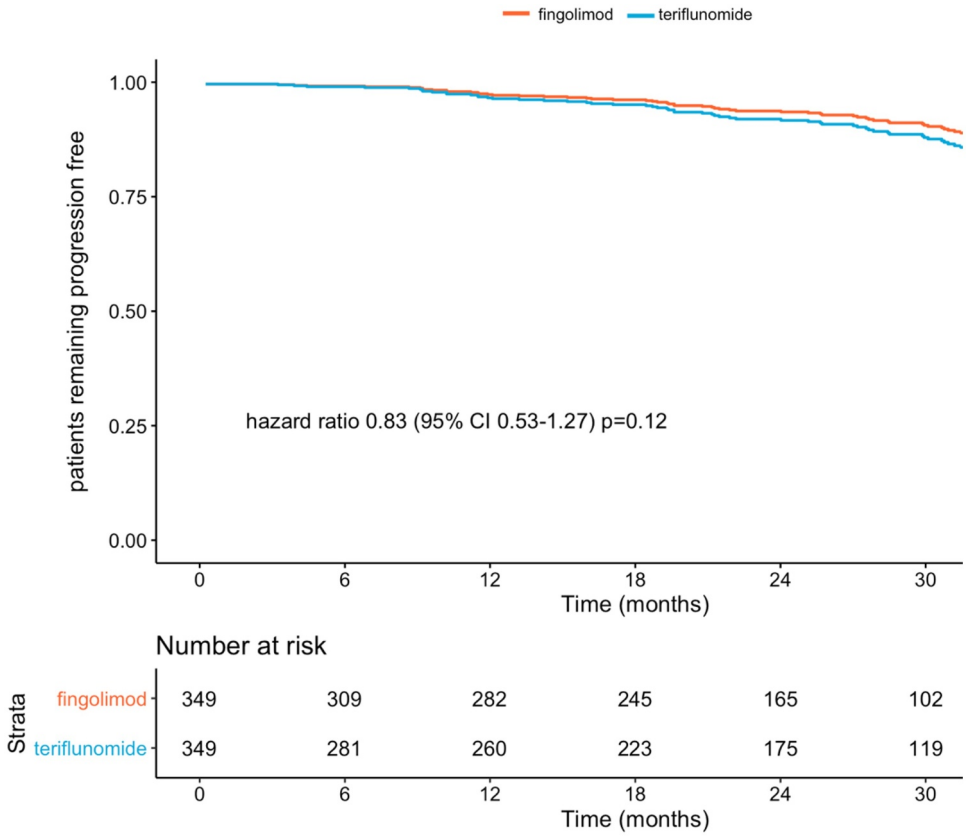

Fig. 4. Proportions of patients free from disability progression.

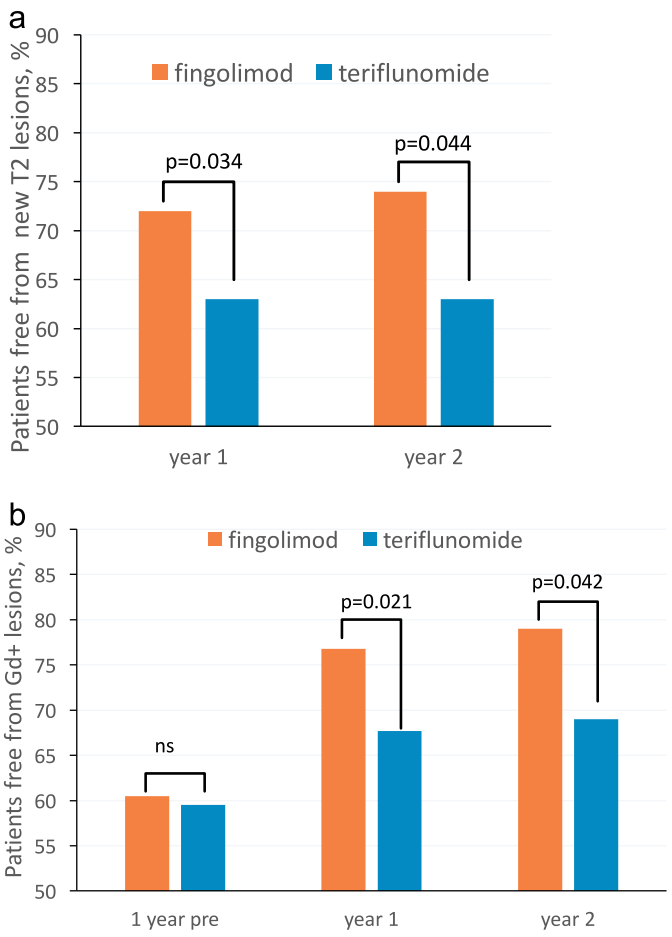

Fig. 5. Proportions of patients free from gadolinium-enhancing lesions (a) and of patients without new or enlarging T2 lesions (b). Percentages of patients with available MRI data for fingolimod and teriflunomide were 65% and 68% at baseline; 63% and 64% at year 1, and 59% and 63% at year 2, respectively. The *p* values are derived from the chi-square test at a significance level of $p < 0.05$.

No head-to-head clinical trials have to date compared the efficacy of oral drugs for MS. However, a recent post-hoc analysis of data from individual clinical trials of three oral drugs demonstrated comparable effects for dimethyl fumarate, fingolimod, and teriflunomide across key clinical outcomes as determined by number needed to treat (NNT) evaluations (Freedman et al., 2016). Using this approach, the authors reported broadly comparable NNTs for dimethyl fumarate, fingolimod, and teriflunomide in terms of relapses and relapses requiring treatment with intravenous (IV) corticosteroids despite differences in relative reductions between the three treatments. Nevertheless, NNTs were marginally lower for fingolimod across both of these relapse outcomes.

A recent large real-world study comparing fingolimod, dimethyl fumarate and teriflunomide in MS reported better outcomes for fingolimod in relapse frequency and persistence, while disability outcomes were similar to those of teriflunomide (Kalincik et al., 2019). A recent network meta-analysis reported a relatively lower effect of teriflunomide on relapse frequency and similar effects on disability outcomes for fingolimod and teriflunomide (Fogarty et al., 2016). An analysis of health insurance claims reported that relapse-related claims are less frequent for fingolimod than for teriflunomide with adjusted incidence rate ratios for relapse of 1.02 (0.85–1.23) for fingolimod and 1.21 (1.00–1.47) for teriflunomide (Boster et al., 2017). However, disability information was typically unavailable in that claim analysis.

In this study, we observed real-life effects of fingolimod and teriflunomide. ARR values after reduction rates from baseline were 71% in year 1 and 81% in year 2 for fingolimod, and 48% in year 1 and 45% in year 2 for teriflunomide. Magnitude of the effects on relapse activity may partly be due to lower pre-treatment disease activity. Pre-treatment disease activity and age are well-known factors affecting on-treatment relapse activity as well as modulators for medication efficacy. Our patient groups were older than those in the pivotal studies (mean age ± SD in our cohort were 41.8 ± 9.5 in the fingolimod group and 41.5 ± 10.4 in the teriflunomide group compared to 37.4 ± 8.9 for fingolimod in the FREEDOMS, and 38.6 ± 8.4 for teriflunomide in the TEMSO trials). Our pre-treatment relapse rates were also lower than pre-treatment relapse rates in pivotal trials (mean ARR in our cohort was 0.58 for fingolimod and 0.56 for teriflunomide compared to 1.5 in fingolimod and 1.4 in teriflunomide trials). Duration of MS since onset of the first symptom was also longer, at a mean 12.4 years for fingolimod and 12.7 years for teriflunomide in our cohort, compared to 8.2 years in the FREEDOMS and 8.6 years in the TEMSO trials.

Although data entry typically occurs in real-time or nearly real-time, some variables such as relapse-related information may be susceptible to detection and reporting bias. However, the follow-up protocols used in this study were largely comparable, and as such, such bias may expected to be minimal.

The main limitation of this study is its observational retrospective design. First, the fingolimod-treated patients exhibited more inflammation at the start of fingolimod therapy than those treated with teriflunomide, which may have affected the comparison results, despite multivariate analysis. The propensity-score model is unable to adjust for unknown confounders such as physicians' treatment decisions. Pairwise censoring was applied to control for attrition bias.

Another limitation was the relatively short follow-up duration. Detecting significant changes in EDSS during this short period is challenging. Findings for disability accumulation therefore require confirmation over a longer observation period.

We were unable to compare our radiological data to those of pivotal studies due to absence of systematic acquisition of radiological outcomes and lack of volumetric analytics. MRI is an important technique for measuring subclinical MS disease activity, with an impact on treatment choice. Consistent acquisition of quantitative MRI data in the context of retrospective multi-center studies still represents a significant challenge. The MRI data in the present study were reported by treating neurologists and were therefore subject to inter-scanner, inter-protocol and inter-rater error. However, lack of a formalized definition of MRI follow-up was not expected to introduce a systematic bias, as the same physician reported MRI in both patient groups and categorized results were subjected to analysis. With the advent of standardized MRI protocols and quantitative volumetric assessments, MRI will doubtless become an integral component of future observational studies.

Most of the patients in the present study were switchers from other types of therapy. Numbers of naïve patients were relatively low. Analyses could not be applied to naïve patients, nor to subjects with low disease activity. Therefore, although the result of this study exhibits greater improvements in relapse rates and MRI activity in patients treated with fingolimod, the same assumption cannot be extended to patients with less disease activity.

Although randomized clinical trials are the mainstay for evaluating drug efficacy and safety, the analysis of observational data provides practical evidence. Efficacy is not the only criterion to be considered in the selection of therapies for an individual patient. Treatment decisions need to be made based on complex evaluations and must include patient preference, adherence, treatment safety, family planning and cost.

In conclusion, this real-world observational study using propensity score-based matching suggests that fingolimod is associated with better relapse control than teriflunomide, although both exhibited similar effects on disability over a period of 2.5 years. Given the uncertainty and variability associated with treatment effects between DMTs, real-world data, preferably from longitudinal follow-up studies will provide additional information with which to assess long-term effectiveness.

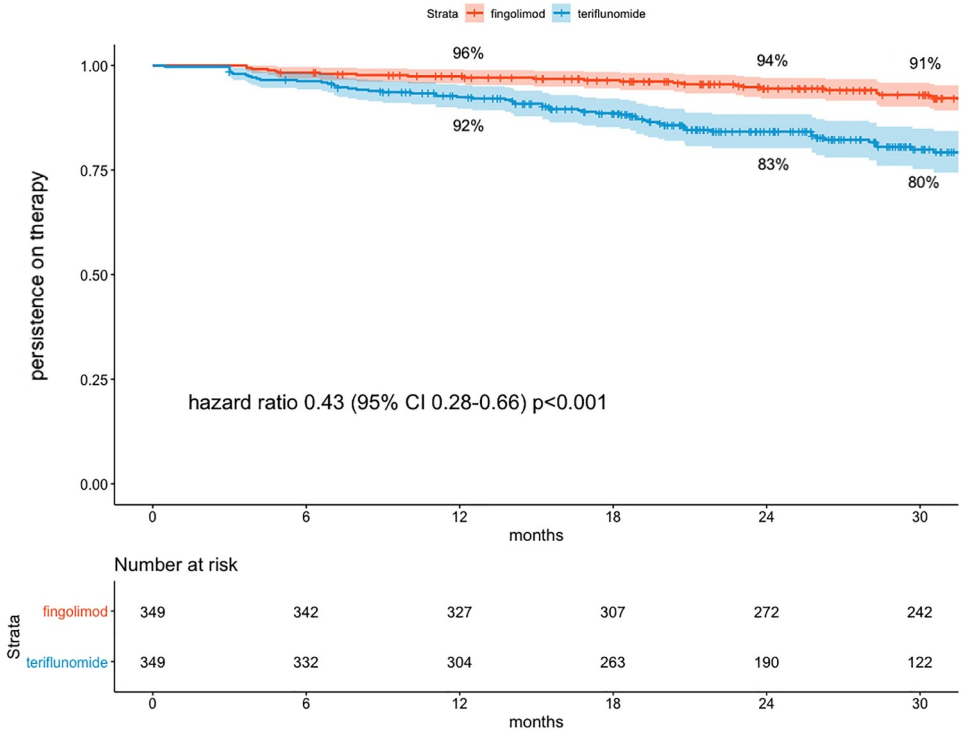

Fig. 6. Therapy persistence
The percentages are relative to the number of patients with available data at follow-up.

Declaration of Competing Interest

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

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

Bilge Ozer did not declare any competing interests.

Recai Turkoglu did not declare any competing interests.

Rana Karabudak did not declare any competing interests related to this study.

Husnu Efendi did not declare any competing interests.

Aysun Soysal did not declare any competing interests.

Serhan Sevim did not declare any competing interests.

Ayse Altintas did not declare any competing interests related to this study.

Nur Yuceyar did not declare any competing interests.

Asli Kurne did not declare any competing interests.

Aylin Akcali did not declare any competing interests.

Gulsen Akman did not declare any competing interests.

Belgin Petek did not declare any competing interests.

Ozgul Ekmekci did not declare any competing interests.

Serap Zengin Karahan did not declare any competing interests.

Meltem Demirkıran did not declare any competing interests.

Ömer Faruk Turan did not declare any competing interests.

Burcu Altunrende did not declare any competing interests.

Gökçen Gözübatık Çelik did not declare any competing interests.

Nilüfer Kale did not declare any competing interests.

Mesrure Köseoğlu did not declare any competing interests.

Serkan Ozakbas did not declare any competing interests.

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Supplementary materials

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