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David-Axel Laplaud, Romain Casey, Laetitia Barbin, Marc Debouverie, Jerome de Sèze, et al.. Comparative effectiveness of teriflunomide vs dimethyl fumarate in multiple sclerosis. Neurology, 2019, 93 (7), pp.e635-e646. 10.1212/WNL.0000000000007938 . inserm-02289153

HAL Id: inserm-02289153

https://inserm.hal.science/inserm-02289153

Submitted on 16 Sep 2019

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Comparative effectiveness of teriflunomide vs dimethyl fumarate in multiple sclerosis

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Neurology® 2019;93:e635-e646. doi:10.1212/WNL.0000000000007938

Abstract

Objective

In this study, we compared the effectiveness of teriflunomide (TRF) and dimethyl fumarate (DMF) on both clinical and MRI outcomes in patients followed prospectively in the Observatoire Français de la Sclérose en Plaques.

Methods

A total of 1,770 patients with relapsing-remitting multiple sclerosis (RRMS) (713 on TRF and 1,057 on DMF) with an available baseline brain MRI were included in intention to treat. The 1- and 2-year postinitiation outcomes were relapses, increase of T2 lesions, increase in Expanded Disability Status Scale score, and reason for treatment discontinuation. Propensity scores (inverse probability weighting) and logistic regressions were estimated.

Results

The confounder-adjusted proportions of patients were similar in TRF- compared to DMF-treated patients for relapses and disability progression after 1 and 2 years. However, the adjusted proportion of patients with at least one new T2 lesion after 2 years was lower in DMF compared to TRF (60.8% vs 72.2%, odds ratio [OR] 0.60, $p < 0.001$). Analyses of reasons for treatment withdrawal showed that lack of effectiveness was reported for 8.5% of DMF-treated patients vs 14.5% of TRF-treated patients (OR 0.54, $p < 0.001$), while adverse events accounted for 16% of TRF-treated patients and 21% of DMF-treated patients after 2 years (OR 1.39, $p < 0.001$).

Conclusions

After 2 years of treatment, we found similar effectiveness of DMF and TRF in terms of clinical outcomes, but with better MRI-based outcomes for DMF-treated patients, resulting in a lower rate of treatment discontinuation due to lack of effectiveness.

Classification of evidence

This study provides Class III evidence that for patients with RRMS, TRF and DMF have similar clinical effectiveness after 2 years of treatment.

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Coinvestigators from the OFSEP and SFSEP groups are listed in appendix 2.

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The Article Processing Charge was funded by Association ANTARES.

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Glossary

CI = confidence interval; **DMF** = dimethyl fumarate; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **IPW** = inverse probability weighting; **MS** = multiple sclerosis; **NEDA** = no evidence of disease activity; **OFSEP** = Observatoire Français de la Sclérose En Plaques; **OR** = odds ratio; **RCT** = randomized controlled trial; **RRMS** = relapsing-remitting multiple sclerosis; **TRF** = teriflunomide.

Over the last 20 years, considerable progress has been achieved with therapeutic innovations reducing the incidence of relapses in multiple sclerosis (MS). These treatments target the immune system and are intended to slow the natural evolution of the disease. Recently, 2 new oral molecules have been marketed for MS: teriflunomide (TRF) and dimethyl fumarate (DMF). Both treatments have demonstrated their efficacy in relapsing-remitting MS (RRMS) to reduce annualized relapse rate, disability accumulation, and T2 lesion accrual at 2 years compared with placebo.[1–7]

Knowing which of the 2 treatments is more effective or better tolerated is of high importance for neurologists and their patients. Recent observational studies have reported inconsistent results regarding clinical MS activity at 1 year (annualized relapse rate, time to first relapse) but none has compared clinical efficacy, MRI disease activity, and treatment withdrawals at 1 and 2 years in a large population of patients.[8–12] Such a study has the advantage of being more representative of real-life practices and effects, even if the treated patients are often noncomparable directly due to indication biases. In this context, taking advantage of the French Multiple Sclerosis Registry (Observatoire Français de la Sclérose En Plaques [OFSEP]), we propose to compare the real-life effectiveness and tolerance of DMF and TRF, using weighted propensity scores to deal with possible confounders.

Methods

Classification of evidence

This observational study provides Class III evidence that the proportion of patients with at least one relapse is similar after 1 year of treatment with TRF or DMF in patients with RRMS.

The OFSEP cohort

OFSEP is a network of French neurologists, mainly from 34 MS centers. Data are collected prospectively during each visit or hospitalization on a standardized clinical form and collected in the European Database for Multiple Sclerosis (EDMUS) software.[13] Individual case reports include identification and demographic data, medical history, biological, electrophysiologic, and MRI data, treatments, as well as key episodes in MS course (date of relapses, date of secondary progression, dates and level of disability progression). Data are checked for consistency using automatic controls in the software.

Standard protocol approvals, registrations, and patient consents

All patients included in the OFSEP cohort sign an informed consent to have their medical data collected in routine practice used after anonymization and aggregation for research purposes. The reasons behind treatment withdrawal were prospectively collected in the OFSEP cohort, as the neurologist following the patient had to fill in a short questionnaire selecting different reasons for treatment discontinuation (local, general, or biological intolerance, lack of effectiveness, pregnancy, desire to become pregnant, other). Local intolerance referred for example to cutaneous adverse event with injectable treatments, general intolerance referred for example to fever or myalgia in case of flu-like syndrome, and biological intolerance referred to a biological abnormality observed under treatment like for example elevated liver enzymes. Serious adverse events are specifically enclosed in the form. The initial folder has received the agreement of the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche (CCTIRS) (December 18, 2013, reference 13.591bis, and June 27, 2014) and the Commission Nationale de l'Informatique et des Libertés (CNIL) (May 6, 2014, request 914.066, authorization decisions DR-2014-110 and DR-2014-327). The OFSEP cohort has been registered in clinicaltrials.gov (NCT02889965). For the current study, data were extracted on December 15, 2017. The study was registered in clinicaltrials.gov (NCT03302442).

Patients

All adults with RRMS defined by the 2010 revised MacDonald criteria[14] and followed in one of the 34 MS centers participating in the OFSEP network were included in the study. The following inclusion criteria were defined: patients with RRMS nonopposed to participation to the study, aged from 18 to 65 years, treatment-naive or previously treated with other first-line disease-modifying therapies (DMTs) (interferons or glatiramer acetate), who initiated either TRF or DMF between May 1, 2014, and January 1, 2016 (as both treatments were available at these dates, avoiding any bias related to positivity assumption), with an available MRI scan and Expanded Disability Status Scale (EDSS) assessment within the 6 months before treatment initiation, and with an EDSS score ranging from 0 to 5.5 at treatment initiation. Patients with prior second-line treatment were not included (natalizumab, fingolimod, cyclophosphamide, mitoxantrone, alemtuzumab, or rituximab). A total of 1,916 patients with nonavailable brain or spine MRI or EDSS evaluation in the previous 6 months before initiating DMF or TRF were not included as these

variables were a priori considered as possible confounders for the comparison of the 2 treatments. Therefore, the study was performed with intention to treat, including the patients who actually started the treatment.

Outcomes

Study schedule

The baseline was the DMF or TRF initiation date. Since our study was based on data from real-life practice, MRI and EDSS evaluations were not scheduled. Therefore, we defined 2 periods. First, we considered data collected between 6 months preinitiation and 3 months postinitiation as baseline MRI or EDSS. In case of multiple visits within this period, we retained the closest visit from the beginning of the treatment. Second, we considered data collected between 9 and 18 months postinitiation as 1-year MRI or EDSS. In case of multiple visits within this period, we selected the closest visit from the first postinitiation anniversary.

Outcomes

The main outcome was the proportion of patients with at least 1 relapse at 1 year postinitiation. Relapses were defined by any new or recurrent exacerbation of neurologic symptoms without fever that lasted for at least 24 hours. Five secondary endpoints were also analyzed after 1 year: the proportion of patients with an increased EDSS score compared to baseline, the proportion of patients with at least one new T2 lesion, the proportion of patients with no evidence of disease activity (NEDA3) (i.e., no new T2 lesion, no increase in the EDSS, and no relapse),[15] the proportion of treatment discontinuation due to inefficacy, and the proportion of treatment discontinuation due to side effects.

We also reported the 6 previous outcomes at 2 years postinitiation. We considered data collected within 21 and 30 months postinitiation as 2-year MRI or EDSS. In case of multiple visits within this period, we retained the closest visit from the second anniversary postinitiation.

Statistical analyses

Baseline comparisons were performed using Student t tests or χ^2 tests for quantitative or categorical variables, respectively. In order to deal with confounders, we chose a propensity score–based approach—the inverse probability weighting (IPW) estimator with stabilized weights[16]—to estimate average treatment effect. Multivariable logistic regressions were used to obtain the weights. Calibration was evaluated by plotting observed vs predicted probability of receiving DMF instead of TRF (figures e-1 to e-12, doi.org/10.5061/dryad.60tv071). Regarding goodness-of-fit for each model, we did not further explore the violation of the log-linearity assumption for continuous explanatory variables. Variables associated with the outcomes were considered as possible confounding factors ($p < 0.20$), in accordance with recent recommendations.[17,18] One propensity score model was therefore constructed for each outcome (table 1). Compared to the consideration of the true confounders subvector, that is, the variables associated with both treatment allocation and outcome, our strategy for variable selection in the propensity score models may improve estimation precision without adding bias.[19] We did not include variables only associated with treatment allocation, since it has been demonstrated that such instrumental variables may increase the bias of the effect estimation.[20] We checked that these possible confounding factors were associated with standardized differences lower than 10% in the corresponding pseudo-samples (tables e-1 to e-12, doi.org/10.5061/dryad.60tv071). For each comparison, a new set of propensity scores was assessed based on the subsets of eligible patients. Positivity assumption was graphically evaluated (figures e-1 to e-12, doi.org/10.5061/dryad.60tv071). The outcomes were then modeled according to logistic regressions by using weighted likelihood maximization and robust variance estimator.

For time-to-event analysis, cause-specific Cox models were estimated by maximizing the partial weighted likelihood with a robust estimator for the variance.[21] The adjusted survival curves were obtained using the weighted Kaplan-Meier estimator and compared using the adjusted log-rank test.[22,23]

All analyses were performed using the 3.3.2 version of R software.

Data availability

Anonymized data can be made available upon reasonable request to the corresponding author.

Results

Baseline characteristics: DMF is used in more active disease

A total of 3,686 patients fulfilled the inclusion criteria, 713 treated with TRF and 1,057 with DMF (figure 1). The characteristics of the 1,916 nonincluded patients due to missing EDSS or MRI at baseline are reported in table e-13 (doi.org/10.5061/dryad.60tv071). When compared to the included patients, the main clinically relevant differences were a lower relapse rate 1 and 2 years prior to treatment initiation, an older age at treatment initiation, a longer disease duration, and a higher previous exposure to DMTs. These results indicate that the patients retained for analysis experienced more active disease than the others. However, it is worth noting that there was no difference in terms of percentage of nonincluded patients for both treatments (51.9% for DMF and 51.9% for TRF).

Baseline demographic, clinical, and MRI characteristics of the 1,770 patients with RRMS included in the study are presented in table 1. Patients treated with DMF were younger with a shorter disease duration. In addition, there were more DMF- than TRF-treated patients with at least one relapse within a year or 2 preceding treatment initiation and at least one active lesion on baseline MRI scans. When considering only patients with relapse in each group in the year before initiating

Table 1 List of variables taken into account for each outcome, in each propensity score model

	Age at initiation	Sex	Disease duration	Treatment-naive vs treatment switch	Center with >50 included patients	EDSS level	Relapse within the previous year	Gadolinium-positive enhancement
At least one relapse								
1 year	X		X	X	X	X	X	X
2 year	X		X	X		X	X	X
EDSS increase								
1 year	X	X				X		
2 year	X	X		X		X	X	
New T2 lesions								
1 year	X		X	X	X		X	X
2 year	X		X	X	X		X	X
NEDA								
1 year	X		X	X	X		X	X
2 year				X	X		X	X
Withdrawal due to inefficacy								
1 year	X	X	X	X	X	X	X	X
2 year	X		X			X	X	X
Withdrawal due to adverse event								
1 year	X	X	X	X	X	X	X	X
2 year	X	X	X			X		X

Abbreviations: EDSS = Expanded Disability Status Scale; NEDA = no evidence of disease activity.

the treatment, the number of relapses was 1.24 in the TRF group and 1.33 in the DMF group. These baseline comparisons suggest that patients treated with DMF experienced more clinically and radiologically active MS than patients treated with TRF. Of note, no difference was observed in terms of sex distribution or percentage of treatment-naive patients.

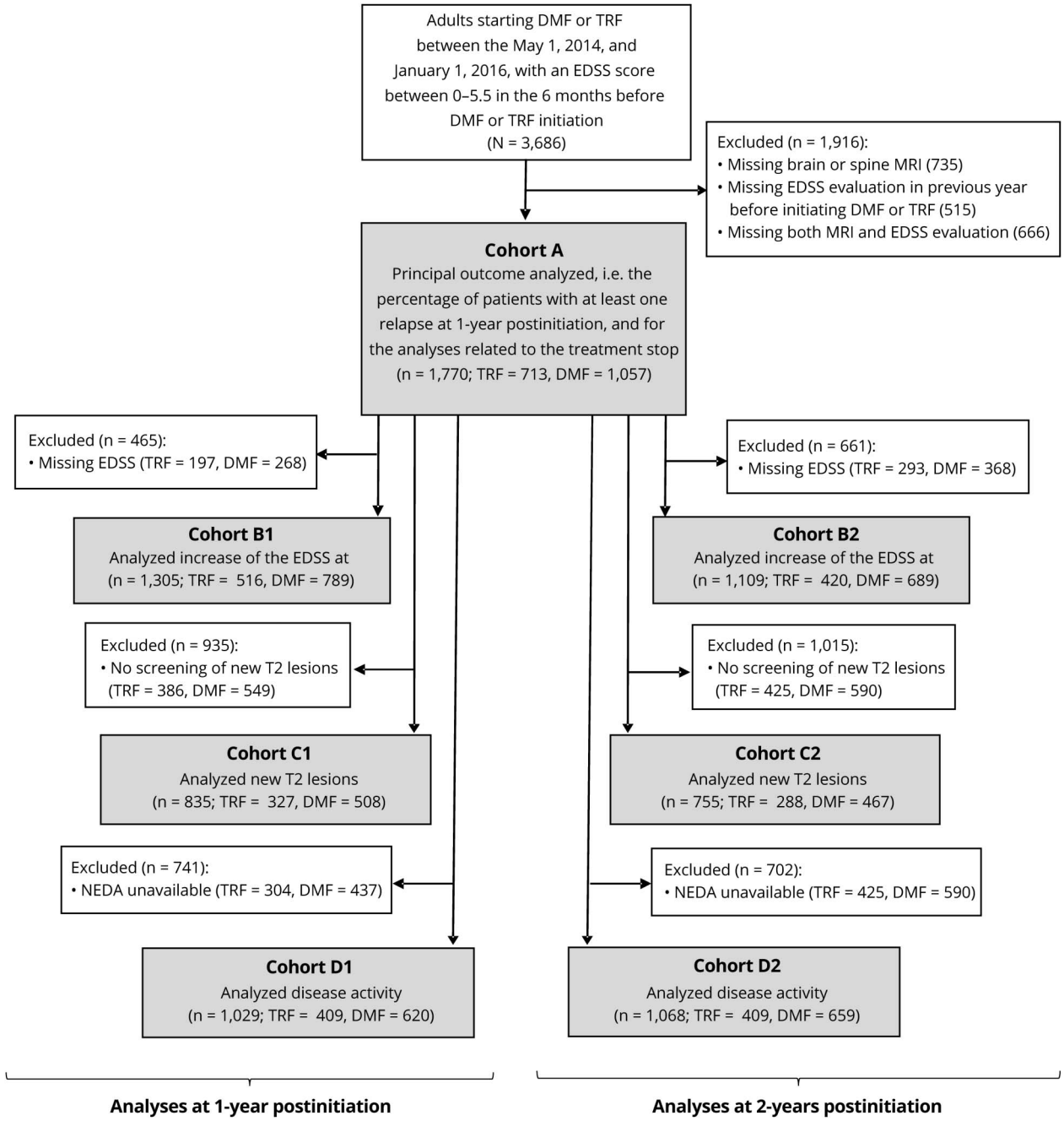
Clinical outcomes: No difference between TRF- and DMF-treated patients

The observed crude proportion of patients with at least one relapse at 1 year postinitiation was 19.4% (n = 138) in the TRF group vs 21.6% (n = 230) in the DMF group (p = 0.2214). This small difference was also observed at 2 years postinitiation: 28.1% (n = 200) in the TRF group vs 30.9% (n = 327) in the DMF group (p = 0.1928). These first results may suggest that both treatments are efficient in controlling the risk of relapse after 1 and 2 years, seeing as a year prior to treatment initiation, the percentage of relapse was 48.5% in the TRF group and 60.1% in the DMF group.

However, the 2 groups are not directly comparable at baseline (table 1), probably due to indication biases. In order to compare these 2 groups, we performed an inverse probability weighting on propensity scores. The confounder-adjusted percentage of patients with at least one relapse 1 year postinitiation was 21.6% (95% confidence interval [CI] 18.5%–24.9%) in the TRF group vs 20.2% (95% CI 17.6%–22.6%) in the DMF group. The corresponding odds ratio (OR) for patients treated with DMF vs TRF was 0.92 (95% CI 0.73%–1.16%, figure 2). At 2 years, the results were similar as confounder-adjusted percentage of patients with at least one relapse was 30.4% (95% CI 26.9%–33.9%) in the TRF group vs 29.5% (95% CI 26.6%–32.2%) in the DMF group. The corresponding OR for patients treated with DMF vs TRF was 0.96 (95% CI 0.78–1.19, figure 3), confirming a nonsignificant difference on effectiveness in terms of relapses.

When considering time to first relapse, as shown in figure 4 representing the confounder-adjusted survival curves, no statistically significant difference was observed between the 2 treatments (p = 0.7224, adjusted log-rank test). The corresponding cause-specific hazard ratio of DMF vs TRF was 0.97 (95% CI 0.81–1.16).

Figure 1 Patient selection diagram

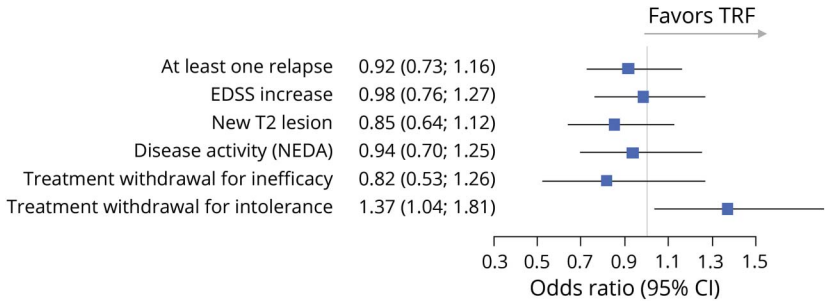


DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; NEDA = no evidence of disease activity; TRF = teriflunomide.

This lack of difference between the 2 treatments at 1 and 2 years postinitiation was also observed for the proportion of EDSS increase. We selected the patients for whom an EDSS was available at 1 (n = 1,305) or 2 (n = 1,109) years postinitiation. When comparing included and excluded patients due to non-available EDSS, no significant difference was observed, except for the percentage of previously treated patients for the analysis after 2 years (tables e-14 and e-15, doi.org/10.5061/dryad.60tv071).

Among the 1,305 patients (cohort B1, figure 1), the observed crude percentage of patients with an increase in EDSS level was 27.3% in the TRF group vs 26.4% in the DMF group (p = 0.7007). The confounder-adjusted percentage was 27.4% (95% CI 23.6%–31.4%) in the TRF group vs 27.1% (95% CI 24.1%–30.4%) in the DMF group. The corresponding OR for patients treated with DMF vs TRF was 0.98 (95% CI 0.77–1.27, figure 2). The same results were found after 2 years of follow-up as the confounder-adjusted percentage of patients with an increase in the EDSS level was 41.6% (95% CI 36.8%–46.6%) in the TRF group vs 40.6% (95% CI 36.8%–44.2%) in the DMF group. The corresponding OR for patients treated with DMF vs TRF was 0.96 (95% CI

Figure 2 Comparison of outcomes at 1 year



Forest plot summarizes the odds ratio obtained for comparison of dimethyl fumarate and teriflunomide (TRF) on clinical outcomes (relapses, Expanded Disability Status Scale [EDSS]), MRI outcomes (T2 lesions), no evidence of disease activity (NEDA), treatment withdrawal for lack of effectiveness, and treatment withdrawal for adverse events after 1 year. CI = confidence interval.

0.74–1.23, figure 3), confirming the absence of significant difference between the treatments.

MRI-based outcomes: Better control of MRI activity with DMF at year 2

Among the 1,770 patients of the main analysis, 935 patients were excluded because no MRI was performed at 1 year postinitiation. Compared to the 835 included patients, they had a longer disease duration, a higher exposure to previous DMTs, and a lower relapse rate within the year prior to initiation (table e-16, doi.org/10.5061/dryad.60tv071). This suggests, as expected, that patients with more active disease are more likely to have control MRIs after 1 or 2 years.

For this subgroup of 835 patients (cohort C1, figure 1), after weighting on the propensity scores, the confounder-adjusted percentage of patients with new T2 lesions was 46.9% (95% CI 41.3%–52.3%) in the TRF group vs 42.9% (95% CI 38.6%–47.1%) in the DMF group, showing a lack of significant difference (OR 0.85, 95% CI 0.64%–1.13%, figure 2).

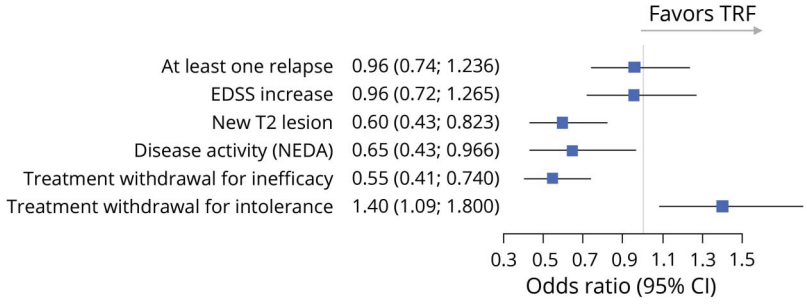
In the 2 years postinitiation, 1,015 patients were excluded because no MRI was performed and compared to the included patients (table e-17, doi.org/10.5061/dryad.60tv071), confirming more active disease in patients with a control MRI. The confounder-adjusted percentage of patients with new T2 lesions after 2 years was 72.2% (95% CI 66.8%–77.2%) in the TRF group vs 60.8% (95% CI 56.3%–65.3%) in the DMF group, showing a significant effect of DMF reducing the risk of new T2 lesions (OR 0.60, 95% CI 0.43–0.82, figure 3).

When comparing NEDA3 at 1 and 2 years postinitiation, similar results were found and explained by the difference observed in terms of risk of new T2 lesions after 2 years. After 1 year, the proportion of patients who reached NEDA3 was similar after weighting on the propensity scores (figure 2). After 2 years, the confounder-adjusted percentage of patients with active disease was 90.2% (95% CI 87.2%–92.9%) in the TRF group vs 85.6% (95% CI 82.9%–88.4%) in the DMF group, confirming the previous results on MRI measures (OR 0.65, 95% CI 0.43–0.95, figure 3).

Reasons for treatment withdrawals were different between TRF and DMF

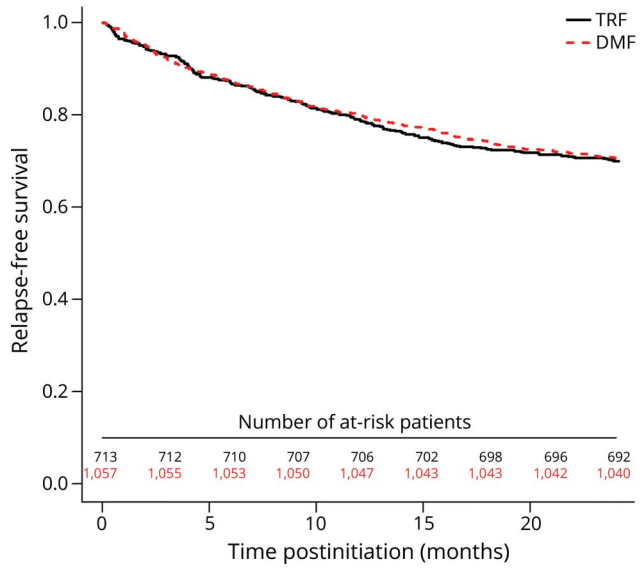
The analyses were performed on cohort A (figure 1), composed of 1,057 patients treated with DMF and 713 with TRF. As shown in table 2, the rate of treatment discontinuation was different in patients treated with TRF or DMF at 6 months and 1 year but similar at 2 years. However, the reasons for withdrawal were different for each treatment. The confounder-adjusted percentage of patients who stopped their treatment because of inefficacy at 1 year postinitiation was 5.8% (95% CI 4.0%–7.8%) in the TRF group vs 4.8% (95% CI 3.6%–6.1%) in the DMF group. The corresponding

Figure 3 Comparison of outcomes at 2 years



Forest plot summarizes the odds ratio obtained for comparison of dimethyl fumarate and teriflunomide (TRF) on clinical outcomes (relapses, Expanded Disability Status Scale [EDSS]), MRI outcomes (T2 lesions), no evidence of disease activity (NEDA), treatment withdrawal for lack of effectiveness, and treatment withdrawal for adverse events after 2 years. CI = confidence interval.

Figure 4 Time to first relapse in the 2 treatment groups



Confounder-adjusted survival curves of time to first relapse. The difference was not statistically significant (p = 0.7224, adjusted log-rank test). DMF = dimethyl fumarate; TRF = teriflunomide.

OR for patients treated with DMF vs TRF was 0.82 (95% CI 0.53–1.28, figure 2). Two years after treatment initiation, the confounder-adjusted percentage of patients who stopped their treatment due to inefficacy was 14.5% (95% CI 11.9%–17.3%) in the TRF group vs 8.5% (95% CI 7.0%–10.2%) in the DMF group, indicating a significantly lower percentage of patients stopping DMF after 2 years of treatment due to lack of effectiveness (OR 0.54, 95% CI 0.41–0.74, figure 3).

We also analyzed treatment withdrawals due to the presence of adverse events, as reported by patients and neurologists. The confounder-adjusted percentage of patients who stopped their treatment because of intolerance or side effects at 1 year postinitiation was 12.7% (95% CI 10.3%–15.2%) in the TRF group vs 16.6% (95% CI 14.3%–18.9%) in the DMF group, indicating that DMF was significantly less tolerated than TRF after 1 year (OR 1.37, 95% CI 1.04–1.81, figure 2). Up to 2 years postinitiation, this difference remains significant. More precisely, the confounder-adjusted percentage of patients who stopped their treatment because of intolerance or side effects was 16.0% (95% CI 13.4%–18.8%) in the TRF group vs 21.0% (95% CI 18.6%–23.6%) in the DMF group, with a corresponding OR of 1.39 (95% CI 1.09–1.81, figure 3).

Discussion

With the increasing number of available drugs for preventing relapses and disability progression, and the lack of head-to-head randomized controlled trials (RCTs) comparing their efficacy, neurologists and patients need good quality observational studies to make more informed choices. In this study, we chose to compare TRF and DMF in real-life settings, in a cohort of French patients followed prospectively with a standardized collection of data. By using a propensity score–based methodology, we studied different outcomes at 1 and 2 years postinitiation: 2 were related to the clinical activity (relapse and disability progression), 1 was related to the activity observed on MRI (new T2 lesions), and 1 was a composite measure of disease activity (the NEDA3 score including relapses, disability progression, and new T2 lesion) and the reasons for treatment withdrawal (inefficacy or intolerance/adverse events). Clinical outcomes were not significantly different in DMF- vs TRF-treated patients. By contrast, we found fewer new T2 lesions for DMF than TRF at 2 years postinitiation, correlating with the greater percentage of patients reaching NEDA3 in DMF-treated patients. In agreement, we also reported more frequent treatment withdrawals due to lack of effectiveness after 2 years for patients under TRF. However, a consequence of this higher effectiveness of DMF was a higher rate of treatment withdrawal because of side effects.

Five other studies compared TRF and DMF. The first one was a network meta-analysis of RCTs of the different molecules used for MS,[8] while 2 others were based on a US claims database.[9,10] The last ones were based on observational databases from neurologists in Germany[11] and Italy.[12] In all these studies, save the Italian one, the authors reported on a superior efficacy of DMF over TRF in relapse prevention. However, it is difficult to compare our results with these studies. In Boster et al.[9] and in Ontaneda et al.,[10] besides the fact that the characteristics of the US population differ from the French one, one can expect that their results were biased due to the lack of some confounders, such as the MRI data used to indicate TRF or DMF in clinical practice. Concerning the network meta-analysis from Hutchinson et al.,[8] the heterogeneity of the studies, as acknowledged by the authors, gives additional difficulties for the interpretation of the results. Moreover, this analysis is based on RCTs where the patients were highly selected and weakly representative of the population of patients with MS, as seen in real-life practice.[24] The number of patients in the studies based on observational data[11,12] is lower than in our work, with a shorter follow-up, and they were not able to correct MS activity with MRI at baseline. Finally, they also used propensity matching for statistical analyses, which has proven limitations.[23,25]

The strength of our study is based on the high number of patients included in the main analysis (n = 1,057 for DMF vs 713 for TRF). Moreover, we were able to take into account the MRI data both at baseline (as a confounding factor) and after 1 and 2 years (as an outcome in large subgroups). Indeed, as we previously reported in a similar study in MS comparing fingolimod to natalizumab, the MRI at baseline can be an important confounding factor.[26] This is also the case in this study: the percentage of patients with gadolinium enhancement on baseline brain MRI was higher in patients treated with DMF than TRF, probably explaining part of the indication bias.

Table 2 Characteristics of cohort A regarding analyses related to relapse, treatment discontinuation for inefficacy, treatment discontinuation for intolerance, and according to the treatment group

	Overall (n = 1,770), n (%)	TRF (n = 713), n (%)	DMF (n = 1,057), n (%)	*p* Value
Patient age at MS onset, y, mean (SD)	31.7 (9.7)	32.9 (9.8)	30.9 (9.5)	<0.0001
Patient age at initiation, y, mean (SD)	39.3 (10.7)	41.3 (10.8)	38.0 (10.5)	<0.0001
Male recipient	485 (27.4)	202 (28.3)	283 (26.8)	0.4713
Disease duration, y, mean (SD)	7.6 (7.4)	8.4 (7.8)	7.1 (7.0)	0.0003
Disease-modifying therapy before initiation	1,004 (56.7)	395 (55.4)	609 (57.6)	0.3560
Including interferon		237	369	
Glatiramer acetate		158	240	
EDSS level at initiation, mean (SD)	1.7 (1.3)	1.7 (1.3)	1.7 (1.2)	0.9885
Patients with relapse within the year before initiation	981 (55.4)	346 (48.5)	635 (60.1)	<0.0001
Patients with relapse within the 2 years before initiation	1,227 (69.3)	444 (62.3)	783 (74.1)	<0.0001
No. of relapses in the previous year, mean (SD)	0.72 (0.77)	0.60 (0.73)	0.80 (0.80)	<0.0001
No. of relapses in the 2 previous years, mean (SD)	1.03 (0.96)	0.88 (0.90)	1.14 (0.98)	<0.0001
Gadolinium-positive lesion on MRI at baseline	601 (34.0)	207 (29.0)	394 (37.3)	0.0003
Center with more than 50 included patients	1,612 (91.1)	653 (91.6)	959 (90.7)	0.5354
At least one relapse at 1 year postinitiation[a]	368 (20.8)	138 (19.4)	230 (21.6)	0.2214
At least one relapse at 2 years postinitiation[a]	527 (29.8)	200 (28.1)	327 (30.9)	0.1928
Treatment discontinuation at 6 months[a]	287 (16.2)	98 (13.7)	189 (17.9)	0.0206
Treatment discontinuation at 1 year[a]	474 (26.8)	168 (23.6)	306 (28.9)	0.0121
Treatment discontinuation at 2 years[a]	693 (39.2)	271 (38.0)	422 (39.9)	0.4180

Abbreviations: DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; TRF = teriflunomide.
[a] Postinitiation characteristics.

Nevertheless, the main limitation of our study is the number of patients with missing values for EDSS and MRI. On this particular issue, we chose EDSS and MRI data as secondary outcomes, as there was no central readout and no central quality control for MRI and no ascertainment of irreversible EDSS score. For each outcome, we compared the characteristics of included and excluded patients at the time of the treatment initiation. The consequences were a reduction of the sample size and selection bias. Specifically, baseline MRI was more likely performed in patients with active disease. Similarly, missing MRI data at 1 and at 2 years postinitiation was not random and also depended on disease activity. Another drawback in our study is the impossibility to study additional outcomes such as the annualized relapse rate or the annualized rate of new T2 lesions. To our knowledge, no validated IPW method has been proposed and the data collected in our cohort do not allow to precisely compute the person-time. Furthermore, the choice of treatment may depend on measures other than the ones collected at baseline. Therefore, one cannot exclude possible confounders that were not taken into account. For example, smoking could be relevant information for treatment response that is not collected in the database.[27] Finally, the follow-up was limited to 2 years postinitiation. A longer and more standardized follow-up would have been ideal to correctly perform time-to-event analyses and will be considered in future studies. Considering these weaknesses, interpretations of the results should be made with caution, particularly the lack of clinical difference observed between the 2 treatments after 1 and 2 years of use, which is probably restricted to the more active patients of the cohort and could not be extended to the whole cohort. The lack of statistical differences can be due to the reduced power of our study. Formal computation of the power is a methodologic issue when analyses are based on weighted propensity scores. However, we estimated the power equals 62%, based on a comparable 1:1 RCT based on 713 patients per group, aiming to detect a 5% absolute difference between percentage of patients with at least one relapse 1 year postinitiation in the TRF vs the DMF group with a type I error rate at 5%. We used a 5% threshold for the type I error rate, while we performed multiple comparisons. We did not correct this threshold, resulting in an increased risk to wrongly conclude a difference between the 2 treatments. Nevertheless, this risk is small considering the coherence of

the comparison results. For instance, at 2 years postinitiation, one can see that (1) the 2 clinical endpoints are not statistically different and (2) the endpoint based on MRI results and the endpoint based on treatment withdrawal due to inefficacy are in favor of DMF. The overall coherence of these results decreases the risk of false-negative or -positive statistical differences.

Finally, our cohort-based study found no significant differences between TRF and DMF in terms of clinical activity of the disease, but a better control of MRI activity while on DMF after 2 years. This result must be interpreted with caution, as the possible higher effectiveness of DMF must be counterbalanced with the higher rate of treatment withdrawal due to intolerance. Results obtained from a future comparative RCT will be complementary to the strengths and limitations of this study based on real-life data.

Acknowledgment

The authors thank Sita Shah for English corrections.

Study funding

Supported by Fondation ARSEP, CHU Nantes (Appel d'Offre Interne), and Association ANTARES. The French Observatoire of Multiple Sclerosis is supported by a grant provided by the French State and handled by the Agence Nationale de la Recherche, within the framework of the Investments for the Future program, under the reference ANR-10-COHO-002. The study was supported by West Neurosciences Network and Société Francophone de Sclérose en Plaques, Fondation ARSEP, and by Appel d'Offre Interne du CHU de Nantes.

Disclosure

D. Laplaud has received consulting and lecturing fees, travel grants, and unconditional research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, Sanofi Aventis, MedDay, and Teva Pharma. L. Barbin, R. Casey, and M. Debouverie report no disclosures relevant to the manuscript. J. De Sèze has received consulting and lecturing fees, travel grants, and unconditional research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, Sanofi Aventis, and Teva Pharma. D. Brassat reports no disclosures relevant to the manuscript. S. Wiertlewski has received consulting and lecturing fees and travel grants from Biogen, Genzyme, Novartis, Merck Serono, Roche, Sanofi, and Teva Pharma. B. Brochet reports grants from French Ministry of Health, personal fees, and nonfinancial support from Biogen, grants from Merck, personal fees and nonfinancial support from Novartis, personal fees and nonfinancial support from Genzyme, grants, personal fees, and nonfinancial support from Teva, and grants and nonfinancial support from Bayer, outside the submitted work. J. Pelletier has received consulting and lecturing fees, travel grants, and unconditional research support from Biogen, Genzyme, Novartis, MedDay, Merck Serono, Roche, Sanofi Aventis, and Teva Pharma. P. Vermersch has received honoraria and consulting fees from Biogen, Sanofi-Genzyme, Novartis, Teva, and Merck. Gilles Edan has received consultancy and lecturing fees from Bayer-Schering, Biogen, LFB, Merck, Novartis, Roche, and Sanofi; research grants from Bayer, Biogen, Genzyme, Merck, Novartis, Roche, Teva, and the ARSEP Foundation; and has been principal investigator in phase 2 and 3 clinical studies conducted by Bayer, Biogen, Merck, Novartis, Sanofi-Aventis Teva, and 4 academic programs (Programmes Hospitaliers de Recherche Clinique) on MS sponsored by Rennes University Hospital. C. Lebrun-Frenay received fees for consulting or lectures from Biogen, Merck, MedDay, Roche, and Novartis. Pierre Clavelou received honoraria and traveling fees from Merck, Biogen, Roche, MedDay, Novartis, Genzyme, Teva, and Novartis. E. Thouvenot has received consulting and lecturing fees, travel grants, or unconditional research support from the following pharmaceutical companies: Actelion, Biogen, Genzyme, Merck Serono, Novartis, Roche, and Teva Pharma; has a patent pending for biomarkers of neurodegeneration and neuroregeneration; and received academic research support from PHRC and ARSEP Foundation. J. Camdessanché reports no disclosures relevant to the manuscript. A. Tourbah has received consulting and lecturing fees, travel grants, and research support from MedDay and Biogen. Bruno Stankoff has received consulting and lecturing fees and travel grants from Biogen Idec, Merck-Serono, Novartis, and Genzyme, and unconditional research support from Merck-Serono, Genzyme, and Roche. A. Al-Khedr and P. Cabre report no disclosures relevant to the manuscript. C. Lubetzki received fees for consultancy from Roche, Genzyme, Biogen, EMD-Serono, and Vertex; acted as PI (not coordinator) for trials (in MS) from Roche, Novartis, and Biogen; and received grants from EMD-Serono, Vertex, and Biogen. C. Papeix received conferences and consulting fees from Biogen, Merck, Novartis, Roche, and Sanofi-Genzyme. Eric Berger has received research support from Biogen and honoraria and consulting fees from Novartis, Sanofi Aventis, Biogen, Genzyme, Roche, and Teva Pharma. O. Heinzlef received consulting and lecturing fees from Bayer Schering, Merck, Teva, Genzyme, Novartis, Almirall, and Biogen; travel grants from Novartis, Teva, Genzyme, Merck Serono, and Biogen Idec; and research support from Roche, Merck, and Novartis. T. Debroucker has received fees as scientific adviser from Biogen and Novartis. T. Moreau has received fees as scientific adviser from Biogen, MedDay, Novartis, Genzyme, and Sanofi. O. Gout has received in the last year consulting and lecture fees, travel grants, and research support from Biogen Idec, Novartis, MedDay, Merck-Serono, Sanofi, and Teva Pharma. B. Bourre has served on a scientific advisory board for Biogen, Genzyme, Merck Serono, Novartis, and Roche and has received funding for travel and honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Roche, and Teva. A. Wahab reports no disclosures relevant to the manuscript. P. Labauge has received consulting and lecturing fees, travel grants, and unconditional research support from Biogen, Genzyme, Novartis, Merck Serono, Roche, and Teva Pharma. L. Magy has received consulting, lecturing fees, or travel grants from Biogen, Novartis, Merck, Roche, Teva, MedDay, CSL Behring, LFB, Grifols, Alnylam, and Pharnext. G. Defer received

personal compensation for a scientific advisory board from Biogen, Novartis, Genzyme, Merck-Serono, and Teva, and has received funding for travel and/or speaker honoraria from Merck Serono, Biogen, Sanofi-Genzyme, Novartis, and Teva. His institution received grants supporting research in his department from Merck Serono, Biogen, Genzyme, and Novartis. A. Guennoc received fees for consulting or lectures from Biogen, Merck, Sanofi-Genzyme, and Roche. N. Maubeuge reports no disclosures relevant to the manuscript. C. Labeyrie received consulting and lecturing fees from Biogen, Novartis, and Genzyme. I. Patry has received honoraria and consulting fees from Novartis, Genzyme, and Roche, research support from Biogen and Novartis, and travel grants from Genzyme, Novartis, and Roche. C. Nifle reports no disclosures relevant to the manuscript. O. Casez has received honoraria or travel grants from Biogen, Merck, Novartis, Roche, and Genzyme. L. Michel received honoraria from Biogen, Merck Serono, Novartis Pharma, Sanofi Genzyme, and Roche. F. Rollot reports no disclosures relevant to the manuscript. E. Leray reports consulting and lecture fees or travel grants from Biogen, Genzyme, MedDay Pharmaceuticals, Merck, Novartis, and Roche. S. Vukusic has received grants, personal fees, and nonfinancial support from Biogen; grants and personal fees from Geneuro; grants, personal fees, and nonfinancial support from Genzyme; grants and personal fees from MedDay; grants, personal fees, and nonfinancial support from Merck-Serono; grants, personal fees, and nonfinancial support from Novartis; grants, personal fees, and nonfinancial support from Roche; grants, personal fees, and nonfinancial support from Sanofi; and personal fees from Teva, outside the submitted work. Y. Foucher reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* November 10, 2018. Accepted in final form April 10, 2019.

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Appendix 2 *(continued)*

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Neurology 2019;93;e635-e646 Published Online before print July 12, 2019
DOI 10.1212/WNL.0000000000007938

This information is current as of July 12, 2019

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