Published Ahead of Print on June 6, 2018 as 10.1212/WNL.0000000000005772

ARTICLE CLASS OF EVIDENCE

Fingolimod vs dimethyl fumarate in multiple sclerosis

A real-world propensity score-matched study

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Neurology® 2018;0:1-9. doi:10.1212/WNL.0000000000005772

Abstract

Objective

To directly compare fingolimod (FNG) and dimethyl fumarate (DMF) on no evident disease activity (NEDA) status in patients with relapsing-remitting multiple sclerosis (RRMS) from 7 multiple sclerosis outpatient clinics in Central Italy.

Methods

We analyzed data of patients with RRMS who started an oral agent, namely DMF or FNG, either as first treatment (naives) or after switching from self-injectable drugs (switchers). We performed a propensity score (PS)–based nearest-neighbor matching within a caliper of 0.05 to select patients with homogeneous baseline characteristics. Pairwise censoring was adopted to adjust for difference in length of follow-up between the 2 treatment groups. Comparisons were then conducted in matched samples with Cox models (stratified by center) with NEDA-3 as the main outcome. NEDA-3 was defined as no relapses, no disability worsening, and no MRI activity.

Results

Overall, 483 and 456 patients eligible for analysis started on FNG and DMF, respectively. The PS-matching procedure retained a total of 550 patients (275 per group). After a median on-study follow-up of 18 months, the proportions of patients with NEDA-3 were similar (FNG 73%, DMF 70%; hazard ratio [HR] 0.74, $p = 0.078$). Subgroup analyses showed a comparable effectiveness of the 2 drugs in naives (n = 170, HR 1.15, $p = 0.689$), whereas FNG was superior to DMF in the achievement of NEDA-3 status among switchers (n = 380, HR 0.57, $p = 0.007$).

Conclusion

We found no significant difference between FNG and DMF on NEDA-3 status, while subgroup analyses suggest the superiority of FNG over DMF in patients switching from self-injectable drugs.

Classification of evidence

This study provides Class IV evidence that for patients with RRMS, DMF and FNG have comparable efficacy in treatment-naive patients and that FNG is superior to DMF in patients switching from self-injectable drugs.

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Glossary

CONFIRM = Efficacy and Safety Study of Oral BG00012 With Active Reference in Relapsing-Remitting Multiple Sclerosis; **DEFINE** = Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS; **DMF** = dimethyl fumarate; **EDSS** = Expanded Disability Status Scale; **FNG** = fingolimod; **FREEDOMS** = Fingolimod Research Evaluating Effects of Daily Oral Treatment in Multiple Sclerosis; **Gd** = gadolinium; **HR** = hazard ratio; **MS** = multiple sclerosis; **NEDA** = no evident disease activity; **PS** = propensity score; **RCT** = randomized clinical trial; **RRMS** = relapsing-remitting multiple sclerosis; **TRANSFORMS** = Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis.

Fingolimod (FNG) and delayed-release dimethyl fumarate (DMF) are 2 oral drugs approved for relapsing-remitting multiple sclerosis (RRMS) on the basis of large phase 3 randomized clinical trials (RCTs) showing their efficacy in reducing relapse rate, disability worsening, and MRI activity over placebo.[1–3] In addition, the 12-month head-to-head Trial Assessing Injectable Interferon Versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS) trial showed that FNG was superior to intramuscular interferon beta-1a in reducing relapse rate and MRI activity, namely new or enlarged T2-hyperintense lesions and gadolinium (Gd)-enhancing lesions.[4] Somewhat consistently, a post hoc analysis of the Efficacy and Safety Study of Oral BG00012 With Active Reference in Relapsing-Remitting Multiple Sclerosis (CONFIRM) trial (which included both active comparator and placebo arms) suggested that DMF was superior to glatiramer acetate in reducing the number of new or enlarging T2-hyperintense lesions over 24 months.[5]

Both drugs are rarely associated with serious adverse events such as opportunistic infections, including 19 cases of progressive multifocal leukoencephalopathy in 225,000 FNG-treated patients and 5 cases in 271,000 DMF-treated patients without prior exposure to natalizumab (Novartis data on file, Biogen data on file). Other remarkable safety concerns are herpetic infections, first-dose bradycardia, macular edema, and skin neoplasms for FNG, as well as leukopenia and lymphopenia for DMF. In terms of the tolerability profile, these 2 drugs are quite different. Data from 24-month clinical trials showed that FNG was well tolerated (7.5% of patients discontinued because of tolerability problems), while DMF was associated with flushing and gastrointestinal events, although often transient, causing treatment discontinuation in 12% to 16% of cases.[1,2]

Despite FNG and DMF being approved by the European Medicines Agency for different indications, in clinical practice, both drugs are prescribed as first- and second-line treatments.[6,7] Therefore, a comparison of their effectiveness in the real-world setting is warranted. Indirect comparisons based on data from pivotal RCTs provided conflicting results.[8–10] Real-world data on direct comparisons, although scarce, suggest comparable effectiveness of FNG and DMF in terms of clinical activity and that FNG is better tolerated than DMF.[11–14] However, no postmarketing study has investigated so far which of the 2 drugs is more effective in achieving the no evident disease activity (NEDA-3) status, defined as absence of relapses, disability worsening, and MRI activity.[15] For this purpose, in this study, we sought to directly compare the effectiveness of FNG and DMF in a large cohort of Italian patients with RRMS using NEDA-3 status as the main outcome measure.

Methods

Study design

This was an independent, multicenter, postmarketing study. We retrospectively analyzed data of patients affected by RRMS[16] who regularly attended 7 tertiary multiple sclerosis (MS) outpatient clinics in Central Italy (S. Andrea Hospital, S. Camillo-Forlanini Hospital, Policlinico Umberto I, Policlinico "A. Gemelli," Policlinico Tor Vergata, S. Filippo Neri Hospital, Rome; IRCCS Neuromed, Pozzilli-IS). Clinical and MRI data were prospectively collected by each MS center following the local medication monitoring plan and hospital guidelines and then stored in an ad hoc electronic database for this study (see above).

Standard protocol approvals, registrations, and patient consents

All data were gathered after approval by local ethical committees and informed consent was obtained from each participant. This study was conducted in accordance with specific national laws and the ethics standards laid down in the 1964 Declaration of Helsinki and its later amendments. In no way this study did interfere in the care received by patients.

Participants

We considered data of patients with RRMS who started FNG or DMF as first treatment (naives) or were switched from self-injectable drugs (switchers), namely interferon beta or glatiramer acetate. Included patients had at least 1 relapse in the year before starting FNG or DMF; had no previous exposure to immunosuppressants, monoclonal antibodies, or oral disease-modifying drugs; underwent a brain MRI scan within 1 month of FNG or DMF being started; and had a minimum 3-month persistence on DMF and FNG. The minimum 3-month on-treatment persistence was decided on the basis of a phase 2b trial showing that the reduction in Gd-enhancing lesion activity became statistically significant by 12 weeks after the initiation of DMF treatment.[17] Moreover, other postmarketing real-world data adopted a 3-month threshold as the minimal follow-up time to compare different drugs in patients with RRMS.[18]

We excluded data from those patients who received the first treatment prescription by 1 of the 7 participating MS centers but continued follow-up elsewhere (they were defined as lost to follow-up).

Follow-up assessments

Despite the multicenter study design, monitoring and management of patients with RRMS on disease-modifying treatment are highly homogeneous in Central Italy as a result of a consensus statement reached by stakeholders, including local health authorities, clinicians, health care professionals, patients, and health foundations.[19]

For each patient, clinical visits were scheduled at least every 6 months after the start of treatment and included disability scoring with the Expanded Disability Status Scale (EDSS)[20] performed by certified neurologists (neurostatus.net). Each patient underwent brain and spinal cord MRI scans at baseline (within 1 month before starting FNG or DMF) and at least every 6 months according to standardized procedures using 1.5T magnets.[21] Scans were performed before and after Gd-diethylenetriamine pentaacetic acid with <5-mm slice thickness and included axial T2 (proton density)-weighted fast spin echo, fluid-attenuated inversion recovery sequences, and T1-weighted spin echo post–Gd administration sequences (for brain imaging), and sagittal and axial T2-weighted fast spin echo, T2-short tau inversion recovery, and T1-weighted spin echo post–Gd administration sequences (for spinal cord imaging).[21]

Both preplanned clinical examinations and MRI scans were collected after 1 month of clinical stability and at least 30 days after the last steroid treatment. Unscheduled visits or MRI scans were also performed in case of relapse or any other clinically relevant condition, including adverse events.

Outcome measure definition

As the primary outcome, we estimated the proportions of patients who reached the NEDA-3 status, a combined measure defined as the absence of clinical relapses, disability worsening, and radiologic activity.[15] NEDA has recently been proposed as a main aim in the management of patients with RRMS because it leads to better long-term outcomes.[22,23] We also analyzed each subcomponent of disease activity as secondary outcomes (time to relapse, disability worsening, radiologic activity).

A relapse was defined as any new neurologic symptom not associated with fever or infection lasting for at least 24 hours and accompanied by new neurologic signs.[16]

Disability worsening was defined as 1.5-point increase (if baseline EDSS score was 0), 1.0-point increase (if baseline EDSS score was <5.5), or 0.5-point increase (if baseline EDSS score was ≥5.5) confirmed 6 months apart.[24] Patients whose disability worsening started over the last few months of the preplanned observational period had an additional follow-up to confirm that the outcome was reached.

Radiologic activity was defined as the occurrence of Gd-enhancing lesion on T1-weighted images or new hyperintense lesions on T2-weighted images (compared to the baseline scan) after the fluid-attenuated inversion recovery and short tau inversion recovery sequences for brain and spinal cord, respectively, were checked. We ignored enlarging T2-hyperintense lesions because a previous study demonstrated a poor between-rater agreement for this metric under routine clinical setting.[25]

Data harmonization

In October 2016, clinicians from each MS center participated a workshop in Rome, where a shared electronic spreadsheet for data storage was drawn up after selection of the core data to be analyzed. In February 2017, data were centrally reviewed and checked for consistency by the first 2 authors. The more experienced authors from each MS center jointly reviewed MRIs with doubtful radiologic activity to further reduce discrepancies between sites.

Statistical analysis

Patient characteristics collected at baseline were the following: sex, age, time since first symptom, EDSS score, relapses in the previous year, absence/presence of Gd enhancement, and treatment history (naives or switchers).

Differences in baseline characteristics between the FNG and DMF groups were tested with the Fisher exact test or the Mann-Whitney *U* test as appropriate. Because patients were not randomized to treatment group, we performed a 1:1 matching procedure using a combination of exact matching on previous treatment history (i.e., naives vs switchers) and propensity score (PS)–based nearest-neighbor matching within a caliper of 0.05 (without replacement).[26] Individual PS values were estimated by use of logistic regression with the aforementioned baseline characteristics as covariates and treatment group as the dependent variable. The validity of PS-based matching was tested by analysis of standardized differences (|d|), with |d| > 0.20 considered an imbalance,[27] and with the paired McNemar test or Wilcoxon rank-sum test. Pairwise censoring was adopted to adjust for difference in length of follow-up between the 2 treatment groups; i.e., we right-censored at the shorter individual follow-up periods within each pair.[28] This procedure allowed us to exclusively select patients with similar baseline characteristics and to obtain a comparable follow-up length for each pair. Pairwise censored comparisons were then conducted in matched samples with Cox proportional hazards regression models stratified by center. The length of observation (in months) from baseline to the last available visit or when the outcome was reached (whichever came first) was entered into models as main time variable. The presence of any disease activity (the counterpart of NEDA-3) and of its subcomponents was entered as the primary and secondary outcome, respectively.

To investigate the influence of treatment history on the effectiveness of the 2 drugs, subgroup analyses were also conducted by rerunning all the time-to-event analyses in the naive and switcher subgroups separately.

Postestimation sensitivity analyses, according to the Greenland method, were applied to primary outcome in the whole resampled population and in the subgroups of naives and switchers to test the sensitivity of the matched models to a hypothetical confounder that was either not collected or incompletely observed.[29,30]

All 2-tailed values of $p < 0.05$ were considered significant without correction for multiple comparisons considering the exploratory study design. Data were analyzed with the Statistical Package for Social Sciences, version 16.0 (IBM SPSS, Inc, Chicago, IL).

Data availability

Anonymized data will be shared on request from any qualified investigator.

Results

Participants

From February 2011 to February 2017, a total of 1,347 and 1,089 patients started FNG and DMF, respectively. Of them, 483 on FNG and 456 on DMF were eligible for data analysis, after the exclusion of 796 on FNG and 625 on DMF who did not meet eligibility criteria and additional 68 patients on FNG and 8 on DMF who were lost to follow-up (figure 1).

In the FNG-treated group, reasons for exclusion were previous exposure to monoclonal antibodies (n = 385), other oral drugs (n = 185), or immunosuppressants (n = 128) and baseline MRI scan not available or not acquired within 1 month from the start of treatment (n = 98). In the DMF-treated group, reasons for exclusion were no relapse in the prior year (n = 385) (these were patients who switched to DMF because of tolerability problems); previous exposure to either other oral drugs (n = 86), monoclonal antibodies (n = 66), or immunosuppressants (n = 38); and baseline MRI scan not available or not acquired within 1 month from the start of treatment (n = 50).

Patients excluded from the analysis were older, had a longer time since first symptom, and had fewer pretreatment relapses than those included, regardless of the treatment group ($p < 0.01$).

Figure 1 Study flowchart of patient disposition

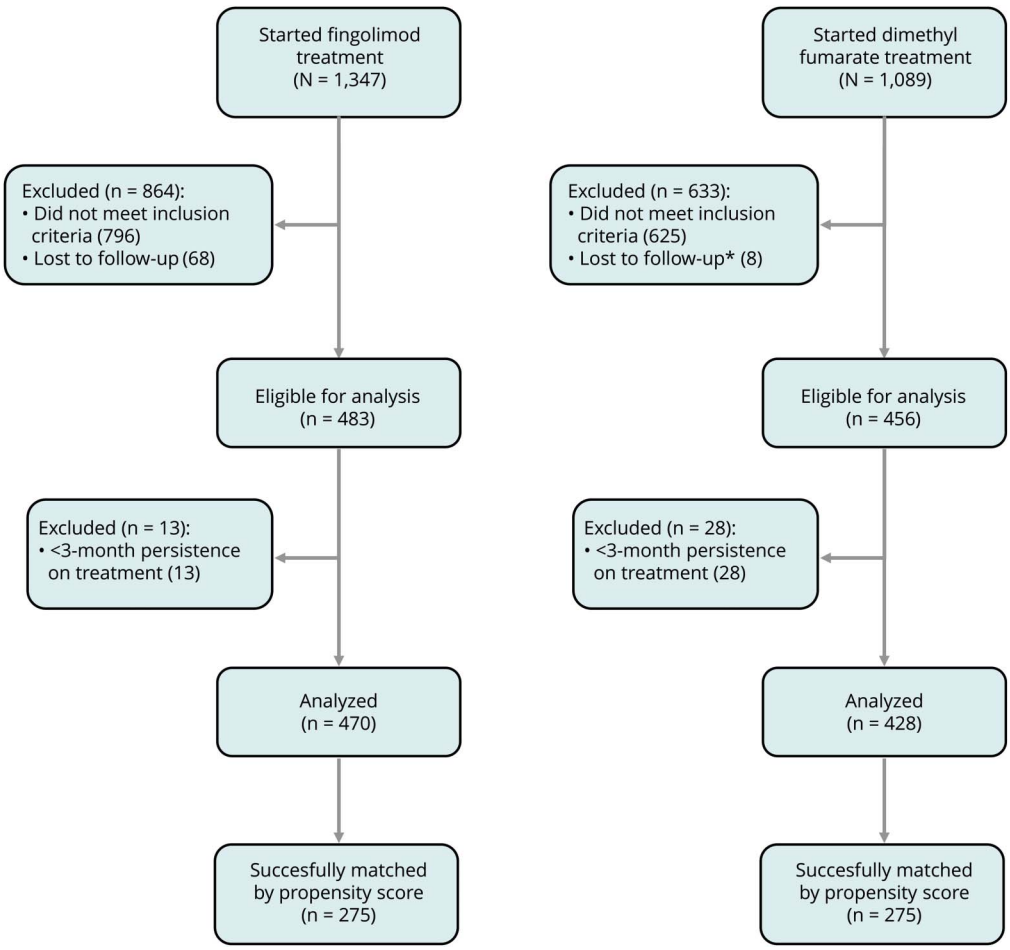


Table 1 Reasons for premature (i.e., <3 month) discontinuation of treatment

	Fingolimod (n = 13), n	Dimethyl fumarate (n = 28), n
Lack of tolerability	0	20
Pregnancy	0	3
Early severe relapse	0	1
Adverse events		
Cardiovascular disorders	4	0
Leukopenia	4	0
Liver enzyme increase	3	3
Dyspnea	2	0
Skin rash	0	1

Premature discontinuation

Even if eligible, we excluded from the main analysis 13 FNG-treated (3%) and 28 DMF-treated (6%) patients ($p = 0.01$ by the Fisher exact test) because of treatment discontinuation within 3 months. Reasons for premature treatment discontinuation were in line with the safety and tolerability profile of the 2 drugs (table 1). When we consider the whole study cohort at baseline, there were no significant differences between patients who prematurely stopped treatment compared to the rest of the sample. However, patients prematurely discontinuing DMF had worse baseline EDSS score ($p = 0.03$) and were more likely to be women ($p = 0.06$).

Analysis of the resampled population

The matching procedure involved data from 470 patients on FNG and 428 on DMF with a median follow-up duration of 30 (interval 6–79) months and 18 (interval 4–51) months, respectively.

The contribution of each participating MS center is shown in table e-1, links.lww.com/WNL/A575. The treatment history of patients included in the data analysis is reported in table e-2.

There was a significant imbalance in prematching baseline characteristics across treatment groups due to the lower EDSS score, fewer pretreatment relapses, and active MRI scans in DMF group ($p \leq 0.001$; table 2). This between-group imbalance did not persist after the matching procedure that retained a total of 550 patients (275 per group). No covariate exhibited large imbalance ($|d| < 0.20$), and the standardized mean difference of PS values decreased from 1.88 to 0.06 (97%), indicating a significant improvement in the overall match (figure 2). The median on-study follow-up duration was 18 (interval 6–36) months for both groups after the pairwise censoring.

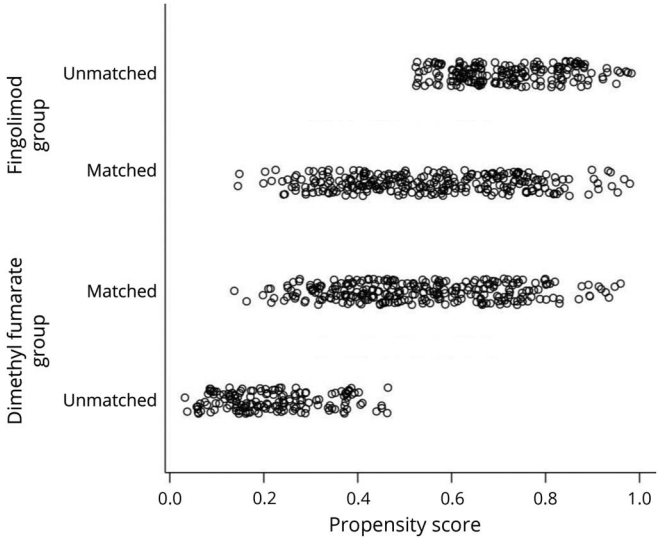
At follow-up, the proportions of patients with NEDA-3 were 73% in FNG group and 70% in DMF group (hazard ratio [HR] 0.74, $p = 0.078$) (figure 3A). Proportions of relapse-free patients did not differ between the 2 groups (88% in the FNG group and 86% in the DMF group; HR 0.69, $p = 0.152$). The risk of disability worsening was lower in the FNG group than the DMF group (96% and 91%, respectively, were free of disability worsening; HR 0.39, $p = 0.011$). Proportions of patients without MRI activity did not differ between the 2

Table 2 Baseline characteristics of the included patients before and after the matching procedure

	Unmatched cohort			Matched cohort		
	Fingolimod	Dimethyl fumarate	|d|	Fingolimod	Dimethyl fumarate	|d|
No.	470	428	N/A	275	275	NA
Male sex, n (%)	148 (31.5)	138 (32.2)	N/A	90 (32.7)	88 (32.0)	NA
Age, y	36.3 (9.5)	37.2 (10.6)	0.17	36.5 (9.3)	37.2 (10.6)	0.13
Time since first symptom, y	7.2 (6.3)	7.5 (8.0)	0.08	8.1 (6.1)	8.4 (8.1)	0.08
EDSS score, median (interval)	2.0 (0–7.0)[a]	1.5 (0–7.0)[a]	1.25	2.0 (0–7.0)	2.0 (0–7.0)	0.06
Relapses in previous year, n	1.48 (0.68)[a]	1.21 (0.46)[a]	0.87	1.34 (0.58)	1.32 (0.53)	0.07
Presence of Gd enhancement, n (%)	350 (74.5)[a]	224 (52.3)[a]	N/A	180 (65.5)	173 (62.9)	NA
Treatment naive, n (%)	135 (28.7)[a]	213 (49.8)[a]	N/A	85 (30.9)	85 (30.9)	NA
Propensity score	0.588 (0.165)[a]	0.452 (0.176)[a]	1.88	0.532 (0.164)	0.527 (0.161)	0.06
Follow-up, median (interval), mo	30 (6–79)[a]	18 (3–51)[a]	2.70	18 (6–36)	18 (6–36)	0

Abbreviations: Gd = gadolinium; NA = not applicable.
All values are reported as mean (SD) unless indicated otherwise. |d| Refers to standardized difference (Cohen *d*).
[a] Reported significant difference at a 2-sided α level <0.05 (between-group differences were tested by the Fisher exact and Mann-Whitney *U* tests in the unmatched cohort and by the McNemar and Wilcoxon rank-sum tests in the matched cohort).

Figure 2 Distribution of propensity scores before and after the matching procedure



groups (78% in the FNG group and 79% in the DMF group; HR 0.88, $p = 0.524$).

Subgroup analyses

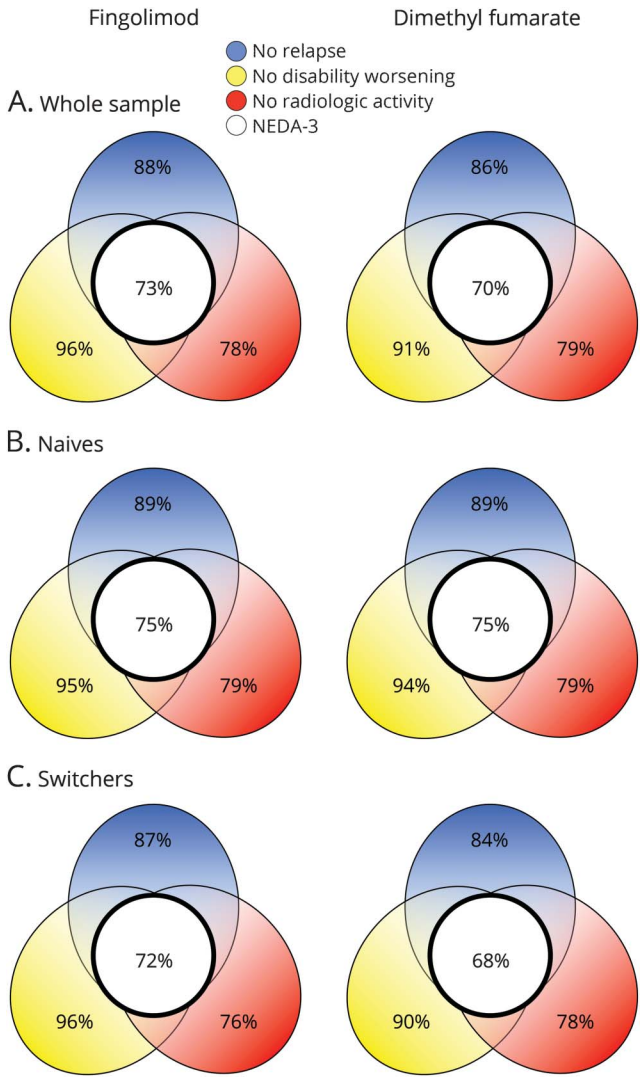
The resampled cohort accounted for 170 naives and 380 switchers.

All baseline variables were well balanced between the FNG- and DMF-treated patients even among subgroups of naives and switchers (table e-3, links.lww.com/WNL/A575).

In the naive subgroup (median length of follow-up 18 months, range 6–36 months), comparable effectiveness between FNG and DMF was found for the primary and secondary outcomes: proportions of patients with NEDA-3 were 75% for both FNG and DMF (HR 1.15, $p = 0.689$); proportions of relapse-free patients were 89% for both FNG and DMF (HR 1.11, $p = 0.842$); proportions of disability worsening–free patients were 95% for FNG and 94% for DMF (HR 0.74, $p = 0.677$); and proportions of MRI activity–free patients were 79% for both FNG and DMF (HR 1.07, $p = 0.845$) (figure 3B).

In the switcher subgroup (median length of follow-up 18 months, range 6–36 months), FNG was superior to DMF in the achievement of NEDA-3 status (72% in the FNG group and 68% in the DMF group; HR 0.57, $p = 0.007$), relapse risk reduction (relapse-free patients: 87% in the FNG group and 84% in the DMF group; HR 0.52, $p = 0.028$), and disability worsening risk reduction (disability worsening–free patients: 96% in the FNG group and 90% in the DMF group; HR 0.33, $p = 0.014$). However, the effectiveness of FNG and DMF did not differ for MRI activity outcome (MRI activity–free patients: 79% in the FNG group and 76% in the DMF group; HR 0.75, $p = 0.241$) (figure 3C).

Figure 3 Proportions of patients achieving the NEDA-3 status and its subcomponents at follow-up in the resampled study cohort



(A) Whole sample; (B) naives; and (C) switchers. NEDA-3 = no evident disease activity.

Table 3 summarizes the main study findings in the resampled whole cohort and subgroup analyses. The proportions of patients with NEDA-3 at 12 and 24 months, with analysis of its subcomponents, are shown in table 4.

Sensitivity analysis

Given the nonsignificant difference between FNG and DMF in the primary outcome (NEDA-3), we did not conduct any sensitivity analysis in either the whole resampled population (n = 550) or the naive subgroup (n = 170). In the switcher subgroup (n = 380), the relative risk estimate and between-group prevalence imbalance of a hypothetical unmeasured binary confounder should be either >1.1% and 40% or >1.2% and 20%, respectively, to alter the significant difference in the proportions with NEDA-3 between FNG and DMF.

Table 3 Cox regression models (stratified by MS center) to reach the primary and secondary outcomes in the resampled study cohort

	Whole sample (n = 550)			Naives (n = 170)			Switchers (n = 380)		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
NEDA-3	0.74	0.53–1.03	0.078	1.15	0.59–2.52	0.689	0.57	0.38–0.86	0.007[a]
No relapse	0.69	0.42–1.14	0.152	1.11	0.40–3.05	0.842	0.52	0.29–0.93	0.028[a]
No disability worsening	0.39	0.19–0.80	0.011[a]	0.74	0.19–2.95	0.677	0.33	0.13–0.80	0.014[a]
No radiologic activity	0.88	0.60–1.29	0.524	1.07	0.52–2.19	0.845	0.75	0.46–1.21	0.241

Abbreviations: CI = confidence interval; HR = hazard ratio; MS = multiple sclerosis; NEDA-3 = no evident disease activity.
HRs <1.0 favor fingolimod.
[a] Reported significant difference at a 2-sided α level <0.05.

Discussion

We conducted a PS-based matched analysis to compare the effectiveness of FNG and DMF in a real-world setting. We also performed a subgroup analyses in naive patients and in those who were switched to FNG or DMF from self-injectable drugs to provide suggestions about the "place in therapy" of these 2 drugs.

The main finding of our study is that the short-term (median follow-up 18 months) probability of NEDA-3 (≈70%) was similar for patients taking FNG and DMF. However, the PS-matched survival analysis revealed an effect in favor of FNG over DMF (HR 0.74) on NEDA-3 status, with a statistical significance approaching the predefined α level ($p = 0.078$). A previously published indirect comparison of currently available oral drugs for MS (FNG, DMF, and teriflunomide), based on sophisticated statistical modeling of data from pivotal RCTs, reported a higher probability of achieving the NEDA status with FNG than with DMF in both unadjusted and adjusted analyses.[8] These discrepancies are considered somehow expected given the different research settings (experimental vs real world) and statistical methods (indirect vs direct) applied to compare the 2 drugs.

The analysis of the subcomponents of NEDA-3 status did not reveal a significant difference between DMF and FNG on relapses and MRI activity. On the other hand, we found a greater proportion of FNG-treated (96%) than DMF-treated (91%) patients who were free from disability worsening ($p = 0.011$). This finding partially conflicts with several indirect comparison analyses showing no difference between FNG and DMF on disability worsening[9,10] and could be explained by the shorter follow-up in our study. We may also speculate about FNG being more effective than DMF in limiting the severity of earlier relapses. This latter hypothesis

Table 4 Proportion of patients achieving the NEDA-3 status and its subcomponents at 12 and 24 months of follow-up in the resampled study cohort

	NEDA-3		No relapse		No disability worsening		No radiologic activity	
	At 12 mo	At 24 mo	At 12 mo	At 24 mo	At 12 mo	At 24 mo	At 12 mo	At 24 mo
Whole sample (n = 550), %								
Fingolimod	77	66	90	83	98[a]	92[a]	82	70
Dimethyl fumarate	77	62	90	81	94[a]	87[a]	83	72
Naives (n = 170), %								
Fingolimod	80	68	93	82	98	91	84	72
Dimethyl fumarate	81	70	92	85	97	89	83	75
Switchers (n = 380), %								
Fingolimod	75	65[a]	89	84[a]	98[a]	93[a]	81	69
Dimethyl fumarate	75	58[a]	89	79[a]	93[a]	86[a]	83	72

Abbreviation: NEDA-3 = no evident disease activity.
Censored individuals are excluded from the denominator at the point when they are censored.
[a] Reported significant difference at a 2-sided α level <0.05 (by the McNemar test).

is supported by a significant risk reduction of relapses leading to hospitalization observed in Fingolimod Research Evaluating Effects of Daily Oral Treatment in Multiple Sclerosis (FREEDOMS) but not in Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS (DEFINE) or CONFIRM.[9] Moreover, the number needed to treat for preventing a relapse requiring intravenous steroid administration was 5 in FREEDOMS and 7 in both DEFINE and CONFIRM.[8] Our study is also in line with recently published real-world data collected in a US tertiary care MS center showing FNG to be more effective than DMF in motor disability, as measured by the 25-ft walking test over a 24-month follow-up period.[14]

Our subgroup analyses revealed a similar effectiveness of FNG and DMF on NEDA-3 and its subcomponents in naive patients, with FNG being a better option for patients who switched from a self-injectable drug. In this latter subgroup, FNG-treated patients had a 43% increased likelihood of achieving NEDA-3 status in the short-term period. This result was driven more by the greater effectiveness of FNG on relapses and disability worsening than by the effect on MRI activity. These findings are somewhat in line with post hoc analyses of the 2 pivotal RCTs.[31,32] Treatment effect of FNG was consistent across different subgroups of patients,[31] whereas DMF was more efficacious in patients who were treatment naive than in those switching from other drugs, especially in terms of annualized relapse rate and disability worsening.[32]

The safety and tolerability profiles of the 2 drugs differed considerably, leading to a premature discontinuation rate of 3% and 6% in FNG group and DMF group, respectively. Patients were more likely to discontinue FNG early for adverse events, including those occurring during the first dose administration (i.e., bradyarrhythmias), leukopenia, and increased liver enzymes. In contrast, the most common reasons for early DMF discontinuation were gastrointestinal symptoms (nausea and diarrhea) and flushing. Our data are in line with previous RCTs in which 7.5% of FNG-treated patients and 12% to 16% of DMF-treated patients discontinued treatment during a 24-month follow-up[1,3,5] and with extension[33,34] and postmarketing studies.[11–14,35]

The present study was preplanned by a spontaneous network initiative among MS tertiary outpatient clinics in Central Italy that provided a consistent amount of patient data and ensured the checking of data quality. However, even if clinical data were collected at regular 6-month intervals for EDSS scoring, we cannot exclude a certain degree of between-center variability in the density of clinical visits per year. Moreover, brain and spinal cord MRIs were acquired at different sites without any central readout of MRI data. We are confident that stratification by MS center might have minimized these potential clinical and MRI data discrepancies.

Our study suffers from other drawbacks due mainly to its observational postmarketing design, namely the small sample size (especially for subgroup analyses), comparison of patients in different treatment eras (FNG was available before DMF), and lack of randomization. Although our statistical approach (based on PS matching and pairwise censoring) allowed us to compare data of patients with similar baseline characteristics and the same follow-up, we cannot overcome limitations of selection and hidden biases.[26,30]

Lastly, we can provide only short-term data (median follow-up 18 months) because FNG and DMF were available for prescription in Italy in 2011 and 2015, respectively. Therefore, we had to censure the length of follow-up at the shorter observation period for each PS-derived pair of treatments, according to a pairwise censoring approach, to control for potential attrition bias.[28]

We provide Class IV evidence that the short-term likelihood of achieving the NEDA-3 status is not affected by starting FNG or DMF, especially in treatment-naive patients with RRMS. However, FNG seems to be more effective than DMF when prescribed to patients failing previous self-injectable drugs. Although the present study should be considered only hypothesis generating, our findings may provide additional information to help neurologists in selecting the most appropriate treatment according to different stages of disease.

Author contributions

L.P.: study design, statistical analysis, and manuscript drafting. M.L., S.H., A.B., P.B., M.C.B., F.B., A.C., L.D.G., R.F., E.F., A. Fornasiero, V.N., S.P., S.R., E.S.: data collection and manuscript drafting. D.C., S.G., A. Francia, C.G., G.A.M., E.M., C.P., M.S., M.M.: study design and data interpretation.

Study funding

No targeted funding reported.

Disclosure

L. Prosperini: consulting fees from Biogen, Novartis, and Roche; speaker honoraria from Biogen, Genzyme, Merck Serono, Novartis, and Teva; travel grants from Biogen, Genzyme, Novartis, and Teva; research grants from the Italian MS Society (Associazione Italiana Sclerosi Multipla) and Genzyme. M. Lucchini and S. Haggiag report no disclosures relevant to the manuscript. P. Bellantonio: funding for travel or speaker honoraria from Biogen, Novartis, and Sanofi-Genzyme. A. Bianco reports no disclosures relevant to the manuscript. M. Buscarinu: advisory board membership and honoraria for speaking from Teva, Novartis, Sanofi, Merck Serono, and Biogen. F. Buttari: advisory board membership for Teva and Merck Serono; honoraria for speaking or consultation fees from Almirall, Biogen Idec, Genzyme, Merck Serono, Novartis, Teva. D. Centonze: advisory board membership for Almirall, Bayer Schering, Biogen, Genzyme, GW Pharmaceuticals, Merck-Serono, Novartis, and Teva; honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen Idec, Genzyme, GW Pharmaceuticals, Merck Serono, Novartis, Sanofi, and Teva; principal investigator in clinical trials for Bayer Schering, Biogen Idec, Merck Serono, Mitsubishi,

Novartis, Roche, Sanofi, and Teva; preclinical and clinical research supported by grants from Bayer, Biogen, Merck Serono, Novartis, and Teva. A. Cortese: honoraria for speaking and travel grants from Biogen, Sanofi-Genzyme, and Teva. L. De Giglio: travel grants from Biogen, Novartis, and Teva. R. Fantozzi: honoraria for speaking or consultation fees from Almirall, Merck Serono, Novartis, Sanofi, Teva, and Biogen; advisory board membership for Teva, Biogen, Merck Serono, and Novartis. E. Ferraro: advisory board membership and/or travel grants from Merck Serono, Sanofi-Genzyme, and Teva. A. Fornasiero: advisory board membership for or honoraria for speaking from Novartis and Teva. A. Francia reports no disclosures relevant to the manuscript. S. Galgani: fees as invited speaker or travel expenses for attending meeting from Biogen, Merck-Serono, Teva, Almirall, Sanofi-Aventis, Novartis, and Genzyme. C. Gasperini: fees as invited speaker or travel expenses for attending meeting from Biogen, Merck-Serono, Teva, Sanofi, Novartis, and Genzyme. G. Marfia: advisory board membership for Biogen, Genzyme, Merck-Serono, Novartis, and Teva; honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, and Teva; principal investigator in clinical trials for Actelion, Biogen Idec, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi, and Teva. V. Nociti: honoraria for speaking, advisory board, consulting from Teva, Genzyme, Almirall, Biogen, Bayer Schering, Merck, and Novartis. S. Pontecorvo: honoraria for speaking from Almirall, Biogen, Teva, and Genzyme; travel grants from CSL Behring, Genzyme, Novartis, Teva, and Kedrion. C. Pozzilli: scientific advisory boards for Actelion, Biogen, Genzyme, Hoffmann-La Roche Ltd, Merck Serono, Novartis, Sanofi, and Teva; consulting and/or speaking fees, research support, and travel grants from Allergan, Almirall, Biogen, Genzyme, Hoffmann-La Roche Ltd, Merck Serono, Novartis, Sanofi, and Teva. S. Ruggieri: speaking honoraria from Merck Serono and Teva. M. Salvetti: consulting fees and/or honoraria for speaking and/or research grants from Biogen, Genzyme, Merck Serono, Novartis, Roche, and Teva. E. Sgarlata reports no disclosures relevant to the manuscript. M. Mirabella: scientific advisory board membership for Bayer Schering, Biogen, Sanofi-Genzyme, Merck Serono, Novartis, and Teva; consulting and/or speaking fees, research support, or travel grants from Almirall, Bayer Schering, Biogen, CSL Behring, Sanofi-Genzyme, Merck Serono, Novartis, Teva, and Ultragenix; principal investigator in clinical trials for Biogen, Merck Serono, Novartis, Roche, Sanofi Genzyme, Teva, and Ultragenix. Go to Neurology.org/N for full disclosures.

Received November 8, 2017. Accepted in final form April 6, 2018.

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Fingolimod vs dimethyl fumarate in multiple sclerosis: A real-world propensity score-matched study

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Neurology published online June 6, 2018
DOI 10.1212/WNL.0000000000005772