Dimethyl fumarate *vs.* fingolimod in multiple sclerosis: an independent, multicentre, real world, quasi-randomized study

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INTRODUCTION

Fingolimod (FNG) and delayed-release dimethyl fumarate (DMF) are two approved oral drugs for relapsing-remitting multiple sclerosis (RRMS) based on large phase III randomized clinical trials (RCTs) showing their efficacy in reducing relapse rate, disability worsening and magnetic resonance imaging (MRI) activity over placebo.

Although FNG and DMT have a different indications according to European Medicines Agency guidelines, in clinical practice both drugs are prescribed as first and second line treatments. However, real world data reporting direct comparison of their effectiveness are still scarce.

Therefore, in this tsudy we aimed to directly compare the effectiveness of DMF and FNG in achieving the No Evidence of Disease Activity (NEDA-3) status, defined as absence of relapses, disability worsening and magnetic resonance imaging activity.

METHODS

We analyzed data of patients with RRMS regularly attending 7 MS Clinics in Central Italy and who started DMF or FNG as first treatment (naïves) or were switched from a self-injectable drugs (switchers). Included patients had at least one relapse in the year prior to DMF or FNG start; had no previous exposure to immunosuppressants, monoclonal antibodies or oral disease-modifying drugs; underwent a brain MRI scan in a span of one month as FNG or DMF were started; had a minimum 3-month persistence on DMF and FNG.

Since patients were not randomized to treatment group, we performed a propensity score (PS)-based nearest neighbour matching within a calliper of 0.05 to select only patients with similar baseline characteristics.

Pairwise comparisons were then conducted in matched samples using a Cox proportional hazards model (stratified by Centre) with the NEDA-3 as main outcome. Pairwise censoring was adopted to adjust for difference in length of follow-up among the two treatment groups.

RESULTS

From 2011 to 2017, a total of 1,347 and 1,089 patients with RRMS started FNG and DMF, respectively. Of them, 483 on FNG and 464 on DMF were eligible for data analysis **[FIG. 1]**.

We excluded from the analysis 13 FNG-treated (3%) and 36 DMF-treated (8%) patients, because of treatment discontinuation within 3 months (p=0.001); main reasons for discontinuation were adverse events for FNG and poor tolerability for DMF.

There was significant imbalance in pre-matching baseline characteristics across treatment groups (FNG=483, DMF=464), due to the lower EDSS score, fewer pre-treatment relapses and active MRI scans in DMF group (p-values< 0.001) [**TABLE 1**].

Such between-group imbalance did not persist after the PS-based 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.

After a median on-study follow-up of 18 months, 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 two drugs in naïves (n=198; HR=1.15, p=0.689), whereas FNG was superior to DMF in the achievement of NEDA-3 status among switchers (n=352; HR=0.57, p=0.007) [**FIG. 2**].

CONCLUSIONS

Our study provides real world evidence that DMF is as effective as FNG in naïves, while FNG would be a better option for achieving NEDA-3 status in RRMS patients switching from self-injectable drugs.

FIG. 1. Study flow-chart of patient disposition.

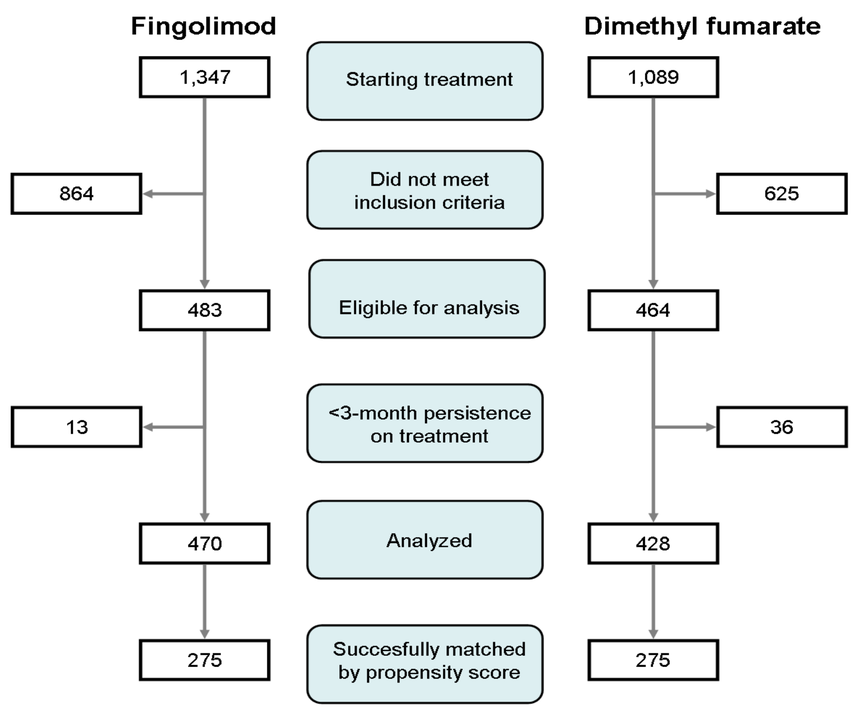
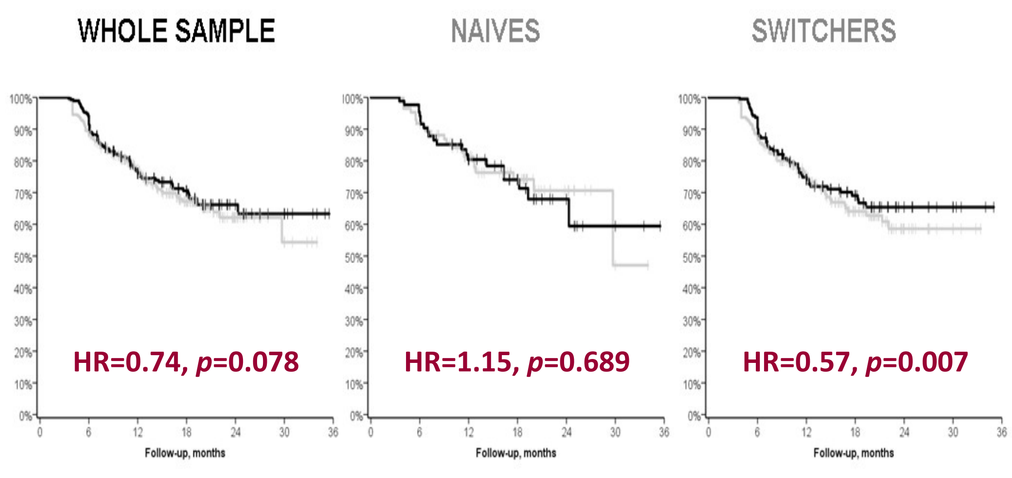


TABLE 2. Baseline characteristics of the included patients before and after the matching procedure.

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

|d|>0.2 were considered as significant imbalance

FIG. 2. Kaplan-Meier curves showing the proportions of patients with NEDA-3 over time.



HR<1.0 favors fingolimod (black lines) over dimethyl fumarate (grey lines)

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