Safety, tolerability and effectiveness of dimethyl fumarate in multiple sclerosis: an independent, multicenter, realworld study.

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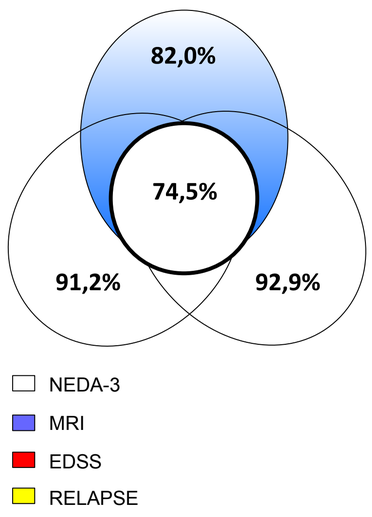
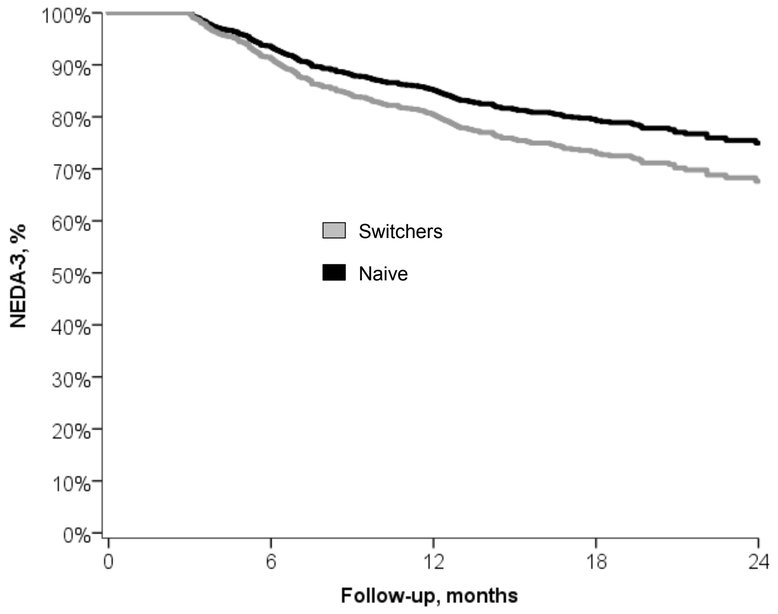
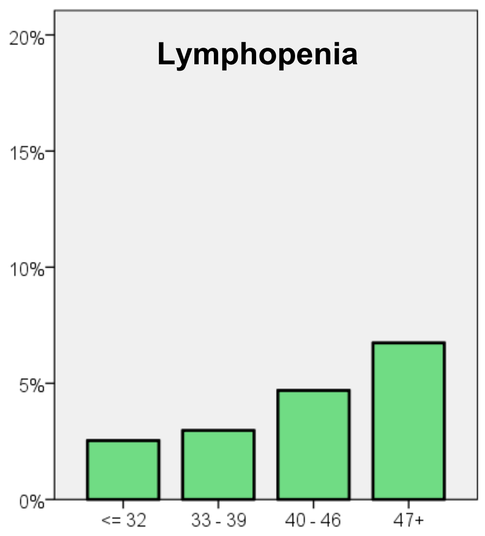
Background. Delayed-release dimethyl fumarate (DMF) exerts significant effects on clinical and radiological disease activity in patients with relapsing-remitting multiple sclerosis (RRMS), as demonstrated in two large phase III trials. However, data on its effectiveness in real-world practice are still scarce.

Objectives. (i) To explore the safety and tolerability profile of DMF; (ii) to estimate the proportion of DMF-treated patients who achieved the no evidence of disease activity (NEDA-3) status; (iii) to identify individual variables associated with a better outcome.

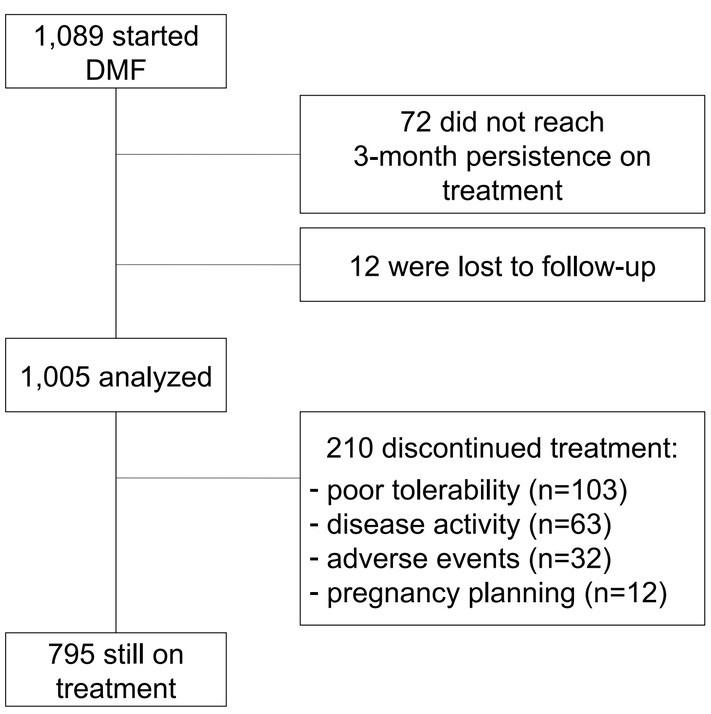
Methods. We collected clinical and MRI data of patients with RRMS regularly attending 7 MS Clinics in Central Italy and who started DMF from October 2012 to February 2017. First, we explored the reasons for discontinuing DMF. Second, the proportion of patients with NEDA-3 (defined as absence of relapses, disability worsening and radiological activity) was estimated in patients with a minimum 3-month persistence on treatment; this threshold was based on the phase IIb trial showing a significant radiological effect of DMF at 12 weeks after its initiation. Third, a Cox proportional hazards model (stratified by Centre) was carried out to investigate which baseline (i.e. at treatment start) variables were associated with the NEDA status at follow-up.







Main side effects	
Flushing	45,5% (n 495)
Gastro-intestinal symptoms	30,2% (n 329)
Diarrhea	15,8% (n 172)



Baseline Features	
Age	38,92 (17-70) (y)
Sex	70,16% (F)
Disease duration	9,59 (0-40) (y)
EDSS	1,95 (0-7)
Relapse	0,55 (0-2)
Gad+	0,67 (0-10)
Naive	30,40%

Reason for DMT discontinuation		
Efficacy	257	33,9%
Tolerability	385	50,8%
Pregnancy	20	2,6%
Safety	83	10,9%
Not specified	13	1,7%

Results. We collected data of 1,089 patients with a mean on-treatment follow-up of 16+/-8 months. Of them, 331 (30.4%) were treatment-naives, while the remaining patients were switched from self-injectable drugs (n=580), oral drugs (n=102), natalizumab (n=64), or other treatments (n=12). A total of 210 (19.3%) patients discontinued DMF for the following reasons: poor tolerability (n=103); disease activity (n=63); adverse events (n=32); pregnancy planning (n=12). Twelve patients who were lost to follow-up and 72 who did not reach the minimum 3-month persistence on DMF were removed from further analyses. At follow-up, 749/1005 (74.5%) patients achieved the NEDA-3 status. The risk of not achieving the NEDA-3 status was associated with younger age (HR=0.97, p<0.001), higher EDSS score (HR=1.18, p<0.001), greater number of Gd-enhancing lesions at baseline scan (HR=1.14, p=0.003) and prior exposure to MS treatments (HR=1.43, p=0.02).

Discussion. This preliminary post-marketing experience provides new insights about the short-term safety, tolerability and effectiveness profile of DMF supporting its use as an early treatment strategy.

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