Dimethyl fumarate safety, tolerability and efficacy: two-year real life analysis in Northern-Italy

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OBJECTIVES

To track and evaluate two-year post-marketing Dimethyl fumarate (DMF) safety, tolerability and efficacy profile in Northern-Italy real word setting

METHODS

Between January 2015 and January 2017 we enrolled patients starting DMF in 9 MS Centres located in Lombardy, Piedmont and Veneto. Patients were prospectively followed, collecting demographic and clinical data as well as laboratory assessment.

RESULTS

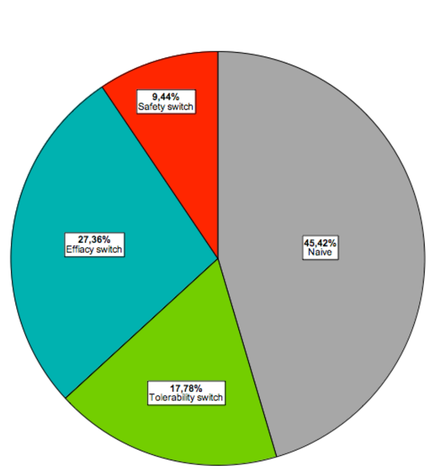
We included 720 relapsing remitting MS patients who started DMF. Three hundred and twenty-seven (45.4%) were naïve to treatment, three hundred and twenty-five switched to DMF from first line treatment due to loss of tolerability (40%) or inefficacy (60%). Sixty-eight (9.4%) switched to DMF from II line treatments because of safety concerns **figure 1**.

Most frequent adverse events (AEs) were flushing (37.2%), gastro-enteric side effects (31.1%), and eczema (1%). Only 5 severe AEs were reported (malignancies). Most frequent laboratory testing abnormalities were lymphopenia (18.7%, none grade III or IV) and ALT increase (1.8%). The odds of DMF withdrawing were about 2.5 times higher when patients were affected by gastro-enteric AEs (OR 2.30 95%CI 1.62-3.26) and about 2 times in patients with lymphocytopenia (OR 2.06 95%CI 1.38-3.07) **figure 2**.

The survival analysis showed that about 83% and 75% of patients were relapse free at 12 and 24 month, respectively. The corrected Cox model showed that patients switched because of efficacy displayed an increased risk of relapse vs naïve patients (hazard ratio of 1.56; IC 95% 1.04-2.35); and that patients switched due to safety had an increased risk of relapse vs naïve patients (hazard ratio of 3.05, IC 95% 1.82-5.09). DMF treatment reduced significantly the annual relapse rate (ARR) to 0.18 ± 0.47 ($p<0.0001$). In the subgroup of patients with 2 years follow up, DMF reduced the ARR both at 12 and 24 months in every patients group ($p<0.0001$) **figure 3**.

During the follow up, one hundred and eighty-four patients (29.9%) discontinued DMF; among them, the main cause of treatment withdrawal was the presence of side effects (64%) **figure 4**.

Sex F/M	478/242
Age (years)	38.8 ± 10
Previous use of DMT (n)	1 (1-8)
MS duration (years)	9.8 ± 8.2
Annual relapse rate (2years before DMF start)	0.49 ± 0.53
EDSS	2 (0-6.5)
MSSS	3.05 ± 2.08
Follow up (months)	17 (0-40)



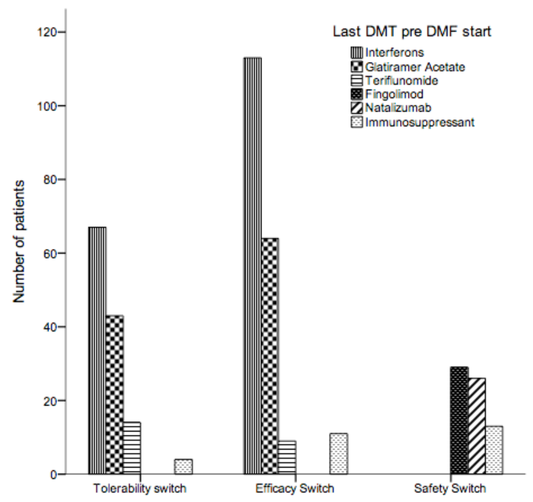
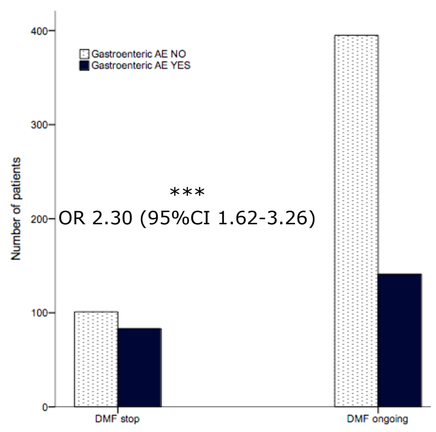


Figure 1. The table on the left reports demographical and clinical patients baseline characteristics; the pie graph in the middle represents the reason of DMF start; the bar graph on the right reports the last DMTs before the switch to DMF.

	n
Flushing/rush	268
Gastro-enteric AEs	224
Lymphocytopenia	135
Eczema	25
Headache	7
Arthralgia	7
Fatigue	6
Malignancies	5
Herpes Zoster	3
Others	30



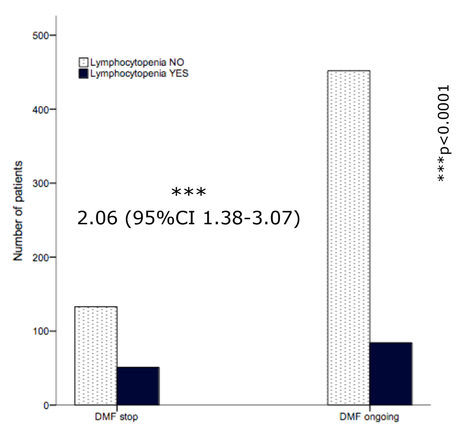
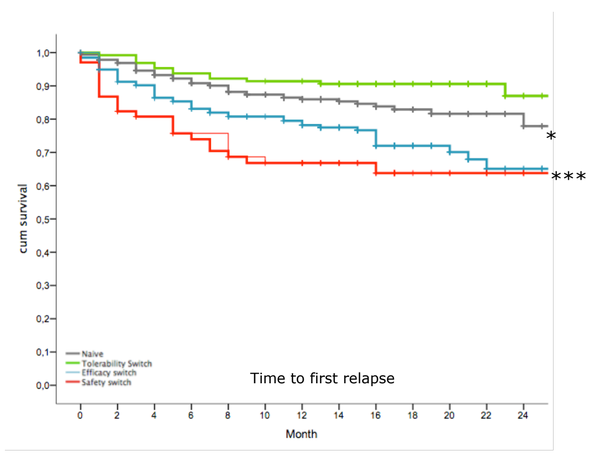
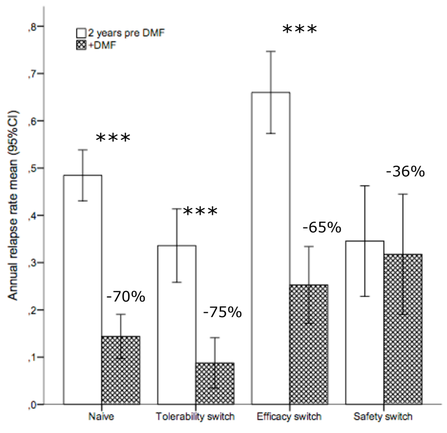


Figure 2. The table on the left reports AEs during DMF; the bar graphs show that patients with gastro-enteric AEs (in the middle) or lymphocytopenia (on the right) have a significantly increased risk of DMF stop compared to patients with no gastro-enteric AEs or normal lymphocytes.





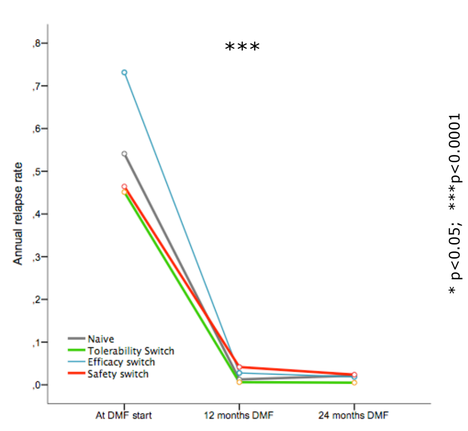
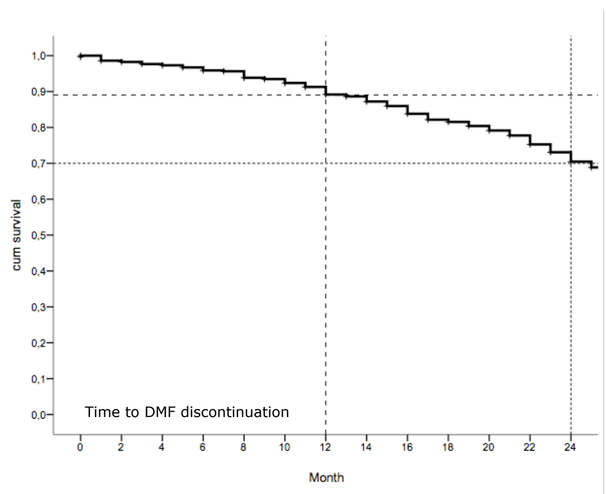


Figure 3. The Kaplan Meier curve on the left shows the time to first relapse during the follow up categorized by the reason of DMF start. Hazard ratio to first relapse is significantly increased in patients switched because of efficacy and safety vs naïve patients . The bar graph in the middle reports the ARR before and after DMF in the four different patient type group. The bar graph on the right displays the ARR during the time for patients with at least two years of follow up (manova, $p<0.0001$).



	Hazard ratio	IC 95% min-max
Relapse free (y)	0.60	0.43-0.83
Any adverse event (y)	2.76	1.89-4.02
Age at DMF start	1.027	1.01-1.04
Tolerability switch (vs naïve)	0.49	0.31-0.79

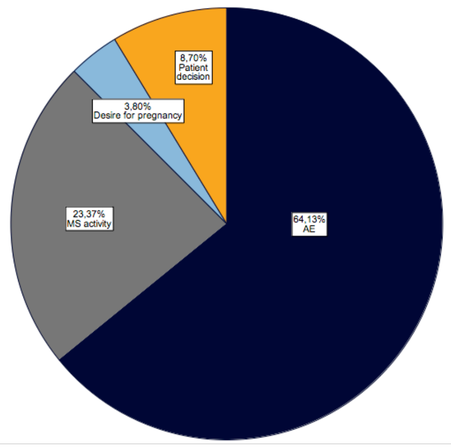


Figure 4: The Kaplan Meier curve on the left shows that at 12 months about 90% of patients were on DMF and at 24 moths 70% of patients were still on DMF. DMF drop out is significantly favorite by relapse, AEs, older age and patient's type. The pie graph on the right shows the causes of DMF discontinuation.

CONCLUSIONS

Although the frequency of some AEs (such as flushing and gastrointestinal side effects) was mildly higher than that reported in previous studies, our observational data confirm the good tolerability and safety profile of DMF, as well as its efficacy in reducing ARR