Multiple Sclerosis and Related Disorders 38 (2020) 101871

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Clinical predictors of Dimethyl Fumarate response in multiple sclerosis: a real life multicentre study

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ARTICLE INFO

Keywords:
Dimethyl-fumarate
Multiple sclerosis
Real life
Efficacy
Persistence

ABSTRACT

Background: Dimethyl-fumarate (DMF) was effective and safe in relapsing–remitting multiple sclerosis (MS) in randomized clinical trials. We aimed to evaluate the efficacy and safety of DMF and factors related to drug response in real-life setting.

Methods: We analysed prospectively collected demographic and clinical data for patients treated with DMF in six multiple sclerosis (MS) centers from 2015 to 2017 in Campania region, Italy. We performed univariate and multivariate analyses to assess relationships between baseline parameters and DMF efficacy outcomes, Annualized Relapse Rate (ARR), Expanded Disability Status Scale (EDSS) progression and No Evidence of Disease Activity (NEDA-3) status.

Results: we analyzed data of 456 patients (67% female subjects, mean age 40 ± 12 years, mean disease duration 9 ± 9 years, mean treatment duration 18 ± 11 months, median EDSS 2.5, 0–8). Proportion of Naïve versus pretreated with other DMTs patients was 149/307 (32.7%), with 122 patients switching to DMF for disease activity (26.7%) and 185 for safety and tolerability issues (40.6%).

During treatment with DMF, the annualized relapse rate was reduced by 75% respect to the pre-treatment ARR [incidence-rate-ratio (IRR) = 0.25, $p < 0.001$, CI 0.18–0.33]. Factors influencing ARR rate while on DMF were relapsing remitting (RR) MS course (IRR = 2.0, $p = <0.001$, CI 1.51–2.73) and previous DMTs status: de-escalating from second-line therapies was associated to higher risk of relapsing (IRR = 1.8, $p < 0.001$, CI 1.39–2.31). At multivariable Cox proportional hazard model, only age of onset was related with rate or relapses, with younger age being protective (HR 0.96, $p = 0,02$). EDSS remained stable in 88% of patients. Disease duration was associated with higher rate of NEDA-3 failure, that was instead maintained in 65% of patients at 24 months. 109 patients (22%) discontinued therapy after a mean of 1.1 ± + 0.7 years. Reasons for DMF discontinuation over time were lack of efficacy (50%), safety issues (30%), tolerability (7%), poor compliance (7%), and pregnancy (4%). Higher pre-treatment EDSS was associated with DMF discontinuation ($p = 0.009$). Only 33 patients dropped out due to safety reasons (7%), the most frequent safety issues driving to drop out being lymphopenia, liver/pancreatic enzymes increase, gatrointestinal severe tolerability issues. We recorded 95 cases (24%) of lymphopenia: 60 grade I (13%), 31 grade II (7%) and 4 grade III (1%).

Conclusions: We confirm that DMF shows a good efficacy in both naïve patients and patients switching from other first-line DMTs, especially in patients with early onset of disease. Higher baseline EDSS was a risk factor for

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https://doi.org/10.1016/j.msard.2019.101871
Received 9 May 2019; Received in revised form 8 September 2019; Accepted 24 November 2019

discontinuing DMF therapy, while shorter disease duration was protective for both EDSS progression and NEDA-3 status maintenance.

1. Introduction

In recent years, therapeutic options for relapsing remitting (RR) Multiple Sclerosis (RR-MS) have largely increased. The European Medicines Agency and the Italian regulatory agency has classified Disease Modifying Therapies (DMTs) as first- or second-line, according to the risk/benefit profile found in clinical trials (European Medicines Agency (EMA) 2016, European Medicines Agency (EMA) 2016).

Dimethyl fumarate (DMF) was approved as a first-line treatment for RRMS and available for patients in Italy since 2014. The efficacy and the safety profile of DMF was investigated in randomized clinical trials (RCTs) (Fox et al., 2012, Gold et al., 2012) and in extended studies (Gold et al., 2017). RCTs are the gold standard for establishing efficacy, safety and tolerability profile for new drugs; however, they operate in a controlled environment, and include a limited and highly selected population. Post-marketing real-world studies, conducted on general population in a real-world setting, provide additional data about efficacy and safety for the specific drug. In particular, real-world data are more representative of the MS population than RCTs; they contribute to our knowledge about the use of novel drugs and help identifying patients that will benefit the most from selected treatments (Trojano et al., 2017). Since there are no clear predictors of efficacy based on patients' baseline characteristics, therapy choice depends mainly on personal attitude towards single DMTs, patients' preferences, and co-existing comorbidities (Zhang et al., 2016, Laroni et al., 2017). In Campania Region several real life studies have already been conducted (Iolascon et al., 2013, Menditto et al., 2018, Menditto et al., 2017) and, building on this experience, we obtained real-world data on DMF use in MS specialized Campania centers, to analyze possible predictors of efficacy, providing evidence for MS neurologists in daily clinical practice.

2. Methods

2.1. Study design and data acquisition

This is a retrospective analysis on prospectively collected data, involving 6 MS centers from the Campania region of Italy. We included all MS patients who started on DMF according to clinical practice between January 2015 and December 2017. The centers were required to provide a minimum dataset for each patient, which included demographic data (i.e. gender and date of birthday), history of MS [i.e. MS onset date, number of relapses, MS course, annual relapse rate (ARR) 2 years before DMF start, and expanded disability status scale (EDSS) at DMF onset)], date of DMF start, previous DMTs, date of last DMT prescription and reason of switch, adverse events (AEs) during DMF treatment and clinical outcomes (i.e. number of MS relapses, ARR, EDSS). Patients were classified as naïve if never treated before, or on ``no therapy'', when untreated for at least 12 months before DMF. MS course was defined as RR or Progressive Relapsing (PR), when patients experienced both relapses and relapses- independent disease progression (Lublin and Reingold, 1996).

Additional information included MRI outcomes, such as date of MRI, presence of gadolinium-enhancing T1 lesions and new or enlarging T2 lesions in comparison with the previous MRI. Data were collected during the follow-up according to clinical practice.

NEDA-3 (No Evidence of Disease Activity) status was calculated (Giovannoni et al., 2017) in patients who had performed at least a baseline brain MRI and an MRI >300 days afterwards. In detail, NEDA-3 status was determined by its three components: (i) no 12 weeks confirmed disability progression (CDP), (ii) no relapse activity, and (iii) no radiological activity. The 12 weeks CDP was defined as (i) ≥ 1.5-point increase if EDSS = 0 at baseline, or (ii) ≥ 1.0-point increase if EDSS = 0.5–5 at baseline, or (iii) ≥ 0.5-point increase if EDSS > 5.0 at baseline. EDSS collected during MS relapses (± 30 days) were excluded from the analysis. Relapse activity was defined as new or recurrent neurological symptoms not associated with fever or infection lasting for ≥24 h and accompanied by new neurological signs. Radiological activity was defined as the appearance of contrast-enhancing lesions, or new or enlarging T2-hyperintense lesions, compared with the previous scan.

The study was conducted in accordance with specific national laws and the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Given its observational design, in no way this study did interfere with the care received by patients.

2.2. Statistical analysis

Characteristics of the study population were presented using descriptive statistics. Mean and standard deviation (SD) values were calculated for continuous variables, whilst frequencies were reported for categorical variable. Subgroups of patients were characterized in 3 groups by different reasons of DMF start: (i) naïve, (ii) switch to DMF due to tolerability or safety concerns (tolerability switch); (iii) switch to DMF due to inefficacy with previous DMT (efficacy switch). Efficacy of DMF was evaluated analyzing (i) ARR, (ii) time to first relapse from the beginning of the therapy, (iii) CDP, and (iv) time to exiting NEDA-3.

Information about NEDA-3 was available only for a sub-sample of the study population (207 subjects corresponding to 45% of the whole sample). Therefore, we conducted a missing pattern analysis employing a logistic regression model to assess whether demographic and clinical variables might have been associated with presence of missing data. The multivariable model was corrected for sex, age of onset, MS course, previous DMTs status (naïve, first line, second line), and MS center. Considering that in the multivariable model no variable was statistically associated with the missing for NEDA, we concluded that missing data was missing completely at random, which might reduce the risk of biased results when conducting complete-case analyses.

A multivariable multinomial logistic regression model was employed to assess the association between demographic and clinical characteristics and entering the DMF treatment as naive, switch for efficacy, or switch for tolerability. Covariates inserted in the model were age at onset, sex, disease duration (years), pre-treatment DMT, MS course, ARR pre-treatment, EDSS pre-treatment, age at DMF therapy start. Analyses were further adjusted for MS center to reduce variability across centers. Analyses were repeated considering only those who switched therapy (due to efficacy or tolerability) and in this case a multivariable logistic regression model was performed. Similarly, a multivariable logistic regression model was also employed to assess demographic and clinical characteristics associated with dropping DMF therapy over the follow-up. The multivariable model was corrected for all the aforementioned covariates but EDSS pre-treatment; change of EDSS (considering EDSS at treatment start and at last follow-up), and ARR post-treatment were also included in the model.

A multivariable logistic regression model was employed to assess association between demographic and clinical characteristics and CDP. Multivariable Cox proportional hazard model was employed to model predictors of relapse rate and of exiting NEDA-3 status. Analysis for NEDA-3 status was conducted considering the complete-case sample. Covariates included in the model were age at diagnosis, sex, disease duration before DMF start, MS course, ARR pre-treatment, EDSS pre-treatment, and previous DMTs status before DMF. The logistic regression model was also adjusted for follow-up period (in months). Analyses

were further adjusted for MS center to reduce variability across centers.

Finally, a mixed-effect Poisson regression model was employed to model difference in the ARR before and after the beginning of the therapy. The model was corrected for sex, age at onset, MS course, EDSS, DMTs status before DMF, and MS center. Years was included as off-set in the model. To reduce variability, analyses were repeated considering only number of relapses in the two years before and two years after commencing the therapy.

3. Results

We included 494 patients. After excluding incomplete or censored records, we analyzed the records of 456 patients, whose demographic and clinical characteristics at DMF start (67% female subjects, mean age 40 ± 12 years, mean disease duration 9 ± 9 years, mean treatment duration 18 ± 11 months, median EDSS 2.5, 0–8) are summarized in Table 1.

Proportion of Naïve versus pretreated with other DMTs patients was 149/307 (32.7%), with 122 patients switching to DMF for disease activity (26.7%) and 185 for safety and tolerability issues (40.6%).

Fifty-six out of 456 (12%) of included patients switched to DMF after a ``second line" treatment (31 patients from natalizumab and 25 patients from fingolimod). Reason for ``de-escalating" to DMF was efficacy in 16% (3% for natalizumab and 32% for fingolimod treated patients) and tolerability in 85% (97% in natalizumab, mainly for JCV positivity, and 68% in fingolimod treated patients).

As compared with naive patients, those who switched to DMF due to efficacy were more likely to have younger age at onset (Adjusted Odds Ratio (AOR) = 0.95, 0.92–0.98), lower pre-treatment ARR (AOR = 0.82, 0.71–0.95), with a higher pre-treatment EDSS (AOR = 1.39, 1.08–1.78). Patients who switched due to tolerability issues were more likely to have younger age at onset (AOR = 0.96, 0.93–0.99), to be RR (AOR = 2.95 1.12–7.74), lower pre-treatment ARR (AOR = 0.62, 0.48–0.81), higher pre-treatment EDSS (AOR = 1.30, 1.02–1.63) and longer disease duration (AOR = 1.05, 1.00–1.10) compared to naïve patients. At logistic regression, comparing switchers to DMF for efficacy or tolerability, the first group patients were more likely to have PR course of disease (AOR = 0.41, p = 0.032, CI 0.18–0.92) respect to tolerability switchers.

3.1. Efficacy

Since data were missing for some patients, efficacy analyses are based on 447 subjects. Overall, we observed a reduction in the ARR after treatment with DMF (0.30 ± 0.42 to 0.08 ± 0.30, $p < 0.001$). Naïve patients experienced a reduction of mean ARR from 0.42 ± 0.38, to 0.05 ± 0.18 ($p < 0.001$). Patients who switched for lack of efficacy from a previous treatment showed an ARR reduction from 0.36 ± 0.53, to 0.12 ± 0.45 ($p < 0.001$), while switchers for tolerability from a previous treatment showed an ARR reduction from 0.15 ± 0.32, to 0.07 ± 0.24 ($p < 0.001$) (see Fig. 1).

We analyzed the change of ARR, when controlling for confounders, and we found that, considering only the 2 years before DMF treatment and available follow-up after, relapses were reduced by 75% [Incidence rate ratio (IRR) = 0.25, $p < 0.001$, CI 0.18–0.33].

Factors influencing ARR on DMF therapy were RR MS course (IRR = 2.0, $p < 0.001$, CI 1.51–2.73) and previous DMTs status: de-escalating from II line therapies was associated to higher risk of relapsing (IRR = 1.8, $p < 0.001$, CI 1.39–2.31). At multivariable Cox proportional hazard model, however, only age at onset was related to rate or relapses, with younger age being protective (HR = 0.96, p = 0.02), while only a trend for a protective role of male gender emerged (HR = 2.11, p = 0.051).

Median follow up EDSS was 2.5 (0–8.5). EDSS remained stable in 87.8% of patients. At multivariable logistic regression patients who progressed were less likely to be RR (AOR = 0.27, p = 0.006, CI 0.10–0.68), and had a longer disease duration (AOR = 1.03, p = 0.02, CI 1.00–1.06).

Baseline brain MRI was collected in 384/495 patients. One hundred and twenty-eight patients (33%) were active at MRI scan, i.e. showing enhancing lesions or new lesions respect to a previous MRI, while 256 were not active (67%). After a mean of 9.6 months of therapy, we collected 272 new MRIs: 68 patients showed MRI activity (25%). After a mean of 20 months, we collected 230 s follow-up MRIs, which still showed 25% active scans (58 patients).

To obtain NEDA3 outcome result, we selected 256 patients according to methods. We observed 65% (166 patients) NEDA3 status patients.

In detail, MRI-NEDA status was obtained in 204 patients (80%), relapse-free status was maintained in 81% of patients (n = 206) while no CDP was maintained in 89% of patients (n = 214) (see Fig. 2a).

The only significant variable at Cox regression analysis was disease duration, which was associated with higher rate of NEDA 3 failure.

3.2. Persistence

109 (22%) of patients discontinued therapy after a mean of 1.1 ± 0.7 years. Thirty-three dropped patients were naive (30%), whilst 77 (70%) switched from a previous DMT.

Reasons for DMF discontinuation over time were lack of efficacy (n = 55, 50%), safety issues (n = 33, 30%), tolerability (n = 8, 7%), poor compliance (n = 8, 7%), and pregnancy (n = 4, 4%) (Fig. 2b). At multivariable logistic regression, patients who discontinued DMF showed a higher pre-treatment EDSS (AOR = 1.3, p = 0.009, CI 1.08–1.65) and displayed a more aggressive disease course under DMF therapy, with a higher ARR at last follow up (AOR = 5.2 p = 0.010, CI = 1.49–18.16) and a higher EDSS increase (AOR = 2.50, $p < 0.001$, CI = 1.67–3.75).

3.3. Safety

We analyzed the safety data of 33 patients dropped out due to safety reasons (7%, see Table 2). The most frequent safety issues driving to drop out were: lymphopenia (4 patients, 3 grade III and 1 grade II, with associated gastro-enteric side effects); liver/pancreatic enzymes increase in 2 patients; 7 gastrointestinal severe tolerability issues; 2 cancers (a 40 years old patient was diagnosed with breast cancer after 46 days and a 52 years old male patient was diagnosed with a colon

Table 1
Demographical and clinical characteristics at DMF start of MS patients.

Number of subjects (N = 456)	N (%)
Sex	
Male	150 (32.89)
Female	306 (67.11)
Age, mean (SD) (years)	40.4 (11.8)
ARR, mean (SD)	0.59 (0.83)
EDSS, median (range)	2.5 (0–8)
Age at onset, mean (SD) (years)	31.1 (10.3)
Disease duration, mean (SD) (years)	9.3 (8.7)
DMF treatment duration mean (SD) (months)	18.2 (11)
MS course	
Relapsing-Remitting	423 (92.76)
Progressive-Relapsing	33 (7.24)
Previous Therapy	
First line	235 (51.54)
Second line	56 (12.28)
Naive	149 (32.67)
No therapy	16 (3.51)
Switch reason	
Efficacy	122 (26.75)
Tolerability	185 (40.57)
Drop	109 (23.9)

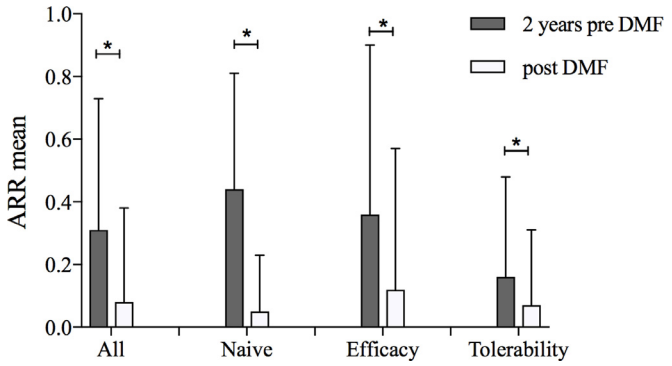

Fig. 1. Annualized Relapse Rate changes after DMF treatment.
The box plot shows the mean ARR before and after DMF treatment. Overall, DMF treatment significantly reduced ARR (0.30 ± 0.42 to 0.08 ± 0.30). Moreover, mean ARR reduced from 0.42 ± 0.38 to 0.05 ± 0.18 in naive patients, from 0.36 ± 0.53 to 0.12 ± 0.45 in patients switching for efficacy from a previous DMT and from 0.15 ± 0.32 to 0.07 ± 0.24 in patients switching for tolerability (*$p < 0.001$).

Table 2
Adverse events leading to drug discontinuation.

Adverse event	Number of patients	%
Severe Gastrointestinal effects	7	1.5
Lymphopenia	4	0.9
Altered liver/pancreatic enzymes	2	0.4
Cancer	2	0.4
Dizziness	2	0.4
Flushing	1	0.2
Not specified	14	3
Overall	**33**	**7**

Table 3
Lymphopenia details on a sample of 393 patients.

Lymphopenia	N	%
Total	95	24
Grade 1	60	13
Grade 2	31	7
Grade 3	4	1

carcinoma after 246 days). Lymphopenia data were collected from 393 patients: we recorded 95 cases (24%) of lymphopenia: 60 grade I (13%), 31 grade II (7%) and 4 grade III (1%) (see Table 3).

4. Discussion

Real-world studies provide valuable insight for daily clinical practice into predictors of MS therapy response and into safety and efficacy therapy's profile (Trojano et al., 2017). Our research was performed in a real-world setting to verify efficacy, tolerability and safety of DMF when administered in clinical practice after its license in 6 MS centers from the Campania region in Italy.

Our results confirm the effectiveness of DMF in reducing risk of relapses. The percentage of relapse-free patients in our study (76%) confirmed what reported in RCTs (Fox et al., 2012, Gold et al., 2012) and in the largest Italian real-life study conducted on DMF so far (Mallucci et al., 2018), and the overall 75% ARR reduction compared to pre-treatment ARR was clear. The variables associated to lower relapse rate on DMF were younger age at MS onset, with a trend towards a better relapses control in males than in females. Moreover, de-

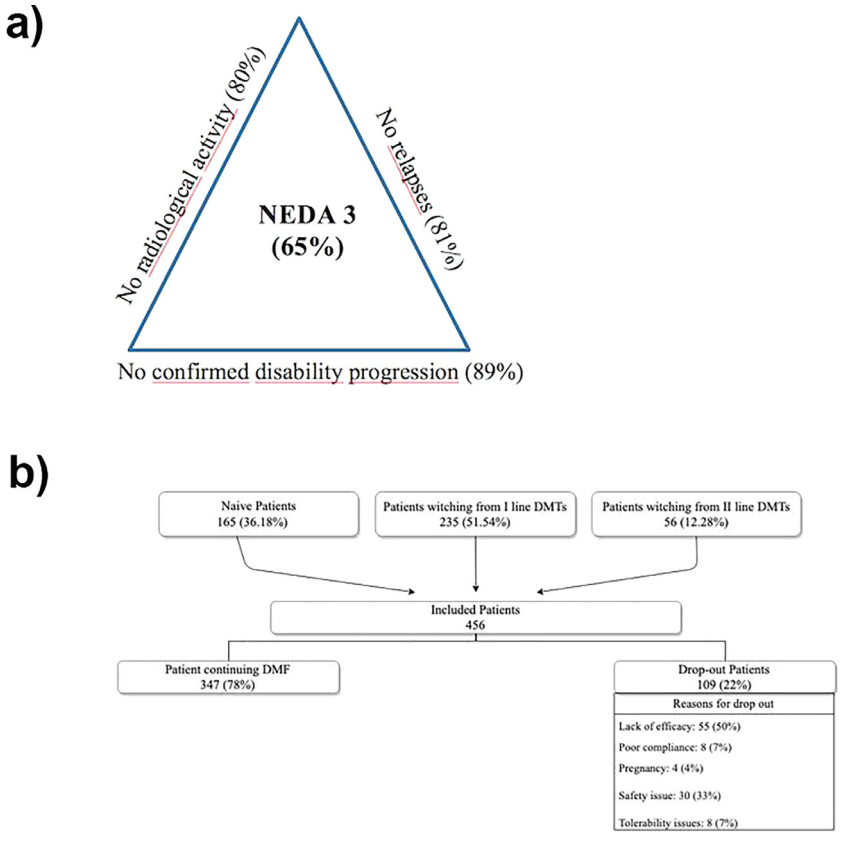

Fig. 2. Different components of NEDA3 status and study flowchart.
a) Different components of NEDA3 status in a subgroup of patients (256) after 24-months follow-up.
b) Number and proportion of patients included in the study according to pre DMF and post DMF treatment.

escalating from a second line therapy was associated with higher risk of relapsing.

Moreover, the multivariate analysis underlined that DMF significantly reduced ARR not only in naïve patients, but also in those who switched to DMF due to suboptimal response or to low tolerability to a previous treatment.

Growing literature is trying to assess when and towards which DMT horizontal switches are recommended. Unfortunately, most of the evidences are indirect. Preliminary data of the observational study RESPOND suggested that 12-month-DMF treatment was associated with lower ARR (reduction of 78%) and improvement in patients switching to DMF after suboptimal treatment with glatiramer acetate (Kresa-Reahl, 2016). In a recent integrated post hoc analysis of the DEFINE/CONFIRM studies, the efficacy of DMF was confirmed in patients previously treated with interferon beta. In particular, DMF showed a significant effect over 2 years vs. placebo and a safety profile consistent with the overall population of RCTs (Fernandez et al., 2017). However, this integrated post hoc analysis did not describe the effect of DMF in patients previously treated with interferon beta. We confirm that both naïve patients and patients switching from other first line DMTs showed a good efficacy of DMF in a real-world setting.

Regarding the so-called ``de-escalation" group (patients switching to DMF after a II line therapy, such as fingolimod and natalizumab), disease control was lower, with higher ARR, respect to patients switching from I line therapies. Patients de-escalating from second line therapies to DMF did so mainly for tolerability or safety reasons (i.e. JCV positivity in natalizumab treated patients), with 30% of cases switching from fingolimod for efficacy. At multivariable Cox proportional hazard model de-escalation did not emerge as a risk factor of relapsing, however, when a mixed-effect Poisson regression model was employed to model difference in the ARR before and after the beginning of the therapy, a role of previous therapy emerged: de-escalating from a second line therapy increased the risk of relapsing (IRR 1.8). These results would suggest that DMF is less likely to control disease activity in patients previously treated with natalizumab or fingolimod, probably due to a higher efficacy of these drugs in controlling very active patients or to the ``rebound" effect already described for natalizumab (Clerico et al., 2014) and still debated for fingolimod (Frau et al., 2018).

In our cohort we observed only 12% of patients progressing on EDSS, over a short follow-up; patients progressing however were more likely to be RPMS patients and to have a longer disease duration.

Patients with both baseline and follow-up MRI were a small proportion, and only 33% of MRI exams were active at baseline, as expected in a real world population of mainly pre-treated patients, in main part switching to DMF for tolerability issues. Therefore, we were able to detect only a small reduction of baseline MRI activity, respect to the more impressive DEFINE and CONFIRM results. In addition, patients undergoing to serial MRIs were doing so for clinicians' decision, and not per-protocol as in a RCT, therefore there could be a bias in MRI patients' selection toward more active ones.

However, NEDA 3 results in our cohort were very promising, although obtained from a subgroup (52%) of patients, corresponding to minimal MRI requirements as for methods. NEDA3 status was maintained in 65% of patients. The main driver of NEDA3 was a shorter disease duration. Our results showed a higher NEDA3 proportion than that described in the Northern Italy multicenter study (Mallucci et al., 2018), however the proportions of the single NEDA sub status were very similar. We also showed better NEDA results than those described in the integrated analysis of the phase III DEFINE and CONFIRM studies (Havrdova et al., 2017), confirming that in real life studies efficacy of drugs might be even better than in RCTs (Lanzillo, 2017). However, our results might be biased by the observational nature of the study, with less strict adherence to relapse definition and less frequent patient assessments, therefore leading to a possible underestimation of the outcomes.

As carried out in recent studies in Italy regarding the persistence on therapy (Iolascon et al., 2016), we observed a significant proportion of patients (22%) dropping DMF therapy over a period of 1.4 years in mean: this proportion is slightly higher than the one observed in a recent larger Italian population (Lanzillo et al., 2018), that showed a higher adherence rate over a shorter period of time, of 1 year, with a drop out proportion of 16%. Our proportion is also similar to the one reported in Northern Italy (Mallucci et al., 2018), in a study that showed 10% drop out rate at 1 year and 30% at 2 years. Interestingly, we are better overlapping Kuwait data (Alroughani et al., 2017), also regarding a lower prevalence of gastro enteric side effects, suggesting a geographical and possibly dietary nearness of southern Italy to Arabic countries.

Similar to a recent study (Guerriero et al., 2017), we also analyzed the predictive factors for therapy switch. We observed that patients who discontinued DMF had a more ``active" disease, with a higher baseline EDSS, experiencing more relapses and EDSS increase while on DMF. This finding seems to confirm the switching determinants resulting from a recent multicenter study that pointed to younger age, short delay between onset and diagnosis, positive spinal MRI, and higher EDSS as predictors of DMT switch due to poor efficacy (Saccà et al., 2018).

Overall, safety data confirmed a favorable profile for DMF: 33 patients (7%) dropped out due to safety or tolerability issues, the most frequent being gastrointestinal tolerability (1.5%). Severe lymphopenia leading to drug interruption was very rare (0.4%), however mild or transient lymphopenia was observed in 24% of patients, as expected from RCTs and previous real life studies (Fox et al., 2012, Gold et al., 2012, Giovannoni et al., 2017), and gastro-enteric issues were recorded in 6% patients. These were slightly less frequent than described in RCTs (Fox et al., 2012, Gold et al., 2012), most probably depending on an under-reporting for the observational nature of the study, but much less than the Northern Italy observational study by Mallucci et al. (2018), and again, we might suppose different regional dietary habits in Italy, protecting Southern Italians from DMF's gastroenteric AEs.

Our study suffers from several limitations due to the observational and retrospective nature of the design that does not allow to fully controlling for possible heterogeneities in patient assessment criteria and data collection procedures across centers. On the other hand, the centers included in this study were all highly specialized MS centers and the adjustment in the analyses for a center effect can limit the potential influence of such heterogeneities. Moreover, the limitation to a single geographical area might be not representative of the national MS population. The absence of standardized MRI procedures and timing might bias radiological efficacy results. Safety and tolerability were reassuring; however, these can still be improved, maybe also evaluating the protective role of Mediterranean dietary habits respect to Northern population's food intake.

In conclusion, this is the first real life observational study conducted in Southern Italy, confirming a good efficacy profile of DMF, both on naïve and on switchers, especially with a younger age of onset and with shorter disease duration, suggesting to use DMF early in disease course to maximize its efficacy. We think that these indications might be helpful for the clinicians, depicting the ``ideal" DMF patient, as a young patient, short disease duration, both naïf or not tolerating or even having disease activity while on any other first line therapy. This data will be further elucidated by the ongoing CONNECT phase 3 trial with DMF in pediatric patients, with safety and efficacy data collected in subjects with very early onset of disease and short disease duration.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

Dr. L. Lavorgna received speaker honoraria from Sanofi, Teva, Novartis, Merck, Roche, Bayer, Biogen.

Dr. L. Sinisi received speaker honoraria and/or travel grants from Merck Serono, Biogen, Teva, Novartis, Almirall, Sanofi Genzyme.

Dr. G.T. Maniscalco has served on advisory boards and/or received travel grants and speaker honoraria from Almirall, Biogen, Merck Serono, Novartis and Teva.

E. Signoriello received travel funding and speaker honoraria from Biogen, Novartis, Sanofi Genzyme, Bayer, Teva.

G. Lus received travel funding, research support, speaker honoraria from Biogen, Novartis, Sanofi Genzyme, Bayer, Teva, Almirall, Allergan, Ipsen.

Marcello Moccia received research grants from MAGNIMS-ECTRIMS and from Merck.

Antonio Carotenuto received travel funding from Roche and research grants from Almirall.

R. Lanzillo, F. Saccà and V. Brescia Morra received personal fees for public speaking or consultancy from Merck, Novartis, Biogen, Genzyme, Teva and Almirall.

Dr. F.Romano, C.V.Russo, A. De Rosa, M.De Angelis, S. Bonavita, C. Florio and B. Ronga have nothing to disclose.

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