Dimethyl fumarate vs Teriflunomide: an Italian time-to-event data analysis

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Abstract

Background The introduction of oral disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) changed algorithms of RRMS treatment.

Objectives To compare effectiveness of treatment with dimethyl fumarate (DMF) and teriflunomide (TRF) in a large multicentre Italian cohort of RRMS patients.

Materials and Methods Patients with RRMS who received treatment with DMF and TRF between January 1st, 2012 and December 31th, 2018 from twelve MS centers were identified. The events investigated were "time-to-first-relapse", "time-to-Magnetic-Resonance-Imaging (MRI)-activity" and "time-to-disability-progression".

Results 1,445 patients were enrolled (1,039 on DMF, 406 on TRF) and followed for a median of 34 months. Patients on TRF were older (43.5±8.6 vs 38.8±9.2 years), with a predominance of men and higher level of disability ($p<0.001$ for all). Patients on DMF had a higher number of relapses and radiological activity ($p<.05$) at baseline. Time-varying Cox-model for the event "time-to-first relapse" revealed that patients on DMF have a lower relapse-hazard before 38 months of treatment ($HR_{t<38DMF}$=0.73, CI=0.52-1.03, $p<.005$). When the time-on-therapy exceeds 38 months, the relapse hazard for DMF patients increase ($HR_{t>38DMF}$=3.83, CI= 0.89-1.02, $p<.005$). Both DMTs controlled similarly MRI activity and disability progression.

Conclusions Patients on DMF had higher relapse free survival time than TRF group during the first 38 months on therapy.

Key words: Multiple Sclerosis, dimethyl fumarate, teriflunomide, efficacy, safety.

Introduction

The introduction of oral disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis (RRMS) changed the therapeutic landscape and algorithms of RRMS treatment (1). In Europe, dimethyl fumarate (DMF) and teriflunomide (TRF) are approved as first-line agents and are often used as the initial therapeutic choice (2, 3). Pivotal trials showed the efficacy of both DMTs on controlling clinical relapses, disability accrual and magnetic resonance imaging (MRI) activity (4-8). Both DMTs had overall good tolerability. There have been no head-to-head randomized trials to compare these two DMTs; however, several real-world evidence (RWE) studies have compared DMF and TRF and provided useful information to guide the selection of either drug for MS patients (9, 10). Although different statistical methods were used, both drugs demonstrated an ability to control disease activity (11-13). In some RWE studies, patients on DMF had a lower relapse rate and a higher relapse-free survival time (11, 12). In this registry-based nationwide cohort Cox-model study, we compared the clinical and radiological activity between patients treated with DMF or TRF.

Methods

Database and study population

Data entry was performed using iMed© software, and the treating clinics used rigorous quality assurance procedures for the patient health records under the coordination by the iMed© software data coordinators (14). Twelve Italian MS centres participated in this study (14).

Key eligibility criteria were: 1) diagnosis of RRMS according to the 2010 McDonald criteria (15); 2) age 18 to 55 years; 3) began treatment with DMF or TRF within the index window (1 January 2012 to 31 December 2018); 4) continuous exposure to one of the two DMTs for ≥6 months.

Exclusion criteria were: 1) age <18 years at treatment initiation; 2) previous participation in clinical trials; 3) history of off-label DMT use (off-label therapy was defined as methotrexate, treosulphan, cyclic prednisone, rituximab, or intravenous human immunoglobulin therapy); 4) >2 previous DMT types; 5) previous stem cell transplantation; 6) insufficient baseline clinical and radiological data or insufficient data quality (e.g., MRI obtained with one Tesla system); 5) patients lost to follow up and/or transferred to other centres.

For patients treated with both TRF and DMF at different time points, we included the first of the two drugs in the study.

Clinicians entered all the clinical and radiological information available at every clinical visit (six months for schedule or earlier, if necessary). The minimum data for all enrolled patients included demographical data (sex, date of birth) and clinical data, which consisted of the year of disease onset and diagnosis, previous DMT use, relapses occurred, Expanded Disability Status Scale (EDSS) scores (within 24 months before treatment start), MRI data, and adverse events (AE, cause and date of treatment discontinuation or switch).

Procedures and Outcomes

Patients were treated with oral DMTs in accordance to the European Medicine Agency (EMA): DMF (120 mg twice per day for the first seven days, then 240 mg twice per day); TRF (14 mg once per day) (16, 17).

Patients were included in the study at the initiation of DMF or TRF treatment (baseline) and monitored over their entire treatment period, with data collection performed at baseline and during

the time of exposure. Patients were censored at treatment discontinuation or the last recorded clinical visit. The data entry portal was iMed® (Merck-Serono, Geneva) (18).

Disability was assessed by EDSS scoring by a Neurostatus-certified MS specialist. MRI data were reported by the treating neurologists (19).

The scanning sessions of the brain MRI sequences were T1- and T2-weighted sequences acquired only with 1.5 Tesla scanners and longitudinally with the same scanner.

The T1-weighted sequences were acquired before and after intravenous injection of gadolinium contrast agent (0.1 mmol/kg). A cerebral MRI acquired within six months before or one week after the treatment start was considered as a baseline MRI. The numbers of brain MRI lesions on T2-weighted, T1-weighted, and post-contrast T1-weighted sequences were recorded at every 12-month follow-up from the beginning of DMT.

Study endpoints

The primary study outcomes for the DMF and TRF cohorts were: 1) time to first clinical relapse after treatment start; 2) time to first MRI activity (see below); 3) time to disability progression (see below). Secondarily, we evaluated the rate of drug discontinuation.

A relapse was defined as the development of new symptoms or exacerbation of existing symptoms that persisted for ≥24 hours, in the absence of concurrent illness or fever, and occurred ≥30 days after a previous relapse.

MRI activity was considered as new T1-gadolinium-enhancing brain lesion and or a new or newly enlarging T2 brain lesion.

Confirmed disability progression was defined as an increase in EDSS by ≥ 1.5 points for those with a baseline EDSS score of 0, by one or more points for a baseline score of ≤ 5.5 or by 0.5 points for a

baseline score of >5.5, which was sustained for 12 weeks or longer. EDSS recorded within 30 days after the onset of a relapse were excluded.

We collected data on the safety and tolerability of the two DMTs evaluated. We reported the frequency of AEs and the proportion of serious AEs (SAEs) using the EMA definitions (20).

Treatment discontinuation events and the main reasons for discontinuation were recorded.

Statistical analysis

Comparisons of the baseline characteristics between the treatment groups were performed using the Wilcoxon rank-sum or Chi-square test, depending on the nature of the variables. All patient characteristics were reported as frequencies (%) for categorical variables and mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables.

Time-to-event data analysis was used because we were interested in studying the delay between the time from treatment initiation to first relapse, the first occurrence of MRI activity, and confirmed disability progression. Events occurring within the first 6 months from the starting of treatment were censored because they cannot be representative of treatment efficacy according to MS treatment algorithms.

Missing data were handled through multiple imputation. The analysis used normalised weights to approximate the inferences in the data with data missing not at random (21). The associations between missingness of the baseline data and other demographical and clinical characteristics were calculated with a multivariable logistic regression analysis ad previously published (22, 23).

Univariate non-parametric Kaplan Meier (K-M) curves and log-rank tests were used to describe the events under investigation. K-M curves are useful to describe events when the predictor is categorical; however, these curves are not as helpful for quantitative predictors.

K-M curves were stratified for the gender and age of patients to individuate some differences between strata for each event under investigation.

To overcome information loss from non-parametric K-M, Cox models were built to account for multiple risk factors simultaneously and obtain the instantaneous incidence rate of the events as a function of time and risk factor.

The Schoenfeld's global test was used to verify the proportional hazards assumption along all the time-on-treatment.

When the proportionality assumption was verified, a Cox proportional model was built. If the assumption could not be verified, a time-varying Cox model was used. When a time-varying Cox model is fitted, the time-varying coefficient can be described with a parametric time function or a step function. We evaluated linear, logarithmic, quadratic and step-time functions. In accordance with the Akaike Information Criterion (AIC)(24), the step-time function best fit our model. Time to first relapse, time to MRI activity, and time to EDSS progression along all the time-on-DMT have been modelled by including sex, age (18-40 vs 41-55), disease duration, status naive/switchers from first line DMT/switchers from second line DMT, baseline EDSS, number of relapses in the previous year, and number of baseline T2 and T1-gad weighted MRI lesions load and treatment group (Group = 1 if DMF; Group = 0 if TRF).

According to the AIC criterium, we selected the model with the best statistical inferential properties. All the models were estimated using the Breslow's tie correction (25).

All analyses were performed using the R package (version 3.6.1).

Protocol Approvals Standard, Registrations, and Patient Consents

The study protocol was approved by the local ethics committee (Comitato Etico Catania 1, n.177/2017/PO) of the coordinating centre (Policlinico Vittorio Emanuele, Catania, Italy) and transmitted to the participating centres. Patients provided written informed consent. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with the appropriate national regulations.

Data availability

Anonymised data will be shared upon request from any qualified investigator for the sole purpose of replicating procedures and results presented in the report provided that data transfer is in agreement with EU legislation on the general data protection regulation.

Results

From a total of 8,475 RRMS patients available in the database, 1,445 patients were eligible for this study (1,039 patients treated with DMF; 406 patients treated with TRF) (Appendix 1).

Table 1 shows the baseline characteristics of the patients within each group. Patients on TRF were older, predominantly male, and had higher levels of disability 6 to 24 months before the start of treatment (EDSS range 1.0 to 3.0 versus 1.0 to 2.5 for DMF) ($p < 0.01$ for all comparisons). Patients on DMF had a higher number of relapses and active gadolinium-enhancing MRI lesions in the year before starting treatment ($p < 0.05$ for both comparisons).

The K-M curves for the events (time to first relapse, time to MRI activity and time to EDSS progression) showed no differences between the two treatment groups (Figures 1-3).

The survival curves were then stratified for different baseline characteristics. The event “time to first relapse” showed differences between age groups when stratified for the different age cut-offs (Figure 4). All three age groups had a similar hazard risk (HR) if the follow-up duration was ≤38 months (log-rank, $p = 0.56$). For follow-up durations greater than 38 months, the HR for patients with ages ranging from 40 to 55 years indicated a lower risk to reach the event (log-rank, $p = 0.02$).

Classical proportional hazard Cox models were built for the events evaluated in this study. The parameter estimates from the three classical proportional Cox models are shown in Figures 5-7. These models did not identify any differences between the two drugs despite the risk of the event

being conditioned to the variables at baseline. For the event "time to first relapse", age was inversely related to the risk of the event during the follow-up period (HR = 0.9, CI = 0.96 to 0.99, p = 0.008). Furthermore, EDSS progression six months before starting treatment was directly related to the risk of experiencing a relapse (HR = 1.13, CI = 1.04 to 1.23, p = 0.044).

Although no differences were found between the two treatment groups for the event "time to MRI activity", a one-point increase in the EDSS score six months before starting DMT appeared to reduce the risk of experiencing MRI activity by 16% (HR = 0.85, CI = 0.73 to 0.99, p = 0.078).

Regarding the event time to disability no differences were found between the two DMTs nor any predictor was recognized.

After-verification of the proportional hazards assumption of the Cox regression model, the null hypothesis was rejected for the event "time to first relapse", revealing that the more appropriate analytical method was the time-varying Cox model that was built with a time step-function based on the AIC criterion (Figure 8).

The age dependence of the event time to first relapse was confirmed also in the time varying model; in detail, for patients of age >40 years the risk of relapse occurrence was 34% lower than for those aged between 18 and 40 years (HR= 0.70, CI = 0.52 to 0.97, p = 0.029) (see Figure 8). Furthermore, a difference in the dependence of the risk on the EDSS score six months before starting DMT (HR = 1.11, CI = 1.03 to 1.21, p = 0.011) was maintained.

We also identified a difference between the two drugs in determining the risk of experiencing a relapse. Patients on DMF had an approximately 1.4 times lower relapse hazard risk before 38 months of treatment than those who took TRF ($HR_{t<38DMF}$ = 0.74, CI = 0.53 to 1.03, p = 0.079). When the follow-up period exceeded 38 months patients on DMF had an approximately 0.3 times

lower relapse hazard risk than those who took TRF ($HR_{t>38DMF}$ = 3.83, CI = 1.11 to 13.23, p = 0.011).

~~Time-varying Cox-model for the event "time-to-first relapse" revealed that patients on DMF have a lower relapse-hazard before 38 months of treatment ($HR_{t<38DMF}$=0.73, CI=0.52-1.03, p<.005). When the time-on-therapy exceeds 38 months, the relapse hazard for DMF patients increase ($HR_{t>38DMF}$=3.83, CI= 0.89-1.02, p<.005). Both DMTs controlled similarly MRI activity and disability progression.~~

The number of observations that exceeded 50 months of follow-up was limited, leading to enormous confidence interval bands.

Treatment persistence and safety profile

During the follow-up period, 292 patients on DMF and 106 on TRF discontinued the prescribed DMT with a median time on therapy of 34 months. The percentage of RRMS patients who experienced an AE during the follow-up period was 35.8% and 23.4% in the DMF and TRF groups, respectively ($p < 0.01$). The rate of SAEs was similar between the two groups (1.3% for DMF; 2.4% for TRF). The AEs caused DMT discontinuation for 15.8% of patients treated with DMF and 12% of patients on TRF.

Discussion

In our study population, treatment with DMF or TRF resulted in the control of radiological disease activity and disability progression during the entire follow-up period. Patients on DMF showed a lower risk of relapse during the follow-up period, particularly during the first 38 months from the start of treatment. We first compared the effectiveness of DMF and TRF using a time-varying Cox proportional model. An imbalance between groups in observational studies is one of the most debated questions, because the sample size cannot be fixed a priori. Thus, we used a conditional

approach to reduce the imbalance between baseline characteristics, which provided more information about the events explored as a continuum during all the follow-up evaluation.

A recent study from the Danish MSbase registry (767 patients on DMF, 1,469 patients on TRF) showed that patients on DMF had higher relapse-free survival proportion after 48 months of follow-up ($p < 0.05$). However, the statistical model of that study (stabilised inverse probability of treatment weights) did not allow the verification of the interaction between the covariates and time. We designed our time-varying model in the attempt to identify a cut-off above which the protective effect of the treatments could be reduced (11). Another recent study that included 1,770 RRMS patients (713 on TRF, 1,057 on DMF) analysed the 1-and 2-year post-treatment initiation outcomes (relapses, increase of T2 lesions, increase in EDSS and reason for treatment discontinuation) using an inverse probability weighting propensity score and logistic regressions. Here, an adjusted proportion of patients with at least one new T2 lesion after two years was lower for the DMF-treated group compared to that of the TRF-treated group (60.8% vs 72.2%, odds ratio [OR] 0.60, $p < 0.001$) (12, 13).

Furthermore, a previous multicentre study on a large Italian cohort (corrected with a neighbour matching propensity score) compared the composite score for “No Evidence of Disease Activity” after 12 months of treatment between the two DMTs (26, 27). Another study compared DMF, TRF and fingolimod treatment for more than 2,000 patients (614 on TRF, 782 on DMF), who were followed up for a median time of 2.5 years (12). While the effect of fingolimod on the relapse frequency was superior to that of TRF or DMF, no differences were found between TRF and DMF, and all three oral therapies had similar effects on the disability outcomes during the first 2.5 years of treatment (12).

The previous studies that compared oral therapies showed some differences in the results that can be attributed to the variability in the source data and methodology (28, 29). Our cohort showed

differences in the baseline characteristics. When they were introduced into the survival models, age was directly related to the risk of relapse and inversely related to the risk of confirmed disability progression, independently of the type of DMT employed. Thus, the choice of DMT should consider cut-offs in age in addition as important prognostic to other baseline and clinical prognostic factors to distinguish phenomena related to advancing age from the disease progression process. It was suggested that inflammation "burnt out" along the ages and the benefits of continued immune modulation with DMT deserve attention. These results may encourage further research for older MS populations, who are still excluded from enrolment in MS clinical trials.

In our study, the percentage of AEs was higher in the DMF group compared to the TRF group.

Despite this finding, the proportion of AEs that led to a discontinuation of treatment with the study drug was similar between the two groups.

The main strengths of our study are represented by the direct comparison of the two DMTs from a uniformed electronic record that included a quality control procedure. Moreover, we used a time-dependent model after verifying the proportionality of the hazard risk. It is worth noting that the primary analysis with a classical proportional Cox model did not find a statistically significant difference for time to first relapse between the DMF and TRF treatment groups. The most used models in this type of study are based on the fundamental assumption that the investigated events have a constant impact on the hazard over time. Thus, appropriate tests to check the validity of this assumption before building a model should be an integral part of time-to-event analysis performed using a Cox model. Indeed, if time-dependent variables are included in an inappropriate model, the results will not be reliable. These technical details could bring interesting and useful information to clinicians that could help in choosing when to start, maintain or stop a DMT. Currently, as novel DMTs become available, there is a lack of a consensus regarding the initiation and sequencing of DMTs for the management of RRMS.

One limitation of our study is its observational nature, which is exposed to an uncorrectable bias underlying the treatment choices, which could not be adjusted. Although the analysis of these observational data is not a substitute for randomized clinical trials, our study provides practical evidence that is representative of clinical care in tertiary MS centres and valuable insights into the challenges of the therapeutic management of RRMS.

Declarations

Funding

The researchers were independent from funders and sponsors. All researchers could access all the data.

Conflicts of interest

Dr Emanuele D'Amico has received personal fees from Biogen and Sanofi. He also received travel funding from Bayer Biogen and Merck.

Dr Aurora Zanghì received travel funding from Bayer-Schering and Sanofi Genzyme outside of the described work.

Dr Mariangela Sciandra has nothing to disclose.

Dr Roberta Lanzillo has received personal fees for public speaking or consultancy from Merck, Novartis, Biogen, Genzyme, Teva, Roche and Almirall.

Dr Graziella Callari has received personal fees from Biogen and Sanofi. She also received travel funding from Bayer Biogen and Merck.

Dr Antonio Cortese has received speaker honoraria from Biogen, Sanofi Genzyme, and Teva, and travel grants from Biogen, Merck, Sanofi Genzyme, and Teva. He also received advisory board member honoraria from Biogen, Merck, Novartis, and Teva.

Dr Giacomo Lus has nothing to disclose related to this manuscript.

Dr Matteo Lucchini has received travel grants from Almirall, Biogen, Sanofi-Genzyme and Roche, speaker honoraria from Biogen and consulting fees from Merck Serono, Almirall and Novartis.

Dr Maria Buccafusca has nothing to disclose related to this manuscript.

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Dr Antonio Gallo has nothing to disclose related to this manuscript.

Dr Erica Curti has nothing to disclose related to this manuscript.

Dr Alberto Gajofatto has nothing to disclose related to this manuscript.

Dr Elisabetta Signoriello has nothing to disclose related to this manuscript.

Dr Alvino Bisecco has nothing to disclose related to this manuscript.

Dr Francesca Gobbin has nothing to disclose related to this manuscript.

Dr Maria Teresa Ferrò has nothing to disclose related to this manuscript.

Dr Paola Valentino has nothing to disclose related to this manuscript.

Dr Massimiliano Mirabella has received honoraria for speaking, serving on the advisory board and consulting for Biogen, Novartis, Merck Serono, Roche, Almirall and Sanofi Genzyme. He has received reimbursement for congress attendance and travel costs from Biogen, Novartis, Sanofi

Genzyme, Roche, Merck Serono and Teva. He was also a principal investigator for clinical trials for Biogen, Merck Serono, Novartis, Roche,Sanofi Genzyme, Teva and Ultragenix.

Dr Franco Granella has nothing to disclose related to this manuscript.

Dr Vincenzo Brescia Morra has nothing to disclose related to this manuscript.

Dr Luigi Maria Edoardo Grimaldi has served on the advisory boards of Bayer, Biogen Celgene, Merck, Novartis, Roche, Sanofi and Teva. He has also received personal fees for speaking activities at congresses or sponsored symposia.

Dr Francesco Patti has served on the advisory boards of Bayer, Biogen Celgene, Merck, Novartis, Roche, Sanofi, Teva and Almirall. He has also received personal fees for speaking activities at congresses or sponsored symposia.

Research ethics and patient consent

The study protocol was approved by the local ethics committee (Comitato Etico Catania 1, n.177/2017/PO) of the coordinating centre (Policlinico Vittorio Emanuele, Catania, Italy) and transmitted to the participating centres. Patients provided written informed consent. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with the appropriate national regulations.

Data availability

Anonymised data will be shared upon request from any qualified investigator for the sole purpose of replicating procedures and results presented in the report provided that data transfer is in agreement with EU legislation on the general data protection regulation.

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Table 1. Baseline characteristics of the two treatment groups

The results are expressed as the mean ± SD, median (IQR) and frequencies (%).

DMT= disease modifying drugs; DMF= dimethyl fumarate; EDSS= Expanded Disability Status Scale; Gd+= gadolineum; m= months; MRI= Magnetic Resonance Imaging; TRF= teriflunomide; y= year.

Figure 1. Kaplan-Meier curves for time to first relapse

The *p*-values from the log-rank test are included in the graphs.

Figure 2. Kaplan-Meier curves for time to MRI activity

The *p-value* from the log-rank test are included in the graphs.

MRI, Magnetic Resonance Activity

Figure 3. Kaplan-Meier curves for time to EDSS progression

The *p-value* from the log-rank test are included in the graphs.

EDSS, Expanded Disability Status Scale

Figure 4: Kaplan-Meier curves for time to first relapse stratified for age

The *p-value* from the log-rank test are included in the graphs.

Figure 5: Cox proportional model for time to first relapse

Figure 6: Cox proportional model for MRI activity

MRI, magnetic resonance imaging

Figure 7: Cox proportional model for EDSS progression

EDSS, Expanded Disability Status Scale

Figure 8: Cox model «time-varying» for time to first relapse

Appendix 1. Patients' selection flow chart

DMF, dimethyl fumarate; PPMS, Primary Progressive Multiple Sclerosis; RRMS, Relapsing Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis; TRF, teriflunomide