Comparative effectiveness of dimethyl fumarate in Multiple Sclerosis

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Research Article

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Abstract

Objectives: To assess the effectiveness of dimethyl fumarate (DMF) on annual rate of relapse (ARR) and disability progression in multiple sclerosis (MS) compared to injectable immunomodulators (IMM), teriflunomide (TERI) and fingolimob (FTY), in real life setting.

Methods: A population-based cohort study was conducted using data of the French nationwide claims database, SNDS. All patients initiating IMM, TERI, FTY or DMF between July 1, 2015 and December 12, 2017, with 4.5 years of database history and 1 to 3.5 years of follow-up were included in this study. DMF patients were 1:1 matched to IMM, TERI or FTY using a high dimensional Propensity Score. Negative binomial regression and a regression logistic models were used to estimate the relative risk (RR ± [95% CI]) of ARR and the Odds Ratio (OR ± [95% CI]) of disability progression, respectively.

Results: Overall, 9 304 subjects were identified: 29.0% initiated DMF, 33.2% TERI, 5.6% FTY and 32.2% an IMM. The matched cohorts consisted of 1779 DMF- IMM, patients, 1679 DMF-TERI patients, and 376 DMF-FTY patients. DMF significantly reduced ARR compared to IMM (RR 0.72 [0.61 - 0.86]) and TERI (0.81 [0.68 - 0.96]). The risk of the progression of MS specific disability was not significantly different for any matched cohorts.

Interpretation: DMF is associated with lower risk of relapse for patients with RRMS than other first-line RRMS agents (TERI and IIM).

Introduction

To date, disease-modifying therapies (DMTs) represent the main therapeutic strategy in Relapsing-Remitting Multiple sclerosis (RRMS), to reduce the risk of relapses and delay disability progression. The first-line generation of medications approved were the Injectable ImmunoModulators (IMM) such as interferon beta-1a and 1b (INF) and glatiramer acetate (GA). Since then, treatment options have broadened to include the orally administered DMTs fingolimod (FTY), which is predominantly indicated as second-line therapy in Europe, and more recently, teriflunomide (TERI) and dimethyl fumarate (DMF). All these drugs showed a significant treatment effect compared with placebo on the occurrence of relapses, disease activity and disability progression [1].

Although head to head randomized clinical trials have been performed for IMM, FTY and TERI [1], well-designed head-to-head trials are lacking for DMF. Its clinical efficacy cannot thus be directly compared with other oral DMTs. A systematic review and meta-analysis of randomized clinical trials found that DMF significantly reduced the occurrence of relapse compared to IFNs, GA and TERI [2]. However indirect comparisons studies are not sufficient to conclude for DMF superiority due to the variability of study population, and endpoint definitions.

Many observational studies have been used to assess the real-world comparative effectiveness of DMF and a number of alternative treatments, using claims based-analyses or registries with mixed results. The

variability of these results may be explained by the various durations of follow-up limited to 1 year in some studies [3–5], or by the use of simple propensity score (PS)-based methods in other studies [3,5–10], which although they can balance observed baseline covariates between groups, do nothing to balance unmeasured characteristics and confounders. In this context, comparative studies from real world practice in large population-based healthcare databases using robust statistical methods to handle confounders are needed to provide valuable evidence that will help clinicians in the choice of treatment.

The aim of this study is to assess the effectiveness of DMF in comparison with the injectable or oral DMTs used in RRMS, in terms of relapse frequency and disability progression using the French nationwide claims and hospital database, SNDS (*Système National des Données de Santé*).

Methods

Design and population

We conducted a cohort study within the general scheme of the SNDS (*Système National des Données de Santé*) claims database. It included all naïve patients initiating an IMM (IFN or GA) or an oral DMT (FTY, TERI or DMF) between 1st July 2015 and 31st December 2017, with a 4.5 years history of data and a follow-up of at least 1 year up to 3.5 years. The index date was the earliest date of dispensing of IMM or oral DMT or of hospitalization for medications used under Temporary Use Authorization (i.e. French procedure allowing the use of a drug before its market authorization) or for medications reimbursed in addition to the procedure-based hospital payment system. Initiation was defined as having no dispensing or hospitalization for one of these drugs or any other drugs for MS (i.e. natalizumab, methotrexate, cyclophosphamide, mycophenolate, azathioprine, rituximab or tacrolimus) during the 4.5 years history period.

Data source

The SNDS has been described in detail elsewhere [11,12]. Briefly, SNDS is the French nationwide claims database with individual information on all reimbursed outpatient claims linked to the national hospital discharge summaries database system and the national death registry, using a unique national pseudonymised identifier. It currently includes about 99% of the French population covered by a dozen of health care insurance systems, representing approximately 67 million persons from birth (or immigration) to death (or emigration), irrespective of socioeconomic status even if a person changes occupation or retires. It contains general characteristics, date and cause of death, all outpatient reimbursed medical and paramedical encounters, all private and public hospital-discharge summaries, and Long Term Disease (LTD) registration that ensures a full coverage for all medical expenses related to most expensive chronic diseases. Reimbursed drugs are identified according to their Anatomic Therapeutic Chemical codes and hospital or LTD diagnoses according to their ICD-10 (International Classification of Diseases, 10th Revision) codes, the quality of this coding being ensured by regular internal and external audits [13].

Outcomes

The primary outcome was the annual rate of relapse (ARR) during the index treatment period. Relapses were identified through an algorithm, developed based on national guidelines[14] and clinicians' medical expertise, that included dispensing of high dose of corticosteroids for outpatients and hospitalizations with MS relapse diagnosis potentially combined with high dose of corticosteroids (Table 1). To be considered as independent events, relapses must be separated by at least 31 days. The diagnostic performance of this algorithm was assessed in a validation study with 95.0% Positive Predictive value. The secondary outcomes were MS disability progression during the index treatment period defined according to new reimbursements related to equipment for motor or sphincter disability or the implementation of a neuromodulation device for the treatment of chronic pain identified in the index period compared with the pre-index treatment period.

Statistical analysis

Baseline characteristics included relapses, MS-related hospitalizations, steroid use, medical visits to the neurologist, lab test and encephalic or spinal cord magnetic resonance imaging in the 2 years prior to the index date. Data related to patient comorbidities and disability were collected during the 4.5 years prior to index date in order to ensure the completeness of the information. Chronic disease burden was measured using a version of the Charlson Comorbidity Index (CCI) score adapted for the SNDS database [15].

Head-to-head comparisons were performed between treatment groups in three separate analyses of DMF versus IMMs, DMF versus TERI or DMF versus FTY based on an "as treated" analysis, in which patients were followed until index treatment switch or discontinuation (i.e. no dispensing of the index drug during 60 days after the end of the last dispensing), death or 31st December 2018, whichever occurred earlier. The probability of discontinuation or switch of the index treatment was described using Kaplan-Meier survival analysis. For each head-to-head comparison, we computed a high dimensional Propensity Score (hdPS), which reflects the probability to be treated by one of the studied DMTs [16,17] adjusting for hidden confounders [18]. It was demonstrated that this approach achieved more plausible effect estimates than conventional PS modelling based on clinically selected variables or simple multivariable modelling. HdPS is estimated using a multivariable logistic regression model with treatment group as dependent variable and a large data set of independent variables collected in the pre-index period provided by six data dimensions (i.e. outpatient drugs dispensing, diagnoses related to hospitalizations and LTD registrations, outpatient and inpatient medical and paramedical visits, lab tests, medical procedures and medical devices) and fixed baseline characteristics (i.e. age, gender, number of relapses, MS medical device and outpatient and hospital costs identified in the pre-index period). We excluded the subjects in both treatment groups who were at or below the 2.5th percentile of the hdPS in the group of subjects who received the treatment predicted by the hdPS, as well as those at or above the 97.5th percentile in the alternative treatment group. This hdPS trimming ensures that each subject has a reasonable probability of receiving either compared treatment, given relevant confounding variables [19]. Remaining patients were 1:1 matched for the comparison. We assessed the predictive performance of the hdPS using the c-statistic and the balancing effect of the hdPS matching with standardized differences in baseline variables before

and after matching, knowing that an absolute standardized difference of 10% or less indicates a negligible difference between groups [20].

For treatment effects, we estimated for the ARRs, the Rate Ratio (RR) and its corresponding Confidence Interval (95%CI) by negative binomial regression and for the disability progression, the Odds Ratio (OR) and its 95%CI by logistic regression. For each outcome, estimates were calculated crude and after hdPS matching. To assess the robustness of our results, we also calculated adjusted results adjusting for hdPS and we modeled analyses by the inverse probability of treatment weights (IPTW), which is a hdPS score-based weight used to control for confounding by indication [21].

We performed statistical analysis using SAS software (version 9.4; SAS Institute, NC) and and hdPS using the routines from Harvard Medical School (SAS pharmacoepi toolbox, www.drugepi.org).

Results

Baseline characteristics

Between the 1st July 2015 and the 31st December 2017, we identified 9,304 subjects in the SNDS meeting the inclusion criteria. Of this cohort, 29.0% of patients initiated DMF, 33.2% TERI, 5.6% FTY and 32.2% an IMM (18.5% INF and 13.7% GA). Three quarters of patients (72.8%) were female with an age of 39.9 (Standard deviation, SD: 12.1) years on average, ranging from 37.5 (11.9) years for IMM to 43.1 (11.7) years for TERI and from a mean (SD) CCI score of 0.58 (1.05) ranging from 0.52 (0.95) for DMF to 0.65 (1.04) for TERI (Table 2). Other baseline clinical characteristics were similar among patients initiating DMF, TERI or IMM: in each treatment group, around 35% of patients had a disability mainly of motor type, the pre-index ARR was on average 0.13, around 40% of patients had a MS-related hospitalization, around 55% of them had a visit to a neurologist and around 90% of them had a cerebral or spinal cord MRI. In comparison with other treatment groups, FTY patients had a specific clinical profile: they were more likely to have a disability (38.6%) and a MS-related hospitalization (71.6%), they had an average pre-index ARR of 0.17, and they were less likely to have a visit to a neurologist (45.5%) or a MRI (85.2%).

For all patients initiating a DMT, the median exposure period (1st quartile; 3rd quartile) was 17.2 (7.4; 27.4) months over the 1 to 3.5 year of follow-up. Exposure periods varied across treatment groups: they were 14.6 (6.4; 24.6) months for IMM, 17.9 (7.8; 29.2) months for DMF, 18.6 (8.6; 28.4) months for TERI and 19.6 (10.0; 32.1) months for FTY. These results were due to the significant difference observed in the probability of treatment discontinuation among treatment groups ($p<0.0001$; Figure 1): this was the highest in IMM (67.8%, CI95% [65.3; 70.3]) and the lowest in FTY (41.5%, CI95% [36.5; 47.0]).

DMF versus IMM

Of the 2697 DMF patients and the 2997 IMM patients, 433 (16.1%) and 395 (13.2%), respectively, were excluded by trimming, and 1780 patients were then matched in each group with a satisfying hdPS overlapping (Figure 2) and a c-statistic at 0.53, as well as good balance on all covariates (Table 3). DMF

was associated with a significantly lower ARR compared to matched IMM patients (RR: 0.72, 95%CI [0.61 - 0.86]; Figure 3). Consistent results were found in the hdPS adjusted and IPTW analyses, which were performed in all patients remaining after trimming. No significant differences in the appearance or worsening of disability were observed between DMF and IMM patients whatever the analysis performed (Figure 4).

DMF versus TERI

Of the 2697 DMF patients and the 3089 TERI patients, 571 (21.2%) and 402 (15.0%), respectively, were excluded by trimming, and 1679 patients were then matched in each group with a satisfying hdPS overlapping (Figure 2) and a c-statistic at 0.56, as well as good balance on all covariates (Table 3). DMF was associated with a significantly lower ARR compared to matched TERI patients (RR: 0.81 [0.68 - 0.96]; Figure 3). This result was confirmed in the hdPS adjusted and IPTW analyses, which were performed in all patients remaining after trimming. No significant differences in the appearance or worsening of disability were found between DMF and TERI patients whatever the analysis performed (Figure 4).

DMF versus FTY

Of the DMF 2697 patients and the 521 FTY patients, 726 (26.9%) and 145 (27.8%) respectively, were excluded by trimming, and 376 were then matched in each group with a c-statistic of 0.60, and some remaining imbalanced covariates (Table 3). There was no statistical difference for ARR between DMF and FTY (RR; 1.38 [0.95 - 1.99]. Consistent results were found in the hdPS adjusted and IPTW analyses, which were performed in all patients remaining after trimming. The hdPS matching did not identify significant difference between DMF and FTY in the MS disability progression, whereas in both hdPS adjusted or IPTW analyses, DMF showed a significant and positive effect in disability progression in comparison with FTY (Figure 4).

Discussion

With the increasing number of DMTs developed in these last 10 years, and the lack of head-to-head randomized controlled trials to assess their comparative efficacy, data of robust observational studies are needed to support decision making by stakeholders and to assist clinicians in choosing the most favorable treatment option for their patients. This nationwide population-based observational study conducted to assess the DMTs effectiveness in a population of DMTs initiators on MS activity using robust hdPS-based methods found that the DMF treatment proved to be associated with better results than TERI and IMM regarding relapse activity, without significant difference on disability progression.

At treatment initiation, DMF patients' characteristics were very similar to those of TERI and IMM patients: their age was 40 years on average, they were mostly female and had an annual rate of relapses of 0.13 during the pre-index period. These findings are consistent with those of other studies [4,6–8,22,23]. Conversely, some baseline characteristics differed between DMF and FTY patients, although their age at treatment initiation was very similar. This suggests that FTY patients had a specific distinct profile at treatment

initiation; fewer FTY patients had a complete medical monitoring before treatment initiation (i.e. medical visits to general practitioner or neurologist, lab tests related to MS or encephalic or spinal cord MRI), their pre-index ARR was slightly higher (0.17), and more patients already had a MS-related disability. These results are expected considering FTY specific indications of rapidly evolving severe RRMS [24].

In this study, DMF showed a higher clinical effectiveness than TERI or IMM with lower relapses rates. Results are consistently significant using various robust statistical methods, whether using hdPS matching which focused on patients with very similar clinical profiles or hdPS adjustment and IPTW, which considers the overall patients with more heterogeneous profiles. These consistent results through multiple methods and overlapping of hdPS between groups are suggestive of balanced groups. In addition, these results obtained in a large population during a long period of follow-up, confirm trends of most of previous real-world observational studies conducted on shorter time periods [4,6–8,22,23]. Compared to FTY, DMF displayed a slightly higher rate of relapses, though the RR did not differ significantly. The partial overlap of the hdPS distribution between both groups confirms that FTY and DMF patients have a very distinct profile and are therefore difficult to compare. Indeed, only about one-fourth of DMF patients remained after matching. These patients shared the same characteristics to FTY patients and referred certainly to patients with high disease activity since FTY is the only DMT labelled specifically for the treatment of such patients. In this specific situation, the effectiveness remained similar between both groups.

In this study, the MS disability progression was found to be similar between DMF and TERI, IMM or FTY. These findings are difficult to compare to the literature, since the most popular and widely used instrument to assess disease progression is the Expanded Disability Status Scale (EDSS) score [25], which includes clinical information not available in the SNDS. Nevertheless, reimbursements for motor or sphincter medical devices or for neuromodulation device are a reliable indicator to estimate MS disability progression, although, in contrast with the EDSS, it does not include mild disabilities without medical device and visual or cognitive impairments. Globally, disability was probably underestimated, but all severe cases requiring medical devices have been identified with accuracy.

One of the main limitations of this study is that the SNDS is a database built for administrative and reimbursement purposes, not for research purposes and important data are lacking: clinical information, severity or stage of the disease, biological results and imaging results which enables to assess treatment effect on the appearance of demyelinating inflammatory lesions and on the development of cerebral atrophy. We thus had to develop an algorithm to identify relapse occurrence based on the specific therapeutic management of MS patients. This complex algorithm, refined by experts of the field, showed good diagnosis performance in a previous validation study (PPV: 95% and NPV 96%), and has allowed to strongly mitigate any potential misclassification bias. To strengthen the validity of this algorithm, we also conducted an additional analysis by extending the period between 2 occurrences of relapses from 31 to 60 days, which did not affect fundamentally the algorithm performance. Some relapses may nevertheless not have been captured, and frequency of relapses could be underestimated but this should similarly affect all treatment groups and thus not bias the results.

As for any claims based real-world studies, this study presents an inherent risk of unmeasured confounding. To address this limit, we applied hdPS-based methods in the analysis of the outcome. The hdPS is a well-known statistical technique that attempts to estimate the effect of a treatment, policy, or other intervention by accounting for the measured and unmeasured covariates that predict receiving the treatment. It summarizes a large set of variables that characterize each subject for status and unmeasured confounders not recorded in a database (i.e. drugs, medical status, hospitalization, other co-morbidities directly, or indirectly linked with unmeasured confounders) [16,17]. Matching, adjusting or weighting on large numbers of covariates ascertained from subject healthcare claims data may improve control of confounding, as these variables may collectively be proxies for unobserved factors. Furthermore, using hdPS adjusting or weighting methods in addition to matching, allowed to include all patients meeting the eligibility criteria of the study, whereas matching method excludes patients not finding a match. Using hdPS weighting or adjustment ensures transparency of included patients and validity of results in the predefined study population.

In conclusion, this study provides further insight into the therapeutic benefit of DMF in real life setting compared to other commonly used agents for RRMS including IMM and another oral drug, TERI. The ARR was significantly lower in patients treated with DMF vs IMM and TERI using robust hdPS based methods. These data will be useful to feed into physician choices of patient's treatment.

Study Highlights

What is the current knowledge of the topic?

Although review and meta-analysis of randomized clinical trials suggest that dimethylfumarate reduces significantly the occurrence of relapse compared to alternative treatment used in relapsing-remitting multiple sclerosis, observational studies report mixed results.

What question did this study address?

Is dimethylfumarate more effective in real world settings than the injectable or oral disease-modifying therapies used in relapsing-remitting multiple sclerosis (injectable immunomodulators, fingolimob, teriflunomide) in terms of relapse frequency and disability progression?

What does this study add to our knowledge?

Our results show that DMF significantly reduces annual rate of relapse compared to injectable immunomodulators (RR 0.72 [0.61 - 0.86]) and teriflunomide (0.81 [0.68 - 0.96]), but does not show significant effect on the risk of the progression of MS specific disability for any alternative treatment.

How might this change clinical pharmacology and translational science?

Dimethylfumarate is an effective therapeutic option to be considered in clinical practice for first line treatment of relapsing-remitting multiple sclerosis.

Declarations

Conflicts of interest

E. M. declares personal fees and non-financial support from Biogen, Novartis, Roche, Merck, Sanofi-Genzyme. B. B. declares personal fees and non-financial support from Biogen, Genzyme, Bayer, Medday, Actelion, Roche, Celgene, Novartis, Merck. F. G. and M.D. declare personal fees and non-financial support from Biogen. C. L. declares consulting or travel fees from Biogen, Novartis, Roche, Sanofi, Teva and Merck Serono, and research grant from Biogen. O. H. declares personal fees and non-financial support from Biogen, Merck, Novartis, Roche, Genzyme. All remaining authors have declared no conflicts of interest.

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Authors contributions

P.B.-L., S.L., P.B., M.D., B.B., F.G., C.L., E.M., O.H., P.D., N.M., C.D.-P. contributed in designing and supervising the study. R.L. and A.A. performed the analyses. All authors discussed the results. P.B.-L., S.L., P.B and P.D. wrote the manuscript in consultation with M.D., B.B., F.G., C.L., E.M., O.H..

References

1. Montalban, X. *et al.* ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Mult. Scler. J.* **24**, 96–120 (2018).
2. Hutchinson, M. *et al.* Efficacy and safety of BG-12 (dimethyl fumarate) and other disease-modifying therapies for the treatment of relapsing–remitting multiple sclerosis: a systematic review and mixed treatment comparison. *Curr. Med. Res. Opin.* **30**, 613–627 (2014).
3. Hersh, C. M. *et al.* Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 12-month follow-up. *Mult. Scler. Relat. Disord.* **10**, 44–52 (2016).
4. Boster, A. *et al.* Comparative Effectiveness Research of Disease-Modifying Therapies for the Management of Multiple Sclerosis: Analysis of a Large Health Insurance Claims Database. *Neurol. Ther.* **6**, 91–102 (2017).

5. D'Amico, E. *et al.* Comparable efficacy and safety of dimethyl fumarate and teriflunomide treatment in Relapsing-Remitting Multiple Sclerosis: an Italian real-word multicenter experience. *Ther. Adv. Neurol. Disord.* **11**, 175628641879640 (2018).
6. Braune, S. *et al.* Comparative effectiveness of delayed-release dimethyl fumarate versus interferon, glatiramer acetate, teriflunomide, or fingolimod: results from the German NeuroTransData registry. *J. Neurol.* **265**, 2980–2992 (2018).
7. Ontaneda, D. *et al.* Comparative effectiveness of dimethyl fumarate versus fingolimod and teriflunomide among MS patients switching from first-generation platform therapies in the US. *Mult. Scler. Relat. Disord.* **27**, 101–111 (2019).
8. Buron, M. D. *et al.* Comparative effectiveness of teriflunomide and dimethyl fumarate: A nationwide cohort study. *Neurology* **92**, e1811–e1820 (2019).
9. Laplaud, D.-A. *et al.* Comparative effectiveness of teriflunomide vs dimethyl fumarate in multiple sclerosis. *Neurology* **93**, e635–e646 (2019).
10. Kalincik, T. *et al.* Comparison of fingolimod, dimethyl fumarate and teriflunomide for multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry* **90**, 458–468 (2019).
11. Tuppin, P. *et al.* Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev. Epidemiol. Sante Publique* **65 Suppl 4**, S149–S167 (2017).
12. Bezin, J. *et al.* The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. *Pharmacoepidemiol. Drug Saf.* **26**, 954–962 (2017).
13. Gilleron, V., Gasnier-Duparc, N. & Hebbrecht, G. Certification des comptes: Une incitation à la traçabilité des processus de contrôle. *Revue Hospitaliere de France* **582**, 6 (2018).
14. *Guide - Affection de Longue Durée: Sclérose en Plaques*. (Haute Autorité de Santé, 2006).at <https://www.has-sante.fr/upload/docs/application/pdf/07-024_sclerose-guide_sans_lap.pdf>
15. Bannay, A. *et al.* The Best Use of the Charlson Comorbidity Index With Electronic Health Care Database to Predict Mortality. *Med. Care* **54**, 188–194 (2016).
16. Schneeweiss, S. *et al.* High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiol. Camb. Mass* **20**, 512–522 (2009).
17. Rassen, J. A. & Schneeweiss, S. Using high-dimensional propensity scores to automate confounding control in a distributed medical product safety surveillance system. *Pharmacoepidemiol. Drug Saf.* **21 Suppl 1**, 41–49 (2012).
18. Guertin, J. R., Rahme, E. & LeLorier, J. Performance of the high-dimensional propensity score in adjusting for unmeasured confounders. *Eur. J. Clin. Pharmacol.* **72**, 1497–1505 (2016).
19. Glynn, R. J. *et al.* Comparison of alternative approaches to trim subjects in the tails of the propensity score distribution. *Pharmacoepidemiol. Drug Saf.* **28**, 1290–1298 (2019).
20. Austin, P. C. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat. Med.* **28**, 3083–3107 (2009).

21. Curtis, L. H., Hammill, B. G., Eisenstein, E. L., Kramer, J. M. & Anstrom, K. J. Using Inverse Probability-Weighted Estimators in Comparative Effectiveness Analyses with Observational Databases. *Med. Care* **45**, S103–S107 (2007).
22. Bowen, J. D., Kozma, C. M., Grosso, M. M. & Phillips, A. L. A real-world comparison of relapse rates, healthcare costs and resource use among patients with multiple sclerosis newly initiating subcutaneous interferon beta-1a versus oral disease-modifying drugs. *Mult. Scler. J. - Exp. Transl. Clin.* **4**, (2018).
23. Granqvist, M. *et al.* Comparative effectiveness of dimethyl fumarate as the initial and secondary treatment for MS. *Mult. Scler. J.* 1352458519866600 (2019).doi:10.1177/1352458519866600
24. gilenya-epar-product-information_en.pdf. at <https://www.ema.europa.eu/en/documents/product-information/gilenya-epar-product-information_en.pdf>
25. Meyer-Moock, S., Feng, Y.-S., Maeurer, M., Dippel, F.-W. & Kohlmann, T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC Neurol.* **14**, 58 (2014).

Tables

Table 1. Description of the criteria included in the algorithm for the identification of multiple sclerosis relapses

Criteria	Definition
1	**≥ 2 one-day hospitalisations** within **10 days** or **hospital stay ≥ 2 days** with, for each of them, **association** of at least one of the following primary, linked or associated diagnosis codes (**G35, G049, G048, H46, H481**) with **Z512** code
2	outpatient dispensing(s) of at **least 2 grams** (up to 5 grams for injectable form, and up to 6 grams for oral form) of high dose corticosteroid therapy (see section 3.2) within **10 days**;
3	2 days of hospitalisation (1-day hospitalisations or not) with at least one of the following primary, linked or associated diagnosis codes (G35, G049, G048, H46, H481), followed by outpatient dispensing of at least 1 gram (up to 5 grams for injectable form, and up to 6 grams for oral form) of high dose corticosteroid therapy within **10 days**;
4	1 day of hospitalisation (1-day hospitalisation or not) with at least one of the following primary, linked or associated diagnosis codes (G35, G049, G048, H46, H481), followed by outpatient dispensing(s) of at least 2 grams (up to 5 grams for injectable form, and up to 6 grams for oral form) of high dose corticosteroid therapy within **10 days**;
5	**3 to 5 days of hospitalisation or consecutive 3 to 5 one-day hospitalisations** with at least one of the following diagnosis codes (**G35, G049, G048, H46, H481**) and no other linked or associated diagnosis code;

Table 2. Baseline demographic and clinical characteristics of MS patients initiating dimethyl fumarate, teriflunomide, fingolimod, or injectable immunomodulators.

	DMF n = 2697	TERI n = 3089	FTY n = 521	IMM n = 2997	Total N = 9304
Female, n (%)	1983 (73.5)	2111 (68.3)	342 (65.6)	2333 (77.8)	6769 (72.8)
Age (years), mean (SD)	39.4 (11.7)	43.1 (11.7)	38.2 (12.7)	37.5 (11.9)	39.9 (12.1)
CCI score, mean (SD)	0.52 (0.95)	0.65 (1.04)	0.61 (1.10)	0.54 (1.13)	0.58 (1.05)
CCI score, n (%)					
0	1875 (69.5)	1898 (61.4)	357 (68.5)	2140 (71.4)	6270 (67.4)
1-2	698 (25.9)	1021 (33.1)	127 (24.4)	705 (23.5)	2551 (27.4)
3-4	107 (4.0)	147 (4.8)	30 (5.8)	125 (4.2)	409 (4.4)
≥ 5	17 (0.6)	23 (0.7)	7 (1.3)	27 (0.9)	74 (0.8)
Disability, n (%)	941 (34.9)	1088 (35.2)	201 (38.6)	1061 (35.4)	3291 (35.4)
Motor disorder	812 (30.1)	949 (30.7)	174 (33.4)	884 (29.5)	2819 (30.3)
Sphincter disorders	220 (8.2)	248 (8.0)	46 (8.8)	281 (9.4)	795 (8.5)
Chronic pain treated with neurostimulator	5 (0.2)	1 (0.0)	0 (0.0)	7 (0.2)	13 (0.1)
Pre-index relapses, n (%)					
0	2097 (77.8)	2410 (78.0)	380 (72.9)	2291 (76.4)	7178 (77.1)
1	516 (19.1)	596 (19.3)	113 (21.7)	622 (20.8)	1847 (19.9)
2	73 (2.7)	69 (2.2)	23 (4.4)	77 (2.6)	242 (2.6)
³ 3	11 (0.4)	14 (0.5)	5 (1.0)	7 (0.2)	37 (0.4)
Pre-index annual rate of relapse, mean (SD)	0.13 (0.27)	0.13 (0.26)	0.17 (0.31)	0.13 (0.26)	0.13 (0.26)
Pre-index MS-related hospitalizations (excluding relapse), n (%)	1120 (41.5)	1188 (38.5)	373 (71.6)	1239 (41.3)	3920 (42.1)
Pre-index medical visits to neurologist, n (%)	1570 (58.2)	1696 (54.9)	237 (45.5)	1529 (51.0)	5032 (54.1)
Pre-index cerebral or spinal cord	2536	2918	444 (85.2)	2775	8673

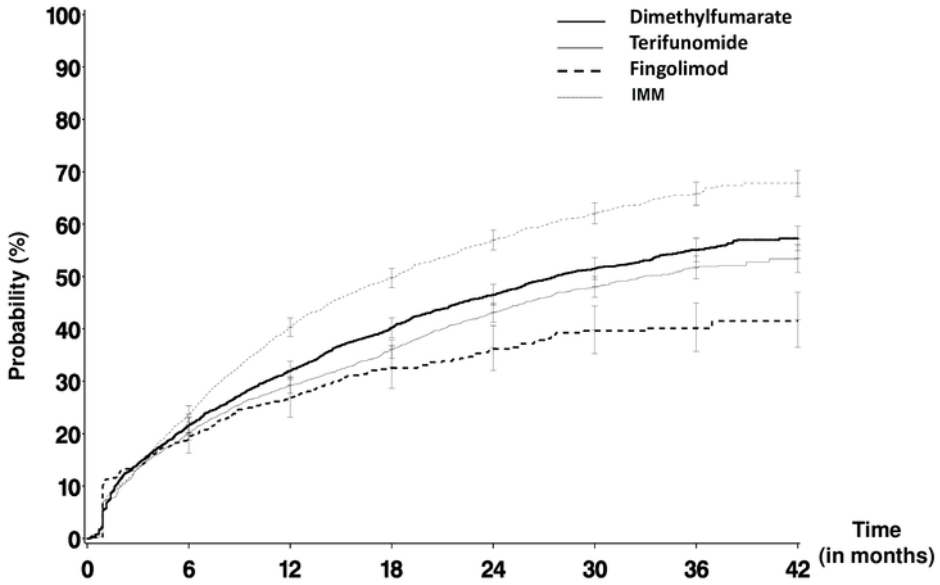
MRI, n (%)	(94.0)	(94.5)		(92.6)	(93.2)
Pre-index lab tests, n (%)	2571 (95.3)	2953 (95.6)	483 (92.7)	2811 (93.8)	8818 (94.8)
Blood test	2465 (91.4)	2816 (91.2)	456 (87.5)	2630 (87.8)	8367 (89.9)
ALT/AST	2160 (80.1)	2540 (82.2)	407 (78.1)	2212 (73.8)	7319 (78.7)
Creatinine	2311 (85.7)	2615 (84.7)	416 (79.8)	2405 (80.2)	7747 (83.3)
Bilirubin	883 (32.7)	1010 (32.7)	254 (48.8)	896 (29.9)	3043 (32.7)
Pre-index corticosteroids dispensing (excluding high dose), n (%)	1266 (46.9)	1507 (48.8)	248 (47.6)	1518 (50.7)	4539 (48.8)
Number of distinct medications (level 3 of the ATC code), median [IQR]	13.0 [9.0;18.0]	13.0 [9.0;19.0]	14.0 [10.0;19.0]	14.0 [9.0;19.0]	14.0 [9.0;19.0]
DMF: Dimethyl fumarate, TERI: Teriflunomide, FTY: Fingolimod, IMM: Injectable Immunomodulators, MS: Multiple Sclerosis, CCI: Charlson Comorbidity Index, MRI: Magnetic Resonance Imaging, ATC: Anatomical Therapeutic Classification, IQR: Interquartile Range, SD: Standard Deviation					

Table 3. Baseline demographic and clinical characteristics of post-matched populations DMF-IMM, DMF-TERI and DMF-FTY

	1:1 Matched			1:1 Matched			1:1 Matched		
	DMF n=1780	IMM n=1780	StD (%)	DMF n=1679	TERI n=1679	StD (%)	DMF n=376	FTY n=376	StD (%)
Female, n (%)	1343 (75.4)	1331 (74.8)	1.6	1193 (71.1)	1218 (72.5)	-3.3	234 (62.2)	248 (66.0)	-7.8
Age (years), mean (SD)	38.9 (10.8)	39.2 (12.2)	-2.7	41.1 (10.7)	40.9 (12.2)	2.3	38.4 (12.2)	38.8 (12.8)	-3.4
CCI score, n (%)			8.4			6.8			13.0
0	1282 (72.0)	1251 (70.3)	3.8	1149 (68.4)	1103 (65.7)	5.8	248 (66.0)	265 (70.5)	-9.7
1-2	427 (24.0)	426 (23.9)	0.1	453 (27.0)	501 (29.8)	-6.3	106 (28.2)	86 (22.9)	12.2
3-4	61 (3.4)	88 (4.9)	-7.6	66 (3.9)	67 (4.0)	-0.3	19 (5.1)	20 (5.3)	-1.2
≥ 5	10 (0.6)	15 (0.8)	-3.4	11 (0.7)	8 (0.5)	2.4	3 (0.8)	5 (1.3)	5.2
Disability, n (%)	595 (33.4)	605 (34.0)	-1.2	561 (33.4)	561 (33.4)	0.0	122 (32.4)	138 (36.7)	-9.0
Motor disorder	504 (28.3)	501 (28.1)	0.4	481 (28.6)	487 (29.0)	-0.8	107 (28.5)	118 (31.4)	-6.4
Sphincter disorders	138 (7.8)	159 (8.9)	-4.3	131 (7.8)	136 (8.1)	-1.1	34 (9.0)	30 (8.0)	3.8
Chronic pain treated with neurostimulator	4 (0.2)	3 (0.2)	1.3	4 (0.2)	0 (0.0)	6.9	1 (0.3)	0 (0.0)	7.3
Pre-index annual rate of relapse, mean (SD)	0.13 (0.26)	0.12 (0.24)	3.4	0.12 (0.27)	0.11 (0.24)	3.3	0.13 (0.26)	0.16 (0.27)	-10.4
Pre-index MS-related hospitalizations (excluding relapse), n (%)	737 (41.4)	706 (39.7)	3.5	664 (39.5)	677 (40.3)	-1.6	199 (52.9)	251 (66.8)	-28.5
Pre-index medical visits to neurologist, n (%)	1004 (56.4)	926 (52.0)	8.8	937 (55.8)	913 (54.4)	2.9	195 (51.9)	159 (42.3)	19.3
Pre-index cerebral or spinal cord MRI, n (%)	1687 (94.8)	1645 (92.4)	9.6	1581 (94.2)	1585 (94.4)	-1.0	338 (89.9)	308 (81.9)	23.1

DMF: Dimethyl fumarate, TERI: Teriflunomide, FTY: Fingolimod, IMM: Injectable Immunomodulators, MS: Multiple Sclerosis, CCI: Charlson Comorbidity Index, MRI: Magnetic Resonance Imaging, ATC: Anatomical Therapeutic Classification, IQR: Interquartile Range, SD: Standard Deviation, StD: Standardized Difference

Figures



Dimethylfumarate								
Nb of patients at risk	2697	2116	1833	1336	935	641	414	4
Cumulative probability %	0.0	21.5	32.0	40.2	46.5	51.5	55.1	57.2
[95% CI]		[20.0;23.1]	[30.3;33.8]	[38.4;42.1]	[44.5;48.5]	[49.4;53.6]	[52.9;57.3]	[54.9;59.6]
Teriflunomide								
Nb of patients at risk	3089	2466	2181	1616	1101	683	298	6
Cumulative probability %	0.0	20.2	29.2	36.1	43.1	48.0	51.7	53.4
[95% CI]		[18.8;21.6]	[27.7;30.9]	[34.4;37.8]	[41.2;44.9]	[46.0;50.0]	[49.5;53.9]	[50.8;56.1]
Fingolimod								
Nb of patients at risk	521	420	382	287	210	154	51	2
Cumulative probability %	0.0	19.4	26.7	32.6	36.2	39.6	40.1	41.5
[95% CI]		[16.2.23.1]	[23.1;30.7]	[28.7;36.8]	[32.1;40.7]	[35.2;44.4]	[35.7;45.0]	[36.5;47.0]
IMM								
Nb of patients at risk	2997	2287	1787	1217	770	447	178	2
Cumulative probability %	0.0	23.7	40.3	49.7	57.0	62.0	65.8	67.8
[95% CI]		[22.2;25.3]	[38.6;42.1]	[47.9;51.6]	[55.1;58.9]	[60.1;64.0]	[63.6;68.0]	[65.3;70.3]

Figure 1

Probability of discontinuation or switch of index treatment (Kaplan-Meier curve) during the 3.5 years follow-up period, according to treatment groups: dimethylfumarate, teriflunomide, fingolimob, injectable immunomodulatory drugs (IMM)

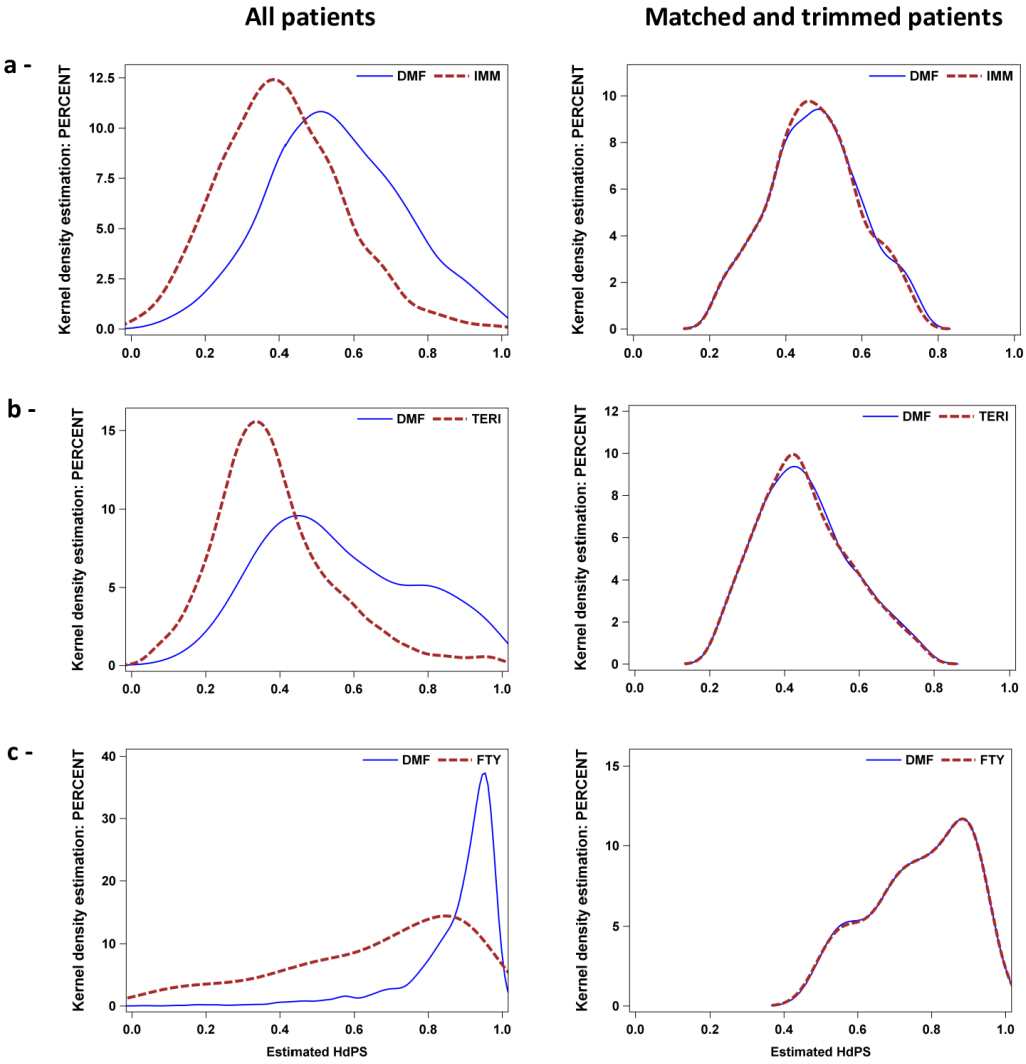


Figure 2

High dimensional Propensity Score (hdPS) distribution in all patients and in hdPS trimmed and matched patients for the following treatment groups: a) dimethyl fumarate (DMF) vs injectable immunomodulatory

drugs (IMM).; b) dimethyl fumarate (DMF) vs. teriflunomide (TERI); c) dimethyl fumarate (DMF) vs fingolimob (FTY)

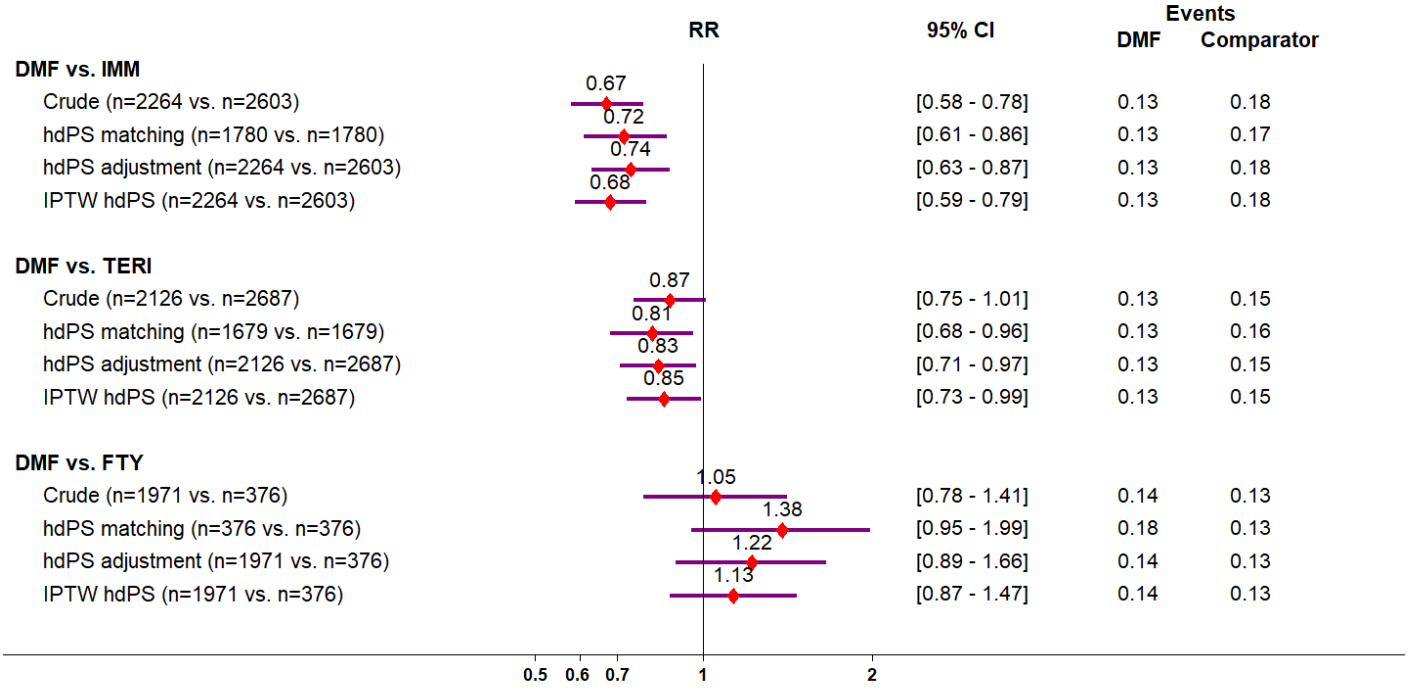


Figure 3

Forest plot of annualized relapse rate (ARR) for DMF versus comparator populations (RR [95% CI]). DMF dimethyl fumarate, TERI teriflunomide, IMM Injectable Immunomodulators, FTY fingolimod.

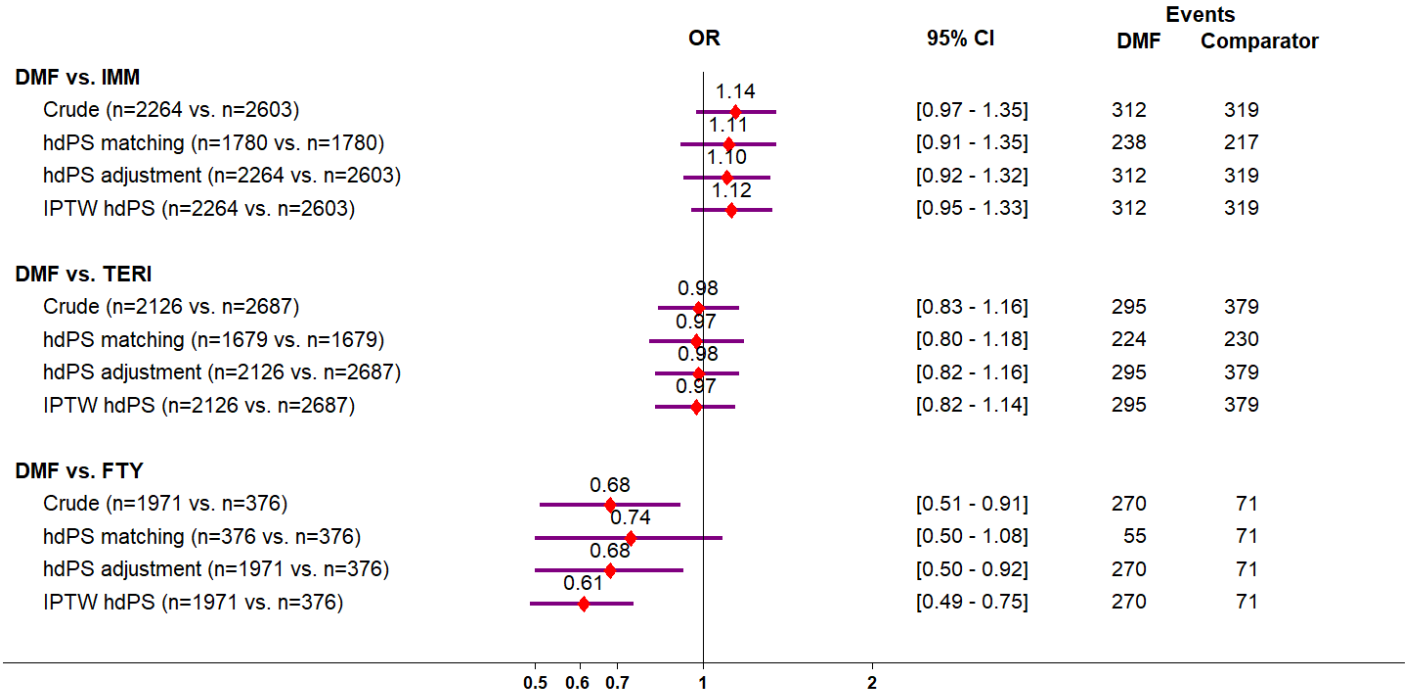


Figure 4

Forest plot of disability progression for DMF versus comparator populations (OR [95% CI]). DMF dimethyl fumarate, TERI teriflunomide, IMM Injectable Immunomodulators, FTY fingolimod.