Comparative effectiveness of teriflunomide and dimethyl fumarate

A nationwide cohort study

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Abstract

Objective

To compare on-treatment efficacy and discontinuation outcomes in teriflunomide (TFL) and dimethyl fumarate (DMF) in the treatment of relapsing-remitting multiple sclerosis (RRMS) in a real-world setting.

Methods

We identified all patients starting TFL or DMF from the Danish Multiple Sclerosis Registry and compared on-treatment efficacy outcomes between DMF using TFL, adjusted for clinical baseline variables and propensity score-based methods.

Results

We included 2,236 patients in the study: 1,469 patients on TFL and 767 on DMF. Annualized relapse rates (ARRs) in TFL and DMF were 0.16 (95% confidence interval [CI] 0.13–0.20) and 0.09 (95% CI 0.07–0.12), respectively. Relapse rate ratio for DMF/TFL was 0.58 (95% CI 0.46–0.73, $p < 0.001$). DMF had a higher relapse-free survival proportion at 48 months of follow-up ($p < 0.05$). We observed no difference in Expanded Disability Status Scale score worsening. Discontinuations due to disease breakthrough were 10.2% (95% CI 7.6%–12.8%) and 22.1% (95% CI 19.2%–25.0%) for DMF and TFL, respectively. A subgroup analysis of ARRs in 708 patients with available baseline MRI T2 lesion amount reported similar results after adjustment.

Conclusion

We found lower ARR, higher relapse-free survival, and lower incidence of discontinuation due to disease breakthrough on treatment with DMF compared with TFL.

Classification of evidence

This study provides Class II evidence that for patients with RRMS, DMF is more effective in preventing relapses and has lower discontinuation due to disease breakthrough compared with TFL.

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Glossary

ARR = annualized relapse rate; **CI** = confidence interval; **CONFIRM** = Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis; **DEFINE** = Determination of the Efficacy and Safety of Oral Fumarate in Relapsing–Remitting MS; **DMF** = dimethyl fumarate; **DMSR** = Danish Multiple Sclerosis Registry; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **IPTW** = inverse probability of treatment weights; **MS** = multiple sclerosis; **OR** = odds ratio; **RRMS** = relapsing–remitting multiple sclerosis; **TEMSO** = Teriflunomide Multiple Sclerosis Oral; **TFL** = teriflunomide; **TOWER** = An Efficacy Study of Teriflunomide in Participants With Relapsing Multiple Sclerosis.

Dimethyl fumarate (DMF) 240 mg and teriflunomide (TFL) 14 mg were approved as oral disease-modifying therapies (DMTs) in 2013 and 2014, respectively, and are typically used as first-line treatment in relapsing–remitting multiple sclerosis (RRMS). Two randomized placebo-controlled phase III trials (Teriflunomide Multiple Sclerosis Oral [TEMSO] and An Efficacy Study of Teriflunomide in Participants With Relapsing Multiple Sclerosis [TOWER]) were performed to investigate efficacy and safety of TFL and demonstrated significant effects of 14 mg daily TFL on annualized relapse rates (ARRs) and 12-week confirmed disability progression compared to placebo. TEMSO also demonstrated significant positive effects on MRI parameters.^{1,2} In addition, compared with placebo, TFL significantly reduced the risk of developing clinically definite multiple sclerosis (MS) in patients with clinically isolated syndrome (CIS).³

Effectiveness of DMF was demonstrated in 2 randomized placebo-controlled phase III trials (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing–Remitting MS [DEFINE] and Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis [CONFIRM]) showing a significant effect on ARR reduction compared with placebo, while only 1 trial (DEFINE) showed significant effects of DMF on disability progression. Both DEFINE and CONFIRM showed significantly positive effects on MRI parameters in patients administered DMF compared to those given placebo.^{4,5} In the CONFIRM study, in which glatiramer acetate was included as a reference arm, DMF showed a numerically but not a statistically significant larger reduction of the ARR.

While randomized trials have shown superior efficacy in reducing disease activity compared with placebo in both formulations, knowledge of the comparative effectiveness between TFL and DMF is sparse. One indirect comparison study has suggested a superior effect of DMF on ARR reduction compared with TFL, while no significant difference was found for disability worsening.⁶ Another study compared the efficacy of TFL and DMF on the basis of insurance claims databases and reported a favorable effect of DMF on ARR compared with TFL.⁷ However, indirect comparison studies will always risk being inherently biased due to heterogeneous patient characteristics, diverging inclusion criteria, and different endpoint definitions.

Assessing the comparative effectiveness of DMF and TFL in a direct population-based head-to-head study could provide

important evidence for future treatment guidelines of patients with MS. We present a nationwide, registry-based, propensity score–adjusted cohort study comparing efficacy and discontinuation outcomes in patients treated with either TFL or DMF.

Methods

Data sources

The health care system in Denmark is government financed with free and equal access for all citizens. All Danish citizens are assigned a unique and permanent civil registration number at birth or immigration that allows cross-linkage of data from Danish nationwide administrative registers.

All DMTs are provided free of charge by the treating hospital, and it is mandatory for the hospital to report clinical data on all treated patients to the Danish Multiple Sclerosis Registry (DMSR). Hence, the registry has a high completeness and density, and it contains information on all patients with MS and clinically isolated syndrome treated with DMT in Denmark. During every clinical visit in the 14 Danish MS clinics, the treating neurologist enters information directly into the registry using an online platform at treatment start and follow-up visits, which are at 3 and 6 months and then every 6 months. Available variables include Expanded Disability Status Scale (EDSS) scores, information on DMT, relapse data, MRI data, adverse effects, cause and date of treatment discontinuation or switch, year of disease onset and diagnosis, disease course, onset symptoms, and diagnosis.^{8,9} We obtained information on sex, date of birth, death, and emigration from the Danish Central Person Registry and cross-linked data to the DMSR.

Data quality is ensured regularly and locally by the treating clinics using patient health records under coordination by the data coordinator at the DMSR. Data quality is also ensured centrally at the DMSR by the associated data manager. The DMSR has the status of a national clinical quality database, enabling Danish health authorities to monitor the quality of MS treatment. This imposes a yearly check of data quality by the Danish government.

Study population and outcomes

We included all patients with RRMS in Denmark diagnosed with relapsing–remitting MS according to the 2001 or 2010

McDonald criteria^{10,11} who had started treatment with TFL or DMF from October 1, 2013, until May 6, 2018, when data were extracted.

We followed up patients from treatment start until treatment switch/discontinuation, death, emigration, or May 6, 2018, whichever came first. Accordingly, this study examined on-treatment effects. Patients not having a clinical visit for 3 years were considered lost to follow-up and censored at the time of the last visit.

Exclusion criteria at baseline were age <18 years at treatment initiation, previous treatment with a high-efficacy DMT, previous treatment with off-label DMT, >2 previous DMT types, previous treatment duration >8 years, and insufficient baseline data on relapse rate and EDSS. These exclusion criteria were selected to minimize potential unmeasured confounding while still providing a fair reflection of the majority of treated patients with either drug. In patients treated with both TFL and DMF at different time points, we included the first of the 2 for the study. High-efficacy treatment was defined as natalizumab, fingolimod, cladribine, alemtuzumab, ofatumumab, daclizumab, mitoxantrone, ocrelizumab, or previous stem cell transplantation. Off-label therapy was defined as methotrexate, treosulphan, cyclic prednisone, rituximab, or IV human immunoglobulin therapy.

The primary outcomes were ARRs and relapse rate ratio between DMF and TFL. Secondary outcomes included time to first relapse, time to 6-month confirmed EDSS score worsening, and cumulative incidence functions for cause-specific treatment discontinuation/switch due to disease breakthrough or adverse events.

We defined time to first relapse as the interval between treatment start and the first occurrence of a relapse.

EDSS score worsening was defined as a sustained increase in EDSS score confirmed on 2 consecutive visits at least 6 months apart. The required increase was defined as ≥ 1.5 point in patients with a baseline EDSS score of 0, ≥ 1 point with a baseline EDSS score of 1 to 5.5, and ≥ 0.5 point with a baseline EDSS score > 5.5 . If we identified confirmed EDSS score worsening, we selected the time to the date of the first visit reporting worsening (not the confirming visit date). As a sensitivity analysis, we also examined 3-month confirmed EDSS score worsening.

When a treatment is discontinued, the treating neurologist has to assign one of the following reasons for discontinuation: disease breakthrough, adverse event, pregnancy related, progression to secondary progressive MS, stable disease, or other cause. The ambiguous discontinuation cause stable disease is used for patients with long treatment durations without signs of activity wishing to stop treatment. For the analysis, we grouped discontinuation reasons into disease breakthrough, adverse event, and pregnancy related and pooled the rest

together as other causes. We then estimated cumulative incidences of discontinuation due to disease breakthrough or adverse events while accounting for competing risks of discontinuation due to other reasons.

For a subgroup of patients, data on numeric baseline T2 lesion number from baseline MRI scans were available in the DMSR. To be considered a baseline MRI scan, it had to be conducted from 6 months before treatment initiation to 1 month after treatment start. If multiple MRIs were available in this time period, we used the MRI scan closest to the start of follow-up. We categorized patients according to the number of lesions on their baseline MRI: 0 to 9, 10 to 20, and > 20 T2 lesions.

Statistical analysis

We described baseline characteristics with means and SDs for continuous variables and in counts and percentages for binary variables.

We modeled ARRs using negative binomial regression and calculated both crude and adjusted results adjusting for age, sex, previous 24-month baseline relapse activity, disease duration, number of previous treatments, and baseline EDSS score group (0, 1–2.5, 3–3.5, 4–4.5, 5–5.5, 6–6.5, and > 6.5). Furthermore, we modeled ARRs by a stabilized inverse probability of treatment weights (IPTW)–weighted negative binomial regression model using a robust variance generalized estimating equation model with an independent covariance matrix.^{12,13} We selected a negative binomial distribution model because data were overdispersed when we applied a Poisson distribution. In addition, we estimated relapse rate ratios using negative binomial regression calculating both crude, adjusted and weighted ratios of DMF/TFL.

For all analyses, we computed IPTW. This is a propensity score–based weight used to control for confounding by indication.^{14,15} We calculated the propensity scores using multivariable logistic modeling for assignment to DMF and included age, sex, prior 24-month baseline relapse activity, disease duration, number of previous treatments, and baseline EDSS score category. Variables were selected on the basis of the presumed predictive value on treatment selection.¹⁶ We assessed the balancing effect of IPTW by comparing standardized differences in baseline variables before and after weighting. Furthermore, we assessed the distribution and means of stabilized IPTW.¹⁶

We calculated the time to first relapse and time to 6-month confirmed EDSS score worsening using nonparametric Kaplan-Meier analyses. We tested for differences between treatment groups using the log-rank test and calculated 95% point-wise confidence intervals (CIs) for the survival estimates.^{17,18} We calculated both crude and stabilized IPTW-weighted analyses for each outcome.^{19,20} As a sensitivity analysis, we performed the stabilized IPTW-weighted analyses using the intention-to-treat principle for the EDSS worsening outcome. In these analyses,

patients were censored at death, emigration, or May 6, 2018. Furthermore, we performed a sensitivity analysis examining IPTW-adjusted time to 3-month confirmed EDSS score worsening.

We analyzed cause-specific discontinuation of treatment due to disease breakthrough or adverse events using IPTW-weighted cumulative incidence functions, accounting for competing risks of discontinuation due to other causes or death, as described previously. We obtained CIs by bootstrapping methods.²¹ The analysis was conducted in a competing risk setting to avoid overestimation.

For patients with available MRI information on baseline lesion load, we repeated the main outcomes of ARRs and relapse rate ratios, adding T2 lesion load as a categorical covariate in the regression models. We tested for a difference in baseline T2 lesion category between treatment groups using the χ^2 test.

Pregnancy is a known modifier of MS activity, mediating lower disease activity during pregnancy and higher activity 3 to 6 months after pregnancy.²² We conducted 2 sensitivity analyses of the primary outcome of relapse rate ratio to assess any potential confounding caused by previous pregnancy. We calculated adjusted relapse rate ratio in 2 subgroups: the first excluding patients with a previous discontinuation due to pregnancy and the second including only male patients.

We performed all analyses with SAS software, version 9.4 (SAS Institute, Inc, Cary, NC).

Standard protocol approvals, registrations, and patient consents

This study was approved by the Danish Data Protection Agency (journal No. RH-2017-347, I-Suite No: 06058). Noninterventional register-based studies do not require ethics approval in Denmark.

Data availability

Anonymized data will be shared on request from any qualified investigator under approval from the Danish Data Protection Agency.

Results

Of 4,227 patients treated with TFL or DMF, a total of 2,236 patients were eligible for inclusion, with 1,469 and 767 patients starting TFL and DMF, respectively (figure 1). Baseline characteristics are shown in the table. Patients treated with DMF tended to be younger, less treatment-naïve, and more often female. In accordance with the exclusion criteria, patients who were previously treated with DMT had received interferons or glatiramer acetate.

The total follow-up time in all patients included was 4,514.5 person-years, with each patient contributing on average with 2.0 years of follow-up time. A total of 8,347 recorded clinical visits were available in the observational period; 78% of these visits were conducted according to the standard follow-up scheme at 3 months after treatment initiation and 6 months afterward, allowing for a deviation of 30 and 60 days for first

Figure 1 Patient inclusion flowchart

Table Baseline characteristics

	Teriflunomide (n = 1,469)	Dimethyl fumarate (n = 767)
Female sex, n (%)	940 (64.0)	581 (75.8)
Mean age (SD), y	41.7 (10.6)	39.0 (10.7)
Mean follow-up (IQR), y	1.9 (0.7–3.0)	2.3 (0.9–3.6)
Mean disease duration (SD), y	6.4 (7.4)	7.1 (7.0)
Mean EDSS score (SD)	2.0 (1.3)	1.9 (1.3)
Mean prior 24-mo relapses (SD), n	1.0 (0.8)	0.8 (0.9)
Prior DMT, n (%)		
0	974 (66.3)	278 (36.3)
1	385 (26.2)	376 (49.0)
2	110 (7.5)	113 (14.7)
MRI subgroup	Teriflunomide (n = 560)	Dimethyl fumarate (n = 148)
T2 lesion amount, n (%)		
0–9	204 (36.4)	60 (40.5)
10–20	202 (36.1)	41 (27.7)
>20	154 (27.5)	47 (31.8)

Abbreviations: DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IQR = interquartile range.

and subsequent visits. Of the 22% not following these criteria, the median delay was 146 days. Nine patients (0.4%) did not have a visit for 3 years and were considered lost to follow-up.

We calculated IPTW from the propensity score for DMF treatment. The multivariate regression model used to calculate the propensity score reported statistically higher propensity for DMF treatment with lower age (odds ratio [OR] 0.97, 95% CI 0.96–0.98), female sex (OR 1.7, 95% CI 1.4–2.1), and increasing DMT attempts (OR 2.5, 95% CI 2.1–2.9). Variables included in the model that were not statistically significant were increasing prior 24-month relapse rate (OR 1.1, 95% CI 0.95–1.2), increasing EDSS score category (OR 0.95, 95% CI 0.84–1.1), and increasing disease duration (OR 1.0, 95% CI 0.99–1.0). When graphically evaluated, the propensity scores of both treatment groups had a high level of common support with no evidence of nonoverlapping areas. The mean of the stabilized weights was 1.00 with an SD of 0.39. We found no evidence of a violation of the positivity assumption in the IPTW weighting. Our assessment of the balancing effect of IPTW weighting found that all baseline variables had mean standardized differences <0.1 after weighting, which indicated

a good balancing effect. Figure 2 provides details on balancing.

A total of 608 relapses occurred during follow-up, 433 in TFL-treated patients and 175 in DMF-treated patients. Crude ARR were 0.20 (95% CI 0.17–0.22) and 0.11 (95% CI 0.09–0.14) for TFL and DMF, respectively. Adjusted ARR were 0.16 (95% CI 0.13–0.20) and 0.09 (95% CI 0.07–0.12) for TFL and DMF, respectively. IPTW-weighted ARR were 0.19 (95% CI 0.16–0.21) and 0.11 (95% CI 0.09–0.14) for TFL and DMF, respectively.

Crude relapse rate ratio (DMF/TFL) was 0.57 (95% CI 0.45–0.72, $p < 0.001$). Adjusted relapse rate ratio (DMF/TFL) was 0.58 (95% CI 0.46–0.73, $p < 0.001$). Stabilized IPTW-weighted relapse rate ratio (DMF/TFL) was 0.60 (95% CI 0.47–0.77, $p < 0.001$).

In the adjusted negative binomial regression models, statistically significant predictive variables of relapse activity were treatment type (TFL vs DMF), decreasing age, decreasing disease duration, increasing baseline relapse activity, and baseline EDSS score category. The dispersion parameter was 1.6 (95% CI 1.2–2.1). When we excluded a total of 55 women with previous treatment discontinuation due to pregnancy, the adjusted relapse rate ratio (DMF/TFL) was 0.55 (95% CI 0.43–0.69, $p < 0.001$). When we included only male patients, the adjusted relapse rate ratio was 0.66 (95% CI 0.43–1.00, $p = 0.054$).

In the analysis of time to first relapse, we found a statistically significant difference between treatment groups in both the crude and IPTW-weighted models when tested with the log-rank test. Estimates of the crude and IPTW-weighted models

Figure 2 Mean standardized baseline differences between treatment groups

DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IPTW = inverse probability of treatment weights. Line indicates a difference of 0.1 between treatment groups.

were similar. The IPTW-weighted survival curve is depicted in figure 3.

Mean EDSS score changes during the study period were 0.03 (SD 1.06) for TFL and -0.02 (SD 0.98) for DMF patients. Six-month confirmed EDSS score worsening occurred in 94 TFL patients and 63 DMF patients. We found no difference between the treatment groups in either crude or IPTW-weighted analyses. The IPTW-weighted survival curve is depicted in figure 4. We found similar results for 3-month confirmed EDSS score worsening. In the intention-to-treat analysis of 6-month confirmed EDSS score worsening, we found a statistically significant difference between treatment groups, with DMF-treated patients having an $\approx 7\%$ higher chance of remaining free of EDSS score worsening at 48 months. Figure 5 provides details.

We report IPTW-weighted cumulative incidences of cause-specific discontinuation due to disease breakthrough or adverse events in figure 6. In total, 917 patients discontinued DMT during follow-up. Four patients (0.4%) did not have a specified cause of discontinuation and were excluded from the analysis. During follow-up, discontinuation incidences due to disease breakthrough were 22.4% (95% CI 20.1%–24.7%) for TFL patients and 10.7% (95% CI 8.7%–12.6%) for DMF patients. Cumulative incidence of discontinuation due to adverse events was 18.5% (95% CI 16.7%–20.2%) for TFL patients and 18.0% (95% CI 15.9%–20.2%) for DMF patients.

Information on baseline T2 lesion number was available for 708 patients. MRI scans were performed on average 56.9 days (SD 43.9 days) before treatment start. When categorized by lesion load, group sizes were comparable, with 264 patients (37.3%) having 0 to 9 lesions, 243 (34.3%) with 10 to 20 lesions, and 201 (28.4%) having >20 lesions (table 1). No

Figure 3 Time to first relapse

Inverse probability of treatment weighted. Kaplan-Meier curve showing the probability of relapse-free survival during treatment. Dashed lines indicate 95% point-wise confidence limits. Patients at risk above the x-axis.

Figure 4 Time to 6-month confirmed EDSS score worsening

Inverse probability of treatment weighted. Kaplan-Meier curve showing the probability of Expanded Disability Status Scale (EDSS) score worsening-free survival during treatment. Dashed lines indicate 95% point-wise confidence limits. Patients at risk above the x-axis.

difference in lesion numbers was observed between treatment groups ($p = 0.16$). Adjusted ARR were 0.18 (95% CI 0.10–0.30) and 0.10 (95% CI 0.05–0.18) for TFL and DMF, respectively. Adjusted relapse rate ratio (DMF/TFL) was 0.55 (95% CI 0.35–0.88, $p = 0.012$). Baseline T2 lesion number category was not a statistically significant predictive covariate for either ARRs or relapse rate ratios in our data.

Discussion

In this nationwide population-based observational study directly comparing efficacy outcomes between 2 DMTs commonly used as initiating therapy in Denmark, DMF showed a superior effect in reducing ARRs compared with TFL.

Figure 5 Time to 6-month confirmed EDSS score worsening

Inverse probability of treatment weighted, intention-to-treat analysis. Kaplan-Meier curve showing the probability of Expanded Disability Status Scale (EDSS) score worsening-free survival until death, emigration, or study end. Dashed lines indicate 95% point-wise confidence limits. Patients at risk above the x-axis.

Figure 6 Cumulative incidences of cause-specific discontinuation

Inverse probability of treatment weighted. Dashed lines indicate 95% confidence intervals.

Analyses of the adjusted relapse rate ratio (DMF/TFL) showed a 42% lower relapse rate in patients treated with DMF. Our main results proved robust after adjustment for potential confounding effects of baseline T2 lesion number.

In line with these results, the risk of having a first relapse was lower in the DMF-treated patients.

We did not find any differences in 3- or 6-month confirmed EDSS score worsening, which was not unexpected because confirmed EDSS score worsening is rather uncommon in patients early in the disease course with a short follow-up period and low EDSS score. Several clinical trials have failed this outcome comparing active treatment with placebo or comparing 2 DMTs.^{4,23–25} The intention-to-treat analysis of 6-month confirmed EDSS score worsening, however, showed a minor but statistically significantly higher proportion of patients free of worsening in the DMF group.

We found a higher incidence of discontinuation due to disease breakthrough in patients receiving TLF compared with those receiving DMF as a reflection of the higher relapse activity shown in the TFL group.

The frequencies of discontinuation due to adverse events were similar in the 2 groups; however, our data do not contain information on either the nature or the severity of the adverse events, which could potentially differ between treatment groups. TFL often causes an increase in liver enzyme function, diarrhea, nausea, and hair thinning,² while the most frequent adverse effects associated with DMF include flushing and gastrointestinal events such as diarrhea, nausea, and upper abdominal pain, as well as decreased lymphocyte counts.⁵

Evidence of the comparative effectiveness between TFL and DMF is rare. An indirect comparison study based on previously published clinical trials using a mixed treatment comparison method reported a relapse rate ratio of 0.78 (95% CI 0.61–0.98) when comparing DMF 240 mg daily to TFL 14 mg daily, which supports our findings. Furthermore, those investigators found no statistically significant difference in 12-week disability progression between DMF and TFL.⁶

A study based on a large US insurance claims database reported a relapse rate ratio of 1.23 favoring DMF in the year after treatment initiation.⁷ An important limitation of that study was the definition of a relapse as insurance claims for MS-related admissions to clinics and reimbursement claims on steroids, as opposed to direct relapse assessment by a treating physician. The DMSR is a nationwide population-based registry with mandatory data collection in daily clinical practice by all treating MS neurologists in Denmark. It contains in-depth information on treatments with DMT and clinical information on MS course. We had access to information on all patients treated with DMF and TFL in Denmark. Only 9 patients on ongoing DMT treatment were lost to follow-up.

The proportion of patients without a first relapse is relatively high in our study, suggesting either effective treatments or disease courses with lower disease activity. Included patients in our cohort are treatment-naïve or have been subject to only a maximum of 2 treatment switches to other moderately effective therapies. Exclusion of patients with previous escalation of treatment could explain the observed low disease activity. However, because both investigated therapies are categorized as moderately effective,

we believe that the study population fairly reflects the target group of both drugs.

By having information on and including patients based on the entire Danish population treated with DMT, our study population is representative of the entire population. Furthermore, because all DMTs for MS in Denmark are government financed and free of charge for the patients, the study has avoided any socioeconomic bias related to treatment allocation caused by differences in the price of DMTs, which can be a problem in many countries.

While population-based real-world studies possess an inherent risk of unmeasured confounding, they also provide valuable information on treatment effectiveness in an applied, clinical context. Pivotal clinical trials are conducted using strict inclusion/exclusion criteria, and the results are not always generalizable. We applied modern propensity score-based adjusting measures to endpoints. The method of using IPTW weighting allows estimation of the average treatment effect in the study population, which is the same effect estimated in randomized clinical trials.²⁶ Furthermore, using propensity score-based weighting methods allowed us to include all patients meeting the eligibility criteria of the study. This is in contrast to matching methods, which exclude patients not finding a match. Using weighting ensures transparency of included patients and validity of results in the predefined study population.

A limitation of our study is the lack of knowledge on pregnancy in patients. In Denmark, women planning pregnancy within the next year are prescribed DMF instead of TFL according to the national Danish treatment guidelines.²⁷ Women considering pregnancy may represent patients with a lower disease activity and thus may skew results in favor of DMF. However, women showing objective signs of high disease activity would probably start treatment with a high-efficacy DMT, not TFL. Furthermore, our results proved robust when we excluded women with previous treatment discontinuation due to pregnancy or conducted the analysis in a male subgroup. The slightly lower difference and borderline lack of statistical significance between the compared treatments in the male subgroup are likely caused by a combination of loss of statistical power and a lower mean disease activity in men.

Patients treated with DMF were on average more often female and had fewer previous DMT types at baseline. This finding quite possibly represents the Danish treatment guidelines having TFL as the default choice of first-line treatment for patients not planning a pregnancy. This difference may cause indication bias, but we were able to account for these differences in the statistical analyses.

We aimed to compare on-treatment effectiveness. Consequently, patients were censored if they were switched from TFL/DMF. This limits the ability to detect EDSS score

changes because most patients probably switched treatment before EDSS score worsening became evident. This may contribute to the finding of the lack of difference in on-treatment EDSS score worsening between treatment groups. The sensitivity analysis using the intention-to-treat principle by following up all patients to the date of study end, death, or emigration showed significant differences between treatment groups. However, this result should be interpreted carefully because different subsequent treatment patterns and discontinuation rates could confound this result.

In this nationwide population-based register study, we provide Class II evidence of an $\approx 42\%$ lower ARR in patients treated with DMF compared with patients treated with TFL. Furthermore, we provide evidence of a lower risk of a first relapse and a lower incidence of discontinuation due to disease breakthrough in patients treated with DMF after adjustment using propensity score-based methods. Results were robust in a sensitivity analysis including MRI T2 lesion numbers at baseline as an adjusting variable.

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Appendix Authors

Name	Location	Role	Contribution
Mathias Buron, MD	Danish Multiple Sclerosis Center, Rigshospitalet, Denmark	Author	Designed and conceptualized the study, extracted and analyzed data, interpretation of results, statistical analysis, wrote the manuscript.
Thor Ameri Chalmer, MD	Danish Multiple Sclerosis Center, Rigshospitalet, Denmark	Author	Interpreted the data, revised the manuscript, assisted in data analysis.
Finn Sellebjerg, MD, PhD, DMSc	Danish Multiple Sclerosis Center, Rigshospitalet, Denmark	Author	Interpreted the data, revised the manuscript.
Jette Frederiksen, MD, PhD, DMSc	Copenhagen University Hospital Rigshospitalet Glostrup, Denmark	Author	Assisted in acquisition and interpretation of data and revised the manuscript.
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Appendix (continued)

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Per Soelberg Sorensen, MD, PhD, DMSc	Danish Multiple Sclerosis Center, Rigshospitalet, Denmark	Author	Conceptualized the study, major role in guidance in design and analysis of the study, major role in interpretation of data and revision of manuscript.
Melinda Magyari, MD, PhD	Danish Multiple Sclerosis Center, Rigshospitalet, Denmark	Author	Conceptualized the study, major role in guidance in design and analysis of the study, major role in interpretation of data and revision of manuscript.

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