ARTICLE OPEN ACCESS

Dimethyl fumarate vs fingolimod following different pretreatments

A retrospective study

Lara Diem, MD, Ariadne Daponte, MD, Oliver Findling, MD, Andrei Miclea, MD, Myriam Briner, MD, Anke Salmen, MD, Ralf Gold, MD, Constantinos Kilidireas, MD, Andrew Chan, MD, Maria Elftheria Evangelopoulos, MD,* and Robert Hoepner, MD*

Correspondence
Dr. Findling
oliver.findling@ksa.ch

Neurol Neuroimmunol Neuroinflamm 2020;7:e660. doi:10.1212/NXI.0000000000000660
e660

Abstract

Objective

Despite frequent use of fingolimod (FTY) and dimethyl fumarate (DMF), studies comparing clinical efficacy and withdrawal rates of DMF and FTY concerning different pretreatment situations are rare. The aim of our study was to compare relapse occurrence and withdrawal rates of DMF and FTY in different pretreatment situations.

Methods

Patients from 4 European centers were retrospectively identified and followed until the 1st relapse after treatment start or if no relapse occurred for a maximum of 2 years. Cox regression analyses adjusted for relapsing-remitting MS (RRMS) disease duration, sex, and region were performed for the following pretreatment situations: treatment naive or injectables or DMF/FTY or natalizumab.

Results

Seven hundred thirty-two patients with RRMS (female/male: 2.4:1.0; DMF n = 409, FTY n = 323) were analyzed. Compared with FTY-treated patients, DMF-treated patients discontinued treatment more frequently mainly because of side effects (DMF/FTY: 29.3%/20.7%). Clinical relapses occurred in 24.5% of the patients within 24 months. Survival analysis demonstrated that compared with FTY treatment, DMF treatment was associated with an adjusted hazard ratio (aHR) for occurrence of relapse of 1.9 (95% CI 1.4–2.6, $p < 0.001$, n = 732). Stratification into pretreatment groups unmasked a higher relapse risk in DMF patients pretreated with natalizumab (aHR [95% CI] 4.5 [1.9–10.8], $p = 0.001$, n = 122) or to a lesser extend also in treatment-naive patients (aHR [95% CI] 1.9 [1.01–3.6], $p = 0.045$, n = 230). No differences were observed in patients pretreated with injectables or the respective other oral drug (injectables: $p > 0.05$, n = 341; other oral: $p > 0.05$, n = 39).

Conclusions

DMF treatment was associated with higher clinical disease activity compared with FTY treatment. A subgroup analysis suggested beneficial effects of FTY in treatment-naive and patients pretreated with natalizumab.

*These authors contributed equally to this work.

From the Department of Neurology (L.D., A.M., M.B., A.S., A.C., M.E.E., R.H.), Inselspital, Bern University Hospital and University of Bern, Freiburgstrasse, Bern, Switzerland; Department of Neurology (A.D., C.K., M.E.E.), Eginition University Hospital, National and Kapodistrian University of Athens, Greece; Department of Neurology (O.F.), Cantonal Hospital Aarau, Tellstrasse, Aarau, Switzerland; Department of Neurology (O.F.), Karl Landsteiner University of Health Sciences, Site Tulln, Austria; and Department of Neurology (R.G.), St. Josef Hospital Ruhr University Bochum, Germany.

Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

Glossary

aHR = adjusted hazard ratio; **DMF** = dimethyl fumarate; **FTY** = fingolimod; **NEDA-3** = no evidence of disease activity-3; **RRMS** = relapsing-remitting MS.

Fingolimod (FTY) and dimethyl fumarate (DMF) are oral immunotherapies approved to treat patients with relapsing-remitting MS (RRMS).[1,2] Several studies have retrospectively compared clinical efficacy between DMF and FTY, demonstrating mostly a similar efficacy.[3–6] Moderate differences between DMF/FTY were present concerning MRI disease activity and treatment tolerability, which was superior in FTY-treated patients. In addition, focusing on the outcome parameter "no evidence of disease activity-3" (NEDA-3), which was reached in DMF- and FTY-treated patients with comparable frequencies, a subgroup analysis, however, unmasked a superiority of FTY in patients switching from self-injectable drugs to the respective oral substance.[6] This different clinical efficacy was not present in treatment-naive patients. Stratification into other pretreatment groups (e.g., pretreatment with natalizumab or the other oral drug) is missing.[6]

Our study will provide real-world data comparing discontinuation rates and clinical efficacy of DMF and FTY concerning the following pretreatment situations: treatment naive, injectables, the other oral drug DMF or FTY, and natalizumab.

Methods

Patient groups studied

We conducted a retrospective observational study over 24 months including 732 patients with RRMS of the 4 participating European centers (figure) who had been treated with DMF (n = 409) or FTY (n = 323). Identification of eligible patients was performed using the following search terms "MS and fingolimod or Gilenya or FTY" in the centers Aarau, Athens, and Bern and "MS and Tecfidera or dimethyl fumarate or fumarate or DMF" in all 4 participating centers to search local clinical information systems within the following time frames for Bern, Aarau, and Athens January 2011–December 2018 and for Bochum January 2011–January 2016. No additional selection criteria were set. All patients identified with this search algorithm were included. MS diagnosis was in accordance with the 2010 McDonald criteria.[7] Definition of clinical MS relapse followed national guidelines. The following variables were extracted from medical records: date of birth, year of MS diagnosis, sex, previous MS medication, date of the adverse event, date of drug withdrawal, date of treatment initiation of DMF or FTY, date of the 1st relapse under DMF or FTY treatment, or if no relapse during the 2-year follow-up occurred date of the last follow-up visit.

Statistical analysis

Categorical data are presented as frequencies and continuous data as means and 95% confidence intervals (95% CI) and compared using for continuous variables Mann-Whitney test and for categorical variables χ^2 test. Survival analyses with the outcome "clinical relapse" were performed using Cox regression analysis adjusted for sex, RRMS disease duration, and region (Switzerland vs Europe). Survival analysis was performed for different pretreatments: (1) treatment naive, (2) previous treatment with injectables (interferon or glatiramer acetate), (3) previous treatment with DMF or FTY, or (4) previous treatment with natalizumab. Level of significance was set to $p < 0.05$.

Ethical approvals

The respective ethic committees Aarau (2016-02233), Bern (2017-01369), Eginition Hospital Athens (1272018-511), and Bochum (5408-15) approved the analysis.

Data availability

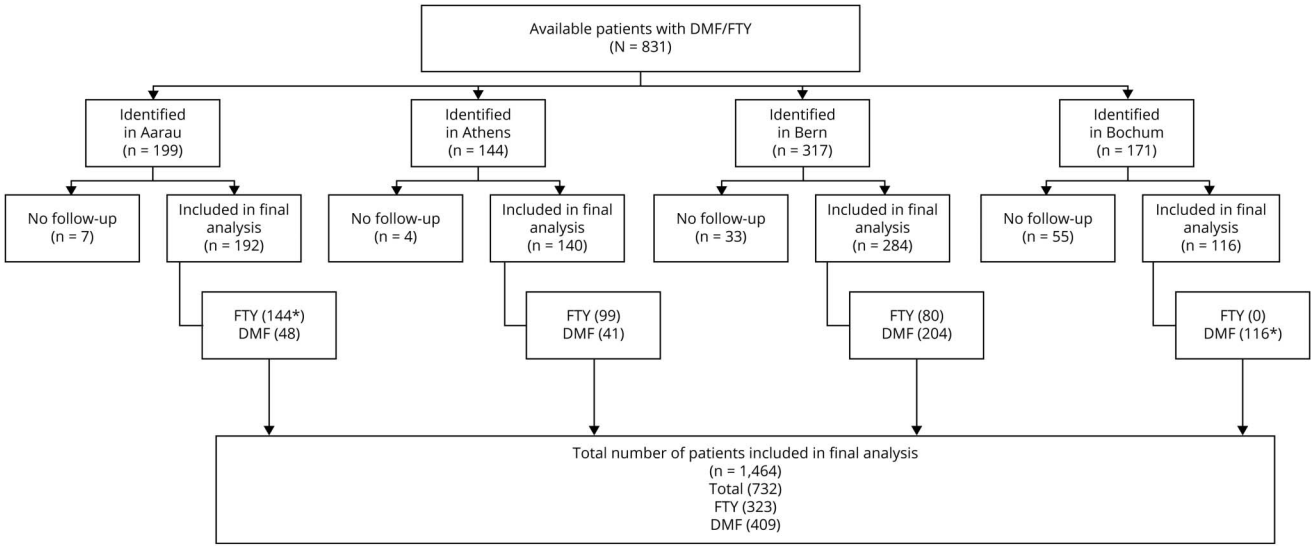
Anonymized source data are available on reasonable request via the corresponding author.

Results

Baseline demographics are shown in table 1. The primary reason for beginning with FTY was disease activity (DMF: 71/409, 17.4% vs FTY: 108/323, 33.4%, $p < 0.001$). Adverse events during previous immunotherapies were the main reason for beginning with DMF (DMF: 113/409, 27.6% vs FTY: 58/323, 18.0%, $p < 0.001$). Drug discontinuation was more common in DMF- than in FTY-treated patients (DMF: 120/409, 29.3% vs FTY: 67/323, 20.7%, $p = 0.008$). Adverse events were the most common reason for withdrawal (table 1). Despite clinical disease activity occurred in 20.4%–27.6% (FTY: 66/323 vs DMF: 113/409) of the patients, in only 33.6%–47.0% (DMF: 38/113 vs FTY: 31/66) of these patients, disease activity let to FTY/DMF withdrawal (table 1). The mean time to the 1st relapse was shorter in DMF-treated patients (years mean [95% CI]: DMF: 0.6 [0.5–0.6], n = 113 vs FTY: 1.0 [0.8–1.1], n = 66; $p < 0.001$), and this differences was the highest in the group pretreated with injectables (years mean [95% CI]: DMF: 0.6 [0.3–0.7], n = 30 vs FTY: 1.1 [0.9–1.3], n = 42; $p < 0.001$, table 1).

Compared with patients treated with FTY, patients treated with DMF had a higher adjusted hazard ratio (aHR) for occurrence of clinical relapse (aHR [95% CI] 1.9 [1.4–2.6], $p < 0.001$, n = 732, table 1). Stratification into pretreatment groups highlighted a higher relapse risk in DMF-treated patients pretreated with natalizumab (aHR [95% CI] 4.5 [1.9–10.8], $p = 0.001$, n = 122, table 1) or to a lesser extent in treatment-naive patients (aHR [95% CI] 1.9 [1.01–3.6], $p = 0.045$, n = 230, table 1). No differences were observed in patients pretreated

Figure Study flowchart



Some patients of this cohort included in (1) Diem et al. TAND 2018 doi: 10.1177/1756286418791103 and (2) Miclea et al. J Neurol 2016 doi: 10.1007/s00415-016-8175-3. Locally used clinical information systems were i-pdos (Phoenix Technologies, Milpitas) in Bern, Orbis (Agfa HealthCare, Mortsel, Belgium) in Bochum, in-house "Demyelinating Diseases Database 1st Department of Neurology" in Athens, and KISIM (Cistec AG, Zürich, Switzerland) in Aarau. DMF = dimethyl fumarate; FTY = fingolimod.

with injectables or the respective other oral drug (injectables: $p > 0.05$, n = 341; other oral: $p > 0.05$, n = 39, table 1).

Discussion

We present a comparison of discontinuation rates and clinical efficacy data of DMF- and FTY-treated patients with RRMS over a follow-up period of 24 months. Taking advantage of the FTY label as 1st-line MS treatment in Switzerland, this study provides a unique patient population for head-to-head comparison of the clinical efficacy of DMF vs FTY in different pretreatment situations including treatment-naive patients.[8] In general, FTY appears to be less frequently withdrawn and clinically more effective in terms of relapse activity in our study. This increased clinical efficacy was present in treatment-naive and in patients pretreated with natalizumab, whereas patients pretreated with injectables or switching from DMF to FTY or vice versa demonstrated to have an equal clinical response to treatment.

In line with previous reports, we demonstrated that discontinuation was more common in DMF- than in FTY-treated patients with adverse drug events being the main reason for drug withdrawal.[5] Concerning disease activity, previous studies reported an equal efficacy[3,4] or a trend toward a higher efficacy of FTY compared with DMF.[5,6] The latter was also present in our study; however, our work provides additional evidence for different drug efficacy in regard to previous immunotherapy. Patients switching from natalizumab and to a lesser degree also treatment-naive patients with MS benefitted from FTY in terms of the outcome "occurrence of relapse", whereas no differences for occurrence of relapses were seen in patients pretreated with injectables or the respective other oral drug.

Prosperini et al.[6] found a superiority of FTY in patients pretreated with injectables, whereas—different to ours—this was not present in treatment-naive patients. Reasons for different findings may be the different end points used and the different drug labels of each study country. Prosperini et al.[6] investigated NEDA-3 status, whereas our investigation purely focused on clinical relapses. Analysis of NEDA-3 status was not possible in our study because of different MRI protocols, frequencies of MRI assessments, and clinical visits between participating centers making a structured end point comparison for MRI and disability readouts prone to centrum biases.

The limitations of our retrospective study will be addressed in the following. Adjustment of the Cox regression analysis for each center was not possible because of small patient and event numbers in each single center, respectively (supplementary table 1, links.lww.com/NXI/A174), creating a limitation of our analysis. We therefore adjusted for region (Switzerland vs EU), as recommended in such cases by the European Medicine Agency.[9] Adjustment for region is justified by the country-specific label of FTY considering 1st- (Switzerland) vs 2nd-line treatment (Europe: Germany and Greece), which might have had the greatest influence on our analysis.[10] Patients were identified in the centers using predefined terms to search the existing local clinical information systems (figure). No other selection criteria were set. Whether in general, the setting of university and large academic MS centers creates a selection bias, cannot be

Table 1 Description of fingolimod (n = 323) or DMF (n = 409) treated patients and Cox regression models to predict clinical disease activity

	FTY	DMF	*p* Value
N (%)	323 (44.1)	409 (55.9)	
Centre, N (%)			
Aarau	144/323 (44.6)	48/409 (11.7)	NA
Athens	99/323 (30.7)	41/409 (10.0)	NA
Bern	80/323 (24.8)	204/409 (49.9)	NA
Bochum	0/323 (0.0)	116/409 (28.4)	NA
Female, N (%)	226/323 (70.0)	292/409 (71.4)	0.674
Age in years, mean (95% CI)	39.6 (37.5–40.0)	40.0 (38.8–41.2)	0.271
Disease duration in y, mean (95% CI)	6.8 (6.1–7.5)	5.9 (5.7–6.6)	**0.001**
MS treatment before DMF or FTY, N (%)			
Treatment naive	66/323 (20.4)	164/409(40.1)	**<0.001**
Injectables	183/323 (56.7)	158/409 (38.6)	**<0.001**
DMF	12/323 (3.7)	NA	NA
Fingolimod	NA	27/409 (6.6)	NA
Natalizumab	62/323 (19.2)	60/409 (14.7)	0.103
Primary reasons for beginning with DMF or FTY, N (%)			
PML risk during NTZ	79/323 (24.5)	52/409 (12.7)	**<0.001**
Medication adverse effects	58/323 (18.0)	113/409 (27.6)	**<0.001**
Disease activity	108/323 (33.4)	71/409 (17.4)	**<0.001**
Postpregnancy	1/323 (0.3)	1/409 (0.2)	0.980
Treatment naive	66/323 (20.4)	162/409 (39.6)	**<0.001**
Unknown	11/323 (3.4)	10/409 (2.4)	0.439
Discontinuation of DMF/FTY, N (%)	67/323 (20.7)	120/409 (29.3)	**0.008**
Disease activity	31/323 (9.6)	38/409 (9.3)	0.888
Medication adverse effects	27/323 (8.4)	64/409 (15.6)	**0.005**
Pregnancy	4/323 (1.2)	9/409 (2.2)	0.328
Unknown	5/323 (1.5)	9/409 (2.2)	0.522
Mean time to discontinuation of DMF/FTY, y (95% CI)	1.5 (1.2–1.8)	0.8 (0.7–1.0)	**<0.001**
Treatment naive	0.8 (0.5–1.1)	0.7 (0.5–0.9)	0.157
Injectables	2.0 (1.5–2.5)	1.1 (0.7–1.4)	**0.005**
Other oral (e.g., DMF → FTY)	1.1 (0.5–1.7)	1.0 (0.2–1.7)	0.307
Natalizumab	0.8 (0.3–1.5)	0.8 (0.3–1.1)	0.905
Clinical relapse within 12 mo, N (%)	37/323 (11.5)	95/409 (23.2)	**<0.001**
Clinical relapse within 24 mo, N (%)	66/323 (20.4)	113/409 (27.6)	**0.025**
Mean time to first relapse in y, mean (95% CI)	1.0 (0.8–1.1)	0.6 (0.5–0.6)	**<0.001**
Treatment naive	0.8 (0.5–1.1)	0.6 (0.5–0.7)	0.375
Injectables	1.1 (0.9–1.3)	0.6 (0.3–0.7)	**<0.001**

Continued

Table 1 Description of fingolimod (n = 323) or DMF (n = 409) treated patients and Cox regression models to predict clinical disease activity *(continued)*

	FTY	DMF	*p* Value
Other oral (e.g., DMF → FTY)	0.9 (−1.1–3.1)	0.6 (0.1–1.2)	0.865
Natalizumab	0.5 (0.0–3.0)	0.4 (0.2–0.6)	0.979

	aHR (95% CI)	N	*p* Value
All patients	1.9 (1.4–2.6)	732	**<0.001**
Treatment naive	1.9 (1.01–3.6)	230	**0.045**
Injectables	1.5 (0.9–2.5)	341	0.085
Other oral (e.g., DMF → FTY)	1.4 (0.2–8.3)	39	0.736
Natalizumab	4.5 (1.9–10.8)	122	**0.001**

Abbreviations: aHR = adjusted hazard ratio; DMF = dimethyl fumarate; DMT = disease-modifying treatment; EU = European Union; FTY = fingolimod; injectables = interferon or glatiramer acetate; NA = not applicable; NTZ = natalizumab; PML = progressive multifocal leukoencephalopathy.
Statistics: for continuous variables, the Mann-Whitney test was used, and for categorical variables, the χ^2 test was used. Cox regression was adjusted for sex, disease duration, and region (Switzerland vs EU). aHRs are displayed for DMF compared with fingolimod. Significant *p* values are written in bold letters. Clinical information systems in use were i-pdos (Phoenix Technologies, Milpitas) in Bern, Orbis (Agfa HealthCare, Mortsel, Belgium) in Bochum, in-house "Demyelinating Diseases Database of 1st Department of Neurology" in Athens, and KISIM (Cistec AG, Zürich, Switzerland) in Aarau.

sufficiently answered, and should be kept in mind when interpreting our data.

In addition, other limitations are the relatively small sample size in the group pretreated with DMF or FTY and the nonstandardized treatment approach within the 4 participating centers, e.g., different washout periods between medication switch, different intervals of MRI, and clinical investigations. However, as we present a real-world study, the latter limitation, which interferes with data analysis, mainly reflects the clinical situation of most neurologists treating patients with MS.

Considering the growing armamentarium of immunotherapies for patients with MS and the known effects of medication withdrawal and switch during MS disease course, our study, which provides evidence for decision-making processes, may guide physicians throughout clinically challenging treatment options.

Study funding

No targeted funding reported.

Disclosure

L. Diem received travel grants from Merck, Biogen, Roche, and Bayer Schweiz. A. Daponte reports no disclosures. O. Findling received compensation for consulting and travel from Bayer, Biogen, Roche, Teva, Sanofi Genzyme, Merck, Allmirall, and Novartis. A. Miclea reports no disclosures. M. Briner received travel grants from Merck and Biogen. A. Salmen received speaker honoraria and/or travel compensation for activities with Almirall Hermal GmbH, Biogen, Merck, Novartis, Roche, and Sanofi Genzyme, none related to this work. R. Gold received speaker's and board honoraria from Biogen Idec, Baxter, Bayer Schering, Chugai Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Aventis, Talecris, and Teva. He also received scientific grant support from Biogen Idec, Bayer Schering, Genzyme, Merck Serono, and Teva. C. Kilidireas has received travel grants and consulting fees from Biogen, Sanofi, Novartis, Roche, Teva, and Serono. A. Chan has received compensation for activities with Actelion, Almirall, Bayer HealthCare, Biogen, Celgene, Genzyme, Merck, Novartis, Sanofi-Aventis, and Teva Neuroscience, all for university research funds, and research support from Biogen, Genzyme, and UCB. M.E. Evangelopoulos has received travel grants and consulting fees from Biogen, Novartis, Genzyme, Teva, Merck, and Roche. R. Hoepner received research and travel grants from Novartis and Biogen Idec. He also received speaker's honoraria from Biogen, Novartis, Merck, and Almirall. Go to Neurology.org/NN for full disclosures.

Publication history

Received by *Neurology: Neuroimmunology & Neuroinflammation* June 17, 2019. Accepted in final form November 22, 2019.

Appendix Authors

Name	Location	Role	Contribution
Lara Diem, MD	Inselspital University Hospital and University of Bern, Bern, Switzerland	Author	Contributed to the design of the study, acquisition of data, analysis and interpretation of the data, and writing and revision of the manuscript

Continued

Appendix *(continued)*

Name	Location	Role	Contribution
Ariadne Daponte, MD	Eginition University Hospital, National and Kapodistrian University of Athens, Athens, Greece	Author	Contributed to the acquisition of data and revised the manuscript for intellectual content
Oliver Findling, MD	Cantonal Hospital Aarau, Aarau, Switzerland, and Department of Neurology, Karl Landsteiner University of Health Sciences, Site Tulln, Tulln, Austria	Author	Contributed to the acquisition of data and revised the manuscript for intellectual content
Andrei Miclea, MD	Inselspital University Hospital and University of Bern, Bern, Switzerland	Author	Contributed to the acquisition of data and revised the manuscript for intellectual content
Myriam Briner, MD	Inselspital University Hospital and University of Bern, Bern, Switzerland	Author	Contributed to the acquisition of data and revised the manuscript for intellectual content
Anke Salmen, MD	Inselspital University Hospital and University of Bern, Bern, Switzerland	Author	Contributed to the interpretation of the data and the writing and revision of the manuscript
Ralf Gold, MD	St. Josef Hospital Ruhr University Bochum, Bochum, Germany	Author	Contributed to the acquisition of data and revised the manuscript for intellectual content
Constantinos Kilidireas, MD	Eginition University Hospital, National and Kapodistrian University of Athens, Athens, Greece	Author	Contributed significantly to the data analysis and digitalization during the review process
Andrew Chan, MD	Inselspital University Hospital and University of Bern, Bern, Switzerland	Author	Contributed to the interpretation of the data and the writing and revision of the manuscript
Maria Eleftheria Evangelopoulos, MD	Eginition University Hospital, National and Kapodistrian University of Athens, Athens, Greece	Author	Contributed to the design of the study, acquisition of data, analysis and interpretation of the data, and writing and revision of the manuscript
Robert Hoepner, MD	Inselspital University Hospital and University of Bern, Bern, Switzerland	Author	Contributed to the design of the study, acquisition of data, analysis and interpretation of the data, and writing and revision of the manuscript

References

1. Calabresi PA, Radue EW, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): A double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13:545–556.
2. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367:1098–1107.
3. Vollmer B, Ontaneda D, Bandyopadhyay A, et al. Discontinuation and comparative effectiveness of dimethyl fumarate and fingolimod in 2 center. Neurol Clin Practica 2018;8:292–301.
4. Ontaneda D, Nicholas J, Carraro M, 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 2019;27;101–111.
5. Hersh CM, Love TE, Cohn S, et al. Comparative efficacy and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 12-month follow-up. Mult Scler Relat Disord 2016;10:44–52.
6. Prosperini L, Lucchini M, Haggiag S, et al. Fingolimod vs dimethyl fumarate in multiple sclerosis: a real-world propensity score-matched study. Neurology 2018;91:e153–e161.
7. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292–302.
8. Arzneimittelinformation, Swissmedic. Available at: swissmedicinfo.ch/. Accessed March 1, 2011.
9. EMA-guideline on Adjustment for Baseline Covariates in Clinical Trials, EMA/CHMP/295050/2013. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-adjustment-baseline-covariates-clinical-trials_en.pdf.
10. Achtnichts L, Chan A, Czaplinski A, et al. Specific aspects of immunotherapy for multiple sclerosis in Switzerland: A structured commentary. Clin Translational Neurosci 2019;3:1–9.

Dimethyl fumarate vs fingolimod following different pretreatments: A retrospective study

Lara Diem, Ariadne Daponte, Oliver Findling, et al.

Neurol Neuroimmunol Neuroinflamm 2020;7;
DOI 10.1212/NXI.0000000000000660