Dimethyl fumarate vs fingolimod following different pretreatments

A retrospective study

Lara Diem, MD, Ariadne Daponte, MD, Oliver Findling, MD, Andrei Miclea, MD, Anke Salmen, MD, Ralf Gold, MD, Constantinos Kilidireas, MD, Andrew Chan, MD, Maria Elferthia Evangelopoulos, MD,∗ and Robert Hoepner, MD∗

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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.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.

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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 \(\chi^2\) 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 with DMF or FTY.
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. 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. Concerning disease activity, previous studies reported an equal efficacy, or a trend toward a higher efficacy of FTY compared with DMF. 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. 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. 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. 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. 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  |
| Injectable                      | 183/323 (56.7) | 158/409 (38.6) | <0.001  |
| DMF                            | 12/323 (3.7)   | NA          |         |
| Natalizumab                    | NA         | 27/409 (6.6)  | NA      |
| Treatment naive                | 66/323 (20.4)  | 162/409 (39.6) | <0.001  |
| 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  |
| Known                          | 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   |
| Injectable                      | 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   |
| Injectable                      | 1.1 (0.9–1.3)  | 0.6 (0.3–0.7)  | <0.001  |

Continued
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.

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### 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 χ² 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, Zurich, Switzerland) in Aarau.

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### 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. |
| 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, Tullin, 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                                                  |

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