Original article
Previous treatment influences fingolimod efficacy in relapsing–remitting multiple sclerosis: results from an observational study

Abstract

Objective: Fingolimod (FTY) is licensed as a disease-modifying treatment in highly active relapsing–remitting multiple sclerosis. The aim of the study was to evaluate the efficacy and safety of FTY in a real-life setting and to explore the possible role of clinical and MRI parameters, including previous treatment type, in predicting its efficacy.

Methods: Clinical and MRI data was collected on 127 patients assigned to treatment with FTY in six multiple sclerosis centers in Emilia-Romagna, Italy, between August 2011 and June 2013.

Results: During a mean follow-up period of 10 months (range 1–22), we observed a total of 47 relapses in 39 patients (30.7%); new T2 lesions or gadolinium-enhancing (Gd+) lesions were present at follow-up MRI in 32/71 patients (45%). Expanded disability status scale (EDSS) at the end of the follow-up period was not different when compared to the baseline EDSS. Serious adverse events occurred in three patients (2.4%). A higher proportion of patients previously treated with natalizumab showed clinical (41%) or MRI activity (54%). Previous treatment with natalizumab increased the risk of a relapse within 30 days (versus immunomodulatory drugs; OR: 4.3; *p* = 0.011) and at survival analysis (versus remaining patients; HR: 1.9; *p* = 0.046). Study limitations include a small population sample, a short observation period with variable timing of follow-up MRI and different baseline characteristics of patients previously treated with natalizumab compared to those treated with immunomodulatory drugs.

Conclusions: This study confirms the efficacy of FTY in reducing relapse rate in patients previously treated with immunomodulatory drugs, while it seems to be less effective in patients discontinuing natalizumab. Due to the short duration of follow-up it is not possible to evaluate disability progression; however, no difference was observed between the groups.

Introduction

The efficacy of fingolimod (FTY) as a treatment for relapsing–remitting multiple sclerosis (RRMS) has been demonstrated in comparison to placebo or once weekly intramuscular interferon-beta-1a. In these trials, FTY was superior in reducing relapse rate, progression of disability and in improving neuroradiological outcomes. FTY was able to reduce the annualized relapse rate by up to 61% compared to interferon-beta in RRMS patients with active disease or patients with rapidly evolving RRMS and was registered in Europe by the European
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Medicines Agency\(^4\) and in Italy by the Italian Medicines Agency\(^5\) as a second-line therapy. Natalizumab (NAT) is currently the only other registered second-line medication for RRMS in Europe\(^6\). The predominant risk associated with treatment with NAT is the possibility of developing progressive multifocal encephalopathy (PML). This risk is greater in patients with positive serology for anti-JCV antibodies (JCV-AB\(^+\)), with more than 24 months of treatment and who have previously been treated with immunosuppressive therapy. An interruption of NAT is, therefore, desirable in these patients and FTY could represent a potential alternative therapy for JCV-AB\(^+\) patients after discontinuation of NAT and for RRMS patients with a high disease activity who have failed previous treatments.

Methods and materials

Study population

Clinical and MRI data pertaining to patients treated with FTY between August 2011 and June 2013 at the Multiple Sclerosis Centers of Ferrara, Parma, Modena, Reggio-Emilia, Fidenza and Piacenza, Emilia-Romagna region, Northern Italy, were collected using paper and electronic medical records. In particular, we recorded demographic, clinical and MRI variables at baseline (including sex, age, age at onset, numbers of relapses in the preceding year, expanded disability status scale (EDSS) at onset, baseline MRI parameters, previous treatment type, duration of wash-out, timing of relapses and treatments during the wash-out period) and during follow-up (including timing and severity of relapses, MRI data, information on adverse events, duration of treatment, EDSS at 6 months and at last follow-up).

Statistical methods

Comparisons between groups were made using Student’s t-test for continuous variables and chi-square test for categorical variables. We considered as binary outcome for logistic regression 1) the occurrence of a relapse (at any time, within 60 and within 30 days), 2) an active MRI at follow-up, 3) the presence of Gd\(^+\) lesions at follow-up MRI, and analyzed the impact of baseline clinical and MRI variables on these outcomes. The time taken for a relapse to occur was used to perform survival analysis. Survival rates were calculated by means of the Kaplan–Meier method, and differences between prognostic factors were evaluated using the log-rank test. The impact of single factors on the probability of experiencing a relapse was studied with the Cox survival model. Data was analyzed using STATA 11 (StataCorp, TX, USA)\(^7\).

Results

Patient characteristics

Of the 127 patients included in the study (baseline characteristics are shown in Table 1), 68 had previously been treated with immunomodulatory treatments (IM) (51 with interferon-beta 1a or 1b and 17 with glatiramer acetate), 39 with NAT, 4 with other treatments (2 with azathioprine, 1 with mitoxantrone, 1 with cyclophosphamide), while 16 had not received other treatments for at least 1 year. Twenty patients were treated with pulsed steroids during the wash-out period following discontinuation of natalizumab. Mean duration of the wash-out
period was 18 ± 8 weeks (range: 12–45), mean duration of follow-up was 10 months (range: 1–22). Twenty-six patients had participated in the Expanded Access Program (CFT720DIT03) shortly before FTY commercialization.

Baseline characteristics of patients, stratified by previous treatment (IM versus NAT), are shown in Table 2.

**Study outcomes**

We observed a total of 47 confirmed relapses, during a mean follow-up period of 10 months, in 39 patients (30.7%); disease activity at follow-up MRI (carried out after a mean period of 11.4 months, range: 1–22) was present in 32/71 patients (45%) and Gd⁺ lesions in 12/71 (16.9%) patients. EDSS at 6 months and by the end of the follow-up period was not different when compared to the baseline EDSS.

Forty patients (31.5%) experienced adverse events (including infections, elevated liver function tests, hypertension) while three patients experienced SAEs leading to hospitalization (severe relapse, acute psychosis and hepatotoxicity). Clinical MRI and safety data at follow-up are shown in Table 3.

None of the considered variables (EDSS at baseline, MRI activity at baseline, pulsed steroids during wash-out period, pre-FTY preventive treatment) increased the risk of a relapse at any time or of an active MRI at follow-up while a higher baseline EDSS (OR: 1.7; p = 0.032) and

| Table 1. Baseline characteristics of patients, stratified by previous treatment. |
|---------------------------------|----------------------------------|-----------------|-----------------|-----------------|
|                                  | No. patients/total (%)           |                  |                  |                  |
| **Sex**                         | F, n (%)                         | 94/127 (74)      |                  |                  |
| M, n (%)                        | 33/127 (26)                      |                  |                  |                  |
| **Age at onset, years**         | 27 ± 9/127                      |                  |                  |                  |
| **Disease duration, years**     | 10.7 ± 7/127                    |                  |                  |                  |
| **Relapses in the preceding year, mean (range)** | 1.2 (0–4)/127                   |                  |                  |                  |
| **EDSS at onset, mean (range)** | 3.1 (0–7)/127                   |                  |                  |                  |
| **Active baseline MRI**         | Yes, n (%)                       | 83/127 (65.4)    |                  |                  |
| No, n (%)                       | 44/127 (34.7)                    |                  |                  |                  |
| **Baseline MRI Gd⁺ lesions**    | Yes, n (%)                       | 40/127 (31.5)    |                  |                  |
| No, n (%)                       | 87/127 (68.5)                    |                  |                  |                  |

*Value expressed as mean ± standard deviation.  **New T2 lesions or presence of T1 Gd⁺ lesions.

Table 2. Baseline characteristics of patients, stratified by previous treatment.

|                                | IM                  | NAT                  | OR (95% CI) | p     |
|--------------------------------|---------------------|----------------------|-------------|-------|
| Patients, n                    | 68                  | 39                   |             |       |
| **Sex**                        | M/F, n (%)          | 15 (22%/53 (78%)     | 11 (28%/28 (72%)) | M/F: 1.4 (0.6–3.4) | 0.47 |
| **Mean baseline age, years**   | 38.7 ± 7.9          | 39.6 ± 8.6           |             | 0.7   |
| **Disease duration, years**    | 9.3 ± 7.1           | 12.7 ± 7.0           |             | <0.01 |
| **Relapses in the preceding year** | 1.5 ± 0.9 (range 0–4) | 0.7 ± 0.8 (range 0–2) |             | <0.01 |
| **Baseline EDSS**              | 2.6 ± 1.5           | 3.6 ± 1.5            |             | <0.01 |
| **Baseline MRI**               | **Active**          | 49 (72)              | 18 (46)   | NAT/IM: 0.3 (0.1–0.8) | 0.01 |
| Stable, n (%)                  | 19 (28)             | 21 (54)              |             |       |
| **Baseline MRI Gd⁺ lesions**   | **Present**         | 25 (37)              | 7 (18)    | NAT/IM: 0.4 (0.1–0.98) | 0.04 |
| Absent, n (%)                  | 43 (63)             | 32 (82)              |             |       |

IM: immunomodulatory treatment; NAT: natalizumab; Odds Ratio (OR).
 Statistical significance set at p < 0.05, statistically significant results in bold.
*Value expressed as mean ± standard deviation.
**New T2 lesions or presence of T1 Gd⁺ lesions.
prior treatment with NAT increased the risk of having Gd+ lesions at follow-up MRI (OR: 5.4; \( p = 0.008 \)).

The risk of a relapse within 60 days was increased by prior treatment with NAT (OR: 3.9, \( p = 0.007 \)) an active baseline MRI (OR 3.38; \( p = 0.005 \)) and a MRI with Gd+ lesions (OR: 8.1; \( p = 0.002 \)).

The risk of a relapse within 30 days was only increased by prior treatment with NAT (OR: 4.3; \( p = 0.011 \)).

Patients previously treated with NAT had higher baseline and follow-up EDSS values when compared to patients who had been treated with IM and more frequently showed Gd+ lesions at follow-up MRI (Table 4).

At survival analysis, of the considered variables (MRI activity at baseline, Gd+ lesions at baseline, pulsed steroids during wash-out period, pre-FTY preventive treatment), only prior treatment with NAT increased the risk of a relapse (HR: 1.9; \( p = 0.046 \)) (Figure 1).

Table 4. Follow-up clinical and MRI data, stratified by previous treatment.

|                | IM          | NAT         | OR (95% CI) | \( p \) |
|----------------|-------------|-------------|-------------|--------|
| Patients, n    | 68          | 39          |             |        |
| Relapse, n (%) | 21 (30.9)   | 16 (41)     | NAT/IM: 1.6 (0.7–3.5) | 0.29   |
| Relapse within 60 days, n (%) | 7 (10.3) | 10 (25.6) | NAT/IM: 3.0 (1.0–8.7) | 0.04   |
| Relapse within 30 days, n (%) | 5 (7.4) | 8 (20.5) | NAT/IM: 3.3 (0.98–10.8) | 0.04   |
| Active follow-up MRI* n (%) | 16/39 (41) | 13/24 (54.2) | NAT/IM: 1.8 (0.6–4.9) | 0.27   |
| Gd+ lesions at follow-up MRI, n (%) | 4/46 (9) | 8 (33.3) | NAT/IM: 4.5 (1.2–17.1) | 0.02   |
| Baseline EDSS \( \infty \) | 2.8 ± 1.5 | 3.6 ± 1.5 | NAT/IM: 1.8 (0.6–4.9) | <0.01   |
| Delta EDSS at 6 months | 0.05 ± 0.7 (51 patients) | 0.09 ± 0.4 (29 patients) | IM: 0.7; NAT: 0.28 |
| Delta EDSS at last follow-up visit | −0.02 ± 0.8 (62 patients) | 0.1 ± 0.6 (38 patients) | IM: 0.8; NAT: 0.14 |

IM: immunomodulatory treatment; NAT: natalizumab; Odds Ratio (OR). Statistical significance set at \( p < 0.05 \), statistically significant results in bold.

*New T2 lesions or presence of T1 gadolinium-enhancing lesions.
\( \infty \) Value expressed as mean ± standard deviation.

Discussion

The results of this observational study confirm that FTY is effective in patients who had been previously treated with IM. Our data were comparable to those of the pivotal trials (FREEDOMS and TRANSFORMS) with regard to the proportion of relapse-free patients (69.1% in our study versus 70.4 in FREEDOMS) and to MRI endpoints; in particular, to the absence of Gd+ lesions (90% in our study versus 89.7 and 90.1% in FREEDOMS and TRANSFORMS, respectively). The proportion of relapse-free patients was 82.6% in the total population of the TRANSFORMS study, but this value is likely to be lower considering the subgroups with higher disease activity3, more similar to our population for baseline characteristics.

In patients previously treated with NAT, only 59% were relapse-free, while in 41% of cases we observed at least one relapse, which often occurred early (in 62% of cases within 60 days and in 50% within 30 days after the introduction of FTY). Fifty-four percent of patients presented one or more new T2 lesion and 33% had Gd+ lesions at follow-up.

Our data are in agreement with a recent report on a limited number of patients switching from NAT to FTY, in which clinical or radiological reactivation of the disease was described in 50% of cases, more than half occurring during the first month of therapy8. Although the biological activity of FTY is rapid (lymphocyte counts decreased by 70% within 14 days)9, the treatment did not seem to significantly protect the patients during the first 2 months of treatment and the authors suggested reducing the wash-out period from NAT to FTY to 1 month8. Similar findings were recently published on eight patients previously treated with NAT: after switching to FTY, five out of eight experienced clinical relapses, while MRI activity was detected in six out of eight patients10.

Data from recent clinical trials regarding the course of disease after discontinuation of NAT11–13 described a
disease reactivation that starts at approximately 12 weeks and peaks at around 16 weeks, even in patients undergoing alternative immunomodulatory treatments (interferon or glatiramer acetate). It is therefore possible that the disease reactivation during FTY therapy reflects this trend, which FTY is not able to influence. On the other hand, Laroni and colleagues reported a lower recurrence of relapses in subjects with an early switch from NAT to FTY compared to those who shifted to IM. The authors suggested a possible synergic effect of FTY and NAT, although FTY does not completely protect from MS reactivation. Data from the TOHNGO study also confirm that patients with a shorter wash-out period from NAT to FTY had a lower risk of relapses or of MRI reactivation.

Recently, several research groups have reported their experiences in the use of FTY in clinical practice. There are currently conflicting data regarding the efficacy of FTY after NAT discontinuation. Some authors described a clinical stability and good control of relapses in most patients, especially if the duration of the wash-out period was shorter, while a longer wash-out period represented a negative prognostic factor for reactivation during FTY therapy. Other studies agree in reporting an early clinical or radiological reactivation in a significant percentage of patients.

Of interest is that severe relapses after switching to FTY treatment were reported by Centonze et al., who described three patients who experienced relapses 6–19 days after initiation of FTY (3–4 months after discontinuation of NAT), and by Jander and colleagues, who reported a case of tumefactive multiple sclerosis 16 weeks after stopping NAT and 8 weeks after commencing FTY. In these cases, authors were unsure as to whether the severe clinical manifestations could be attributed solely to a MS reactivation/rebound following natalizumab cessation or whether immunological mechanisms linked to the initiation of FTY could have played a role.

In our population the duration of the wash-out period from natalizumab was variable (mean: 18 weeks, median: 16 weeks; range: 12–45 weeks) and relapses occurred mostly during the first and second month of treatment with FTY, independently of the duration of the wash-out period. Specifically, the mean duration of the wash-out period was not different in patients who relapsed compared to those who did not (19.4 versus 18.1 weeks, respectively, t-test: p = 0.6) and the duration of the wash-out period did not impact on the risk of a relapse at logistic regression (OR = 1.02; p = 0.6). During the first 40 weeks following NAT discontinuation, 4/17 patients (24%) only relapsed during the wash-out period, 4/17 (24%) relapsed both during the wash-out period and following introduction of FTY, while 9/17 patients (53%) only relapsed following start of treatment with FTY (Figure 2). Patients who relapsed during the wash-out period did so after a mean period of 14 weeks, which is in accordance with literature data, while patients who only relapsed after introduction of FTY did so after a mean period of 26 weeks following NAT discontinuation and after 8 weeks from the introduction on FTY (mean wash-out period: 18 we weeks). These findings are not fully explained as a result of NAT discontinuation. The possibility that the introduction of FTY plays an inductive role is still unclear and the possible

![Figure 2. Graph displaying timing of relapses following natalizumab discontinuation and/or start of treatment with FTY in the first 40 weeks. WO = weeks to relapse occurring during the wash-out period.](image-url)
immunological mechanisms involved are still hypothetical, though it has been suggested that the initiation of FTY in patients with an active disease may result in further relapses due to the reduction or inhibition of regulatory T cells.\(^{28,29}\) Data must be verified in other settings and in broader populations.

FTY was overall safe and well tolerated and the most frequent adverse events were infections, abnormal liver function tests and hypertension (Table 3).

Our study has several limitations due to the observational nature of the investigation. Firstly, the study population is small; however, literature data on larger populations are not currently available, particularly on patients previously treated with NAT. Secondly, the duration of the observation was short and highly variable and the timing of clinical and radiological controls is not homogeneous because patients are consecutively assigned to treatment with FTY according to clinical indications. In addition, our findings could be affected by the different baseline characteristics of the patients previously treated with NAT or IM drugs. In fact, given the current indications by AIFA, the high disease activity found in patients switching from NAT to FTY could partly reflect the pre-NAT activity. Finally, 26 patients were treated with FTY in accordance with including criteria of the Expanded Access Program (CFTY720DIT03): “patients for whom no suitable treatment alternative exists i.e. where alternative therapy has failed”. This criterion could have led to include both patients who did not tolerate injective therapies and patients who failed multiple previous treatments.

Despite their limitations, observational studies can be useful in adding information on the ‘real-life’ efficacy and safety of drugs during the post-marketing phase and in identifying sub-groups of patients who are more likely to respond to a given intervention. They can also help to identify patients who are at risk of not responding to a therapeutic approach, such as patients switching from NAT to FTY, and in encouraging future studies since, to date, the optimal treatment strategy following NAT cessation still needs to be determined.

Conclusion

We conclude that previous treatment influences FTY efficacy: patients previously treated with NAT have an increased risk of a relapse (especially within the first 30–60 days of treatment) and an increased risk of radiological reactivation of the disease, while in patients previously treated with IM therapy, FTY confirmed its efficacy for clinical and neuroradiological outcomes.

Due to the short duration of follow-up it is difficult to establish the long-term effects of FTY in patients switching from NAT, though our preliminary data suggest that there is no disability progression despite the early relapses. We nevertheless suggest a very close clinical and radiological surveillance of patients switching from a NAT to FTY during the first 3 months of treatment.

Transparency

Declaration of funding

Realized with the contribution of an unconditional grant from Novartis Farma Spa through the contest ‘Best in Class – Experience with Oral Therapies in MS’, Thenewway Ltd, Milan, Italy.

Twenty-six out of 127 patients started FTY through the Expanded Access Program, an open-label study protocol (CFTY720DIT03), sponsored by Novartis, that provided FTY at no charge until FTY was commercialized.

Declaration of financial/other relationships

E.M. has disclosed that he has received travel grants and fees for consultancies and scientific production from Novartis, Merck-Serono, Biogen Idec, Sanofi-Genzyme and TEVA. P.S., M.R.T. and L.C. have disclosed that they have received travel grants and/or speaking honoraria from Bayer-Schering, Biogen Idec, Merck-Serono, Novartis, Sanofi-Genzyme and TEVA. D.F. has disclosed that she has received travel grants and/or speaking honoraria from Bayer-Schering, Biogen Idec, Merck-Serono, Novartis and TEVA. E.B. has disclosed that she has received travel grants and/or speaking honoraria from Bayer-Schering, Biogen Idec, Merck-Serono, Novartis and TEVA. E.B. has disclosed that she has received travel grants and/or speaking honoraria from Biogen Idec, Merck-Serono, Novartis and TEVA. F.V., A.G., C.S., E.C., A.M.S., S.M., P.I., I.P., F.G. and L.M. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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