Natalizumab to Fingolimod Switching in Multiple Sclerosis: Results from a “Real World” Retrospective Analysis

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Abstract

Fingolimod is an alternative for patients with multiple sclerosis who discontinue natalizumab because of leukoencephalopathy risk. However, the interruption of natalizumab might cause disease reactivation. We aimed to describe the disease course of patients switching to fingolimod after treatment with natalizumab or β-interferon, in a real-world setting, through a retrospective analysis of data in patients with multiple sclerosis that receiving fingolimod at a single centre in Italy. Ninety patients were divided into two groups: patients switching to fingolimod from natalizumab (n = 43, Group 1), and treatment naïve (n=5) plus patients switching from β-interferon (n = 42) (Group 2). In Group 1, the mean annualised relapse rate significantly increased from 0.36 at natalizumab discontinuation to 0.80 after natalizumab washout and 1.12 after the first 3 months of fingolimod, decreasing thereafter to 0.49 by the end of follow-up. In Group 2, the relapse rate significantly decreased from 1.16 to 0.47 at the end of follow-up. Relapses during natalizumab washout predicted increased disease activity during the first 3 months of fingolimod (p = 0.043). We conclude that fingolimod has a delayed effect in patients switching from natalizumab versus treatment-naïve patients or those switching from β-interferon. Worsening of disease activity during the washout period may be predictive of treatment failure.

Keywords: Fingolimod; Natalizumab; Interferon; Multiple sclerosis

Introduction

In recent years, several new drugs have been approved for the treatment of relapsing remitting multiple sclerosis (RRMS), including natalizumab (Tysabri, Biogen, Cambridge, MA) [1]. Although natalizumab have been shown to have a large effect in reducing disease activity, it also has critical collateral effects. An important safety issue related to natalizumab treatment is progressive multifocal leukoencephalopathy (PML), a demyelinating brain disease triggered by the John Cunningham virus (JCV) [2,3]. The JCV causes an asymptomatic infection in healthy individuals but it can reactivate in immunocompromised patients, determining PML [3]. Critically, the infection is present in the brain before the first clinical symptoms occurred [4], thus leading to a delay in the PML recognition and natalizumab cessation, and consequently, to a worsening of the clinical condition of the patients.

Due to the PML risk, natalizumab is often discontinued leading to MS disease reactivation [5] however, the ideal alternative treatment following natalizumab has not yet been identified [6-8]. Fingolimod (Gilenya, Novartis, Basel, Switzerland) is an option for these patients [1,3,8-12] however, because of the still unknown impact on the immune system of the concomitant presence of these molecules, an interval is recommended between discontinuing natalizumab and starting fingolimod. Studies investigating switching from natalizumab to fingolimod have shown clinically relevant disease activity during the first weeks of fingolimod treatment, challenging its effectiveness in this setting, and highlighting the need to clarify its role in patients with a disease characterized by its severity and rapid evolution, and to improve the switching protocol [9,11].

Reported here are the results of a retrospective analysis of the medical records of patients with RRMS who switched to fingolimod treatment from either natalizumab or β-interferon, and treatment-naïve RRMS patients starting fingolimod. Although this topic has been largely discussed in literature [9,11,12], the current study aims in providing a descriptive analysis of a large cohort of patients followed for many years. Indeed, while previous research only considered patient’s clinical course in the previous year, the objective of this study is to describe the patients’ whole disease course and to analyse predictive factors for disease relapse. Critically, according with our aim to describe population most likely to be seen in clinical practice, no strict and artificial patients inclusion and exclusion criteria are used in the current study, in order to provide a description of what happened in the real clinical population. Thus, all the patients presenting the RMS form who started the treatment with fingolimod were included in the study, and their clinical characteristics were analysed and described.

Materials and Methods

This retrospective analysis was performed on patient data recorded between 1985 and 2013 into the database of the Multiple Sclerosis Center, Spedali Civili of Brescia, Montichiari, Italy, a referral centre for MS, which follows approximately 1/5 of the total MS population of the region of Lombardia, Italy. This database contains records detailing the medical information of all patients with MS who visited the centre from their first visit. The patients are monitored through outpatient visits every 3 months when receiving first line therapy (β-interferon, glatiramer acetate) and fingolimod, and monitored monthly when receiving natalizumab. Magnetic resonance imaging (MRI) is performed every 4-6 months or yearly when receiving natalizumab or other treatments, respectively.

This analysis includes all RRMS patients who initiated fingolimod treatment and had their medical history collected from the time of initial MS diagnosis. All these patients were treated according to guidelines recommended by the Italian Medicines Agency and
European Medicines Agency. According to the Agency guidelines, a therapy with fingolimod should be suggested to patients suffering from a highly active disease i.e. patients experiencing at least two annual relapses, or to patients who did not benefit from at least one first line disease modifying drug. Two main subgroups of patients were identified in the database of the referral center: patients switching to fingolimod after receiving natalizumab treatment (Group 1) and either patients switching to fingolimod after a first-line therapy (β-interferon) or treatment-naive patients with highly active RRMS (Group 2). Patient’s informed consent to treatment and data collection was obtained at baseline. The study details were presented, in accordance with applicable national law, to the Institutional Review Board of the center.

Data on the following were obtained from the database: demographic characteristics, disease duration, number of relapses, Expanded Disability Status Scale score (EDSS), number of new T2 lesions (T2) and gadolinium-enhanced (Gd+) MRI lesions, number and duration of disease modifying therapies and reasons for treatment discontinuation. The disease course was analysed by evaluating changes in annualised relapse rate (ARR), EDSS scores and new T2 and Gd+ lesions. The ARR was defined as the total number of relapses experienced by all patients in a given period divided by the duration of the period in years. Notably, in this observational study, the clinical history of patients has been followed for 28 years. Thus, for instance, if the AAR of a patient is recorded as 1.5, but his disease duration is ten years, this means that he experienced 15 relapses in ten years.

Data from patients in Group 1 were analysed to compare the disease course over time; time periods investigated were the following: pre-natalizumab, natalizumab treatment, natalizumab washout, the first 3 months of fingolimod, and longer-term fingolimod treatment. For Group 2, the observation period was subdivided into the time before and during fingolimod treatment. Data were collected from July 2011 until the database lock on December 31th, 2013.

The data were analysed using descriptive statistics. Variables were compared using the t test, the Χ² test, or by analysis of variance, as appropriate. The changes in the EDSS scores were compared by means of the Wilcoxon signed-rank test. To identify potential predictive factors for relapse, relevant variables were included in a binary logistic regression model for multivariate analysis. A Cox regression model and Kaplan-Meier curves were used to estimate the relapse-free survival of patients during the various treatments administered. Statistical analysis was performed using the IBM SPSS Statistics software for Windows (version 20.0). Statistical significance was defined by a p value <0.05.

Results

Patient characteristics

Ninety patients, all caucasians, with RRMS initiating fingolimod were identified in the database (4.043 clinical evaluations, 856 MRI scans). Their clinical and demographic characteristics are summarized in Table 1. The Group 1 was formed by forty-three patients who switched to fingolimod after natalizumab; the Group 2 was formed by patients who switched to fingolimod after first-line MS therapy (n = 42) or were treatment-naïve (n = 5) (total number of patients included in Group 2 n=47). Mean disease duration was significantly longer in Group 1 than in Group 2 (15.47 vs 11.35 years; p = 0.009). There was no statistically significant difference in the mean number of previous disease modifying therapies in the two groups. After first-line therapies, before initiating natalizumab or fingolimod, patients in Group 1 and Group 2 had a mean ARR of 1.29 and 1.16 (p = 0.552), and a mean EDSS score of 4.27 and 2.80 (p < 0.001), respectively. No significant difference between groups in annualized MRI activity at baseline was identified (T2: 0.75 and 0.84, Gd+: 0.43 and 0.48).

In the cohorts, the mean duration of fingolimod treatment was similar (1.27 and 1.22 years) and 31 (Group 1) and 30 (Group 2) patients were treated for at least 12 months. Positive anti-JCV antibodies and number of infusions (mean natalizumab infusion: 30.37, range 2–52) were the reasons for interrupting natalizumab in 86% of the patients; four patients stopped for increased perception of PML risk despite negative JCV antibodies and two patients discontinued due to allergic reactions. The mean duration of natalizumab washout was 5.76 ± 3.76 months; washout duration ranged from 3 to 5 months in 69.8% of patients and was longer than 5 months in the remaining 30.2%. Results are reported in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 43)</th>
<th>Group 2 (n = 47)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>25 (58)</td>
<td>33 (70)</td>
<td>0.23</td>
</tr>
<tr>
<td>Mean (range) age of disease onset, years</td>
<td>26.26 (11–54)</td>
<td>27.81 (10–48)</td>
<td>0.42</td>
</tr>
<tr>
<td>Mean (range) age at start of fingolimod treatment, years</td>
<td>40.33 (20–64)</td>
<td>37.77 (19–60)</td>
<td>0.20</td>
</tr>
<tr>
<td>Mean ± SD disease duration, years</td>
<td>15.47 ± 6.68</td>
<td>11.35 ± 7.61</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean ± SD number of previous therapies before fingolimod</td>
<td>2.40 ± 1.30</td>
<td>1.94 ± 1.22</td>
<td>0.087</td>
</tr>
<tr>
<td>Mean EDSS</td>
<td>4.27*</td>
<td>2.80a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ARR</td>
<td>1.29*</td>
<td>1.16a</td>
<td>0.552</td>
</tr>
<tr>
<td>Annualised MRI, T2</td>
<td>0.75*</td>
<td>0.84a</td>
<td>0.202</td>
</tr>
<tr>
<td>Annualised MRI, Gd*</td>
<td>0.43*</td>
<td>0.48a</td>
<td>0.873</td>
</tr>
<tr>
<td>Mean ± SD duration of fingolimod treatment, years</td>
<td>1.27 ± 0.58</td>
<td>1.22±0.49</td>
<td>0.713</td>
</tr>
<tr>
<td>Mean (range) of natalizumab doses received</td>
<td>30.37 (2–52)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Ab anti JCV positive, n(%)</td>
<td>37 (86)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Previous immunosuppressive therapies, n (%)</td>
<td>18% (42)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD duration of natalizumab washout, months</td>
<td>5.76 ±3.76</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale score; Gd+, number of new gadolinium-enhanced MRI lesions; JCV, John Cunningham virus; MRI, magnetic resonance imaging; N/A, not applicable; SD, standard deviation; T2, number of new T2 lesions on MRI

*Mean value before initiating natalizumab

Table 1: Demographic and clinical characteristics of patients with relapsing-remitting multiple sclerosis receiving fingolimod including in the analysis (n = 90).
Disease course

Relapse: In Group 1, mean ARR was 0.36 ± 0.54, 0.80 ± 1.55 and 1.12 ± 2.20 at the end of natalizumab treatment, natalizumab washout and the first 3 months of fingolimod treatment, respectively. At the end of the observation period, mean ARR was 0.49 ± 1.00 (Figure 1A) and was similar to that observed during natalizumab treatment (p = 0.471). During the washout period, 11 patients (25.6%) relapsed and 10 of these patients relapsed a further time, five in the first 3 months of fingolimod treatment and five in the following months. After switching to fingolimod, overall 20 patients (46.5%) had at least one relapse, and during the first 3 months of fingolimod treatment the relapse risk was significantly higher in patients who relapsed in the washout period (p = 0.043).

In Group 2, the mean ARR was 1.16 ± 0.82 and 0.47 ± 1.46 (p = 0.007) before and at the end of the fingolimod observation period (Figure 1B), and 13 patients (27.6%) relapsed.

Even though fewer patients in Group 2 relapsed during the study period, there was no statistically significant difference in the proportion of relapse-free patients receiving fingolimod (p = 0.071; Figure 2).

Disability: In Group 1, mean EDSS scores were 4.27, 4.01, 4.29 and 4.32 before and during natalizumab treatment, during the first 3 months of fingolimod and after the first 3 months of fingolimod treatment, respectively. The increase in EDSS scores was significantly influenced by the number of relapses (odds ratio [OR] 5.1; 95% confidence interval [CI] 1.34–19.47; p = 0.014).

In Group 2, mean EDSS score was 2.80 and 2.62 before and during fingolimod treatment. Again, relapses determined individual EDSS fluctuations (OR 4.8; 95% CI 1.13–20.41; p = 0.026).

Fingolimod withdrawal: Fingolimod treatment was discontinued in 30.2% (13/43) of patients in Group 1 and 10.6% (5/47) of patients in Group 2.
Group 2 (p = 0.017). In Group 1, eight patients discontinued due to MS relapse (after a mean 8.13 months of fingolimod treatment, range 3–16 months), two patients due to adverse events (transaminase increase) and one patient due to withdrawal of consent. Furthermore, two patients had a prolonged interruption of fingolimod treatment due to compliance issues. 8 out of 13 restarted the therapy with natalizumab. In Group 2, two patients discontinued fingolimod treatment due to MS relapses, two patients withdrew their consent and one patient was lost to follow-up.

The data of these patients were included in the analysis at three months. However, their data were excluded from the analysis after the discontinuation of fingolimod.

Predictive factors for relapse

Binary logistic regression analysis indicated that the disease duration, ARR and EDSS values, annualized increase in MRI lesions and number of disease modifying therapies before fingolimod initiation did not predict the changes in clinical disease activity observed in the two groups after switching to fingolimod. In contrast, treatment with natalizumab was a statistically significant predictor of relapse in the first 3 months of fingolimod therapy (p = 0.042).

While a trend towards a higher relapse rate was observed with a longer natalizumab washout period, (43.3% and 53.8% relapsed with a washout less than or more than 5 months, respectively), no significant relationship was found between the timing of fingolimod initiation and the subsequent relapse rate (p = 0.526).

Discussion

This retrospective analysis of patients with RRMS who were followed over a 28-year period at a single centre in Italy demonstrated that the efficacy of fingolimod is delayed compared with medication naïve patients and patients taking interferon when it is used in patients who switched from natalizumab to fingolimod. Despite patients in each cohort having no differences in baseline ARR and annualized MRI lesions, patients who switched from natalizumab to fingolimod had considerably more clinical disease activity than patients who were treatment naïve before fingolimod or switched from first-line MS therapies.

In Group 1, the majority of patients withdrew consent for natalizumab therapy because of increased perception of PML risk, despite full control of disease activity. These patients had an extended mean duration of natalizumab treatment (mean 28.35 months), which was followed by a washout period longer than 3 months (the mandatory washout period in Italy). We have recently demonstrated that the effect of natalizumab in restoring the capacity of the immune system to produce new T and B lymphocytes and to enlarge the T-cell diversity declined after the washout period [13]. Furthermore 4 to 7 months are necessary for patients who have received natalizumab for more than 2 years to reach baseline relapse rates after discontinuing natalizumab [7], in the present analysis the clinical data were split into relapses observed in the first 3 months of fingolimod treatment and relapses observed in the subsequent period.

In Group 1, the clinical disease activity gradually returned to pre-natalizumab levels, peaking during the first 3 months of fingolimod (corresponding to the end of natalizumab activity: 3 months of washout and 3 months on therapy). During the washout phase, about a quarter of patients experienced a clinical relapse: these patients also had a higher risk of relapsing during the first 3 months of fingolimod therapy, suggesting that the expected achievement of the historical relapse rate is not prevented by fingolimod when the effect of natalizumab on immune surveillance is declining [14]. Finally, the only statistically significant predictive factor, explaining the disparity in relapse rates between the two groups in this analysis, was whether they received natalizumab previously or not. In Group 1, the delayed effect suggests that fingolimod might have a deferred modulation of the immune response, probably due to the fact that steady-state concentrations of fingolimod are reached only after 1-2 months of daily dosing [10].

The duration of washout period as a predictor of relapse has been previously investigated. Results from the ENIGIM study [9] in 333 patients switching from natalizumab to fingolimod (69.1% patients underwent a 6-month follow up) highlighted the importance of a natalizumab washout duration of less than 3 months, as these patients had a significantly lower risk of relapse than those who underwent a longer washout period. Despite having a similar proportion of relapsing patients, in subgroup with the same washout length, we did not find a relationship between the washout length and the relapse rate, perhaps due to the small number of patients in our study. However, as in the ENIGIM study, we observed that the relapse rate during the natalizumab washout was a statistically significant prognostic factor for disease activity during fingolimod treatment. A washout longer than 2 months was also identified by Jokubaitis and colleagues as an independent predictor of increased relapse risk on fingolimod-treated patients who also showed significantly increased ARR (0.38 vs. 0.26 on natalizumab; p: 0.002) and a disease activity that peaked 5-9 months after natalizumab discontinuation [12]. According to these authors, Comi et al. [15], found evidence of clinical reactivation after natalizumab withdrawal in a post hoc analysis of a phase 3b study, observing an increased relapse rate in the first month after fingolimod initiation in patients who underwent a 3-6 month natalizumab washout (2.05 vs 1.08 observed 1 year before fingolimod) with a subsequent reduction at 4 months of follow up [15]. In our analysis where a longer follow-up period was available, the relapse rate declined after the first 3 months of fingolimod, eventually overlapping the one noted in patients who switched to fingolimod after first-line therapy.

As expected in a period of short observation, the disability worsening, mainly noticed after the natalizumab interruption, was due to MS relapses. Disability and clinical course were also examined by Hoepner et colleagues [11] in a smaller cohort of patients (n = 33) switching from natalizumab to fingolimod. The study found that 61% of patients relapsed after natalizumab discontinuation and 48% relapsed during fingolimod treatment (with a washout no longer than 24 weeks). They also demonstrated that an EDSS score >3 during the switching period was a significant predictive factor for relapse during fingolimod therapy. In our analysis, the relapse trends are similar but we cannot confirm this relevance of the EDSS score, where all instances of disability worsening in the patients were related to relapse, suggesting an unrestrained inflammatory activity.

The limitations of this study include those inherent in the retrospective, observational single-centre design, and the lack of MRI data. Moreover, included patients were all Caucasians, thus the current results are not generalizable to patients belonging to other ethnic groups. The strengths of the study include the extended medical records on database, the number of patients, collected by only one centre and the real-world setting, in which the patients investigated were not selected according to a set of arbitrary inclusion and exclusion criteria and therefore represent the population most likely to be seen in clinical practice.
Conclusions

The current results revealed that fingolimod effectiveness is delayed when it is used after natalizumab therapy versus treatment naïve or those switching from beta interferon. This datum suggests that, in order to decrease the likelihood of relapses in the first months of fingolimod assumption, the washout period might be shortened. However, because of the still unknown impact on the immune system of the concomitant presence of both these drugs, additional research and data from the real practice setting are needed. This information might help to guide to the most appropriate natalizumab washout protocol, such as shortening the 3-month-period.

Clinically, basing on these results, two conclusions needs to be additionally stressed: first, the need to discontinue the natalizumab assumption should be carefully evaluated together with the patients, above all with those patients experiencing many relapses prior to the natalizumab assumption. Second, when the natalizumab is decided to be discontinued, the neurologists should explicitly explain to patients the need to start the new therapy with fingolimod as soon as possible, that, in Italy, is 3 month after the natalizumab withdrawal, according with the local regulation. This approach could be clinical relevant in order to avoid early worsening of disease disability after natalizumab withdrawal.

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Conflict of Interest Statement

Sarah Rasia, Cinzia Cordioli, Nicola De Rossi, Fabiana Pimazzoni and Cristina Scarpazza report no disclosures. Dr. Capra received speaking honoraria from Biogen-Idec, Bayer, Teva, Genzyme, Novartis and Sanofi Aventis, and was a Steering Committee Member for Novartis and Biogen-Idec. Dr. Imberti received support to cover travel expenses for participation to congresses from Biogen-Idec and Teva, and grants from Biogen-Idec and Merck-Serono.

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