Switching From Natalizumab to Fingolimod in Multiple Sclerosis
A French Prospective Study

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IMPORTANCE The safety and efficacy of switching from natalizumab to fingolimod have not yet been evaluated in a large cohort of patients with multiple sclerosis (MS) to our knowledge.

OBJECTIVE To collect data from patients with MS switching from natalizumab to fingolimod.

DESIGN, SETTING, AND PARTICIPANTS The Enquête Nationale sur l’Introduction du Fingolimod en Relais au Natalizumab (ENIGM) study, a survey-based, observational multicenter cohort study among MS tertiary referral centers. Participants were patients for whom a switch from natalizumab to fingolimod was planned. Clinical data were collected on natalizumab treatment, duration and management of the washout period (WP), and relapse or adverse events during the WP and after the initiation of fingolimod.

MAIN OUTCOMES AND MEASURES Occurrence of MS relapse during the WP or during a 6-month follow-up period after the initiation of fingolimod.

RESULTS Thirty-six French MS tertiary referral centers participated. In total, 333 patients with MS switched from natalizumab to fingolimod after a mean of 31 natalizumab infusions (female to male ratio, 2.36; mean age, 41 years; and Expanded Disability Status Scale score at the initiation of natalizumab, 3.6). Seventy-one percent were seropositive for the JC polyomavirus. The Expanded Disability Status Scale score remained stable for patients receiving natalizumab. Twenty-seven percent of patients relapsed during the WP. A WP shorter than 3 months was associated with a lower risk of relapse (odds ratio, 0.23; \( P = .001 \)) and with less disease activity before natalizumab initiation (\( P = .03 \)). Patients who stopped natalizumab because of poor tolerance or lack of efficacy also had a higher risk of relapse (odds ratio, 3.20; \( P = .004 \)). Twenty percent of patients relapsed during the first 6 months of fingolimod therapy. Three percent stopped fingolimod for efficacy, tolerance, or compliance issues. In the multivariate analysis, the occurrence of relapse during the WP was the only significant prognostic factor for relapse during fingolimod therapy (odds ratio, 3.80; \( P = .05 \)).

CONCLUSIONS AND RELEVANCE In this study, switching from natalizumab to fingolimod was associated with a risk of MS reactivation during the WP or shortly after fingolimod initiation. The WP should be shorter than 3 months.
Fingolimod was licensed in France in early 2012 for patients with active relapsing-remitting multiple sclerosis (MS), with identical conditions of prescription compared with natalizumab. Therefore, fingolimod and natalizumab are supposed to be comparable in terms of prescription intent, efficacy, and safety.

Depending on the patient or neurologist, switching from natalizumab to fingolimod can be considered an option in various situations, including patients treated with natalizumab who have tolerance or efficacy issues and patients who have a high risk of developing progressive multifocal leukoencephalopathy (PML). However, the safety and efficacy of switching from natalizumab to fingolimod have not been evaluated in a large cohort of patients with MS to date.

Several variables need to be clarified. The requirement of a washout period (WP) between natalizumab withdrawal and fingolimod initiation is mandatory because of the immunosuppressive mechanisms of each molecule, but its exact duration has yet to be determined. Medical authorities have not reached a consensus concerning the WP. It should be as short as possible because of the known risk of a return of MS disease activity after natalizumab discontinuation. The use of intravenous corticosteroids and immunomodulatory drugs during the WP could be helpful, but their efficacy in this situation is limited. Furthermore, the use of an immunomodulatory drug between natalizumab withdrawal and fingolimod initiation for less than 3 to 6 months raises an efficacy issue.

We present a national prospective study of patients with MS for whom a switching strategy from natalizumab to fingolimod was chosen. The safety and outcome were assessed.

Methods

The Enquête Nationale sur l’Introduction du Fingolimod en Relais au Natalizumab (ENIGM) study, a national survey on switching from natalizumab to fingolimod, is a French prospective multicenter study. The aim of the ENIGM study was to assess the safety of the treatment and its efficacy on the outcome of patients switching from natalizumab to fingolimod.

Every MS tertiary care center in France was contacted to prospectively collect real-life data from patients for whom a switching strategy from natalizumab to fingolimod was intentionally planned at the time of natalizumab withdrawal. Patients who stopped natalizumab and who were then unexpectedly treated with fingolimod were not included. Data were anonymously collected using a Google Docs form (http://www.google.com/google-d-s/createforms.html). All study patients gave oral informed consent to be included in the European Database for Multiple Sclerosis (http://www.edmus.org). Therefore, no additional consent or institutional review board approval was obtained for patients’ participation in this study.

To determine the PML risk according to the current risk stratification, we collected the following demographic and clinical data during the natalizumab treatment period: the annualized relapse rate during the year before natalizumab initiation, the number of administered infusions, the Expanded Disability Status Scale (EDSS) score at the initiation and at the final infusion, and the JC polyomavirus status and the history of immunosuppressive treatments. The main reason for natalizumab discontinuation was chosen from the following list of possible answers: fear of PML, a natalizumab tolerance issue, the development of anti-natalizumab antibodies, a perceived lack of natalizumab efficacy by the physician, and a decision by the patient or physician.

Data concerning the WP included the duration, the use of a rescue or planned treatment (methylprednisolone or an immunomodulatory drug) during the WP, and the occurrence of relapse during this period. Data concerning fingolimod treatment initiation included the EDSS score at the initiation and the occurrence of a relapse or adverse event during the first 6 months of treatment.

All anonymous data were gathered in the MS tertiary care center in Nice, France, on behalf of the Club Francophone de la Sclérose en Plaques, a French-speaking MS club. The ENIGM study included patients who were managed in real-life settings; therefore, the assessment of treatment efficacy and relapse was left to the discretion of each physician.

A univariate statistical analysis was performed using the t test for comparison of continuous variables and the χ² test for comparison of the distribution of categorical data between groups. Relevant data were then included in a binary logistic regression model for multivariate analysis. Statistical analysis was performed using available software (SPSS Statistics version 20; SPSS Inc) on a personal computer (Mac OS X; Apple Inc). Results were considered statistically significant at P < .05.

Results

All 36 French MS tertiary referral centers participated in the survey. Between April 10 and August 31, 2013, a total of 333 patients having MS treated with natalizumab were facing a switching strategy. The demographic and clinical features of the cohort are summarized in Table 1. Patients had received a mean of 31 natalizumab infusions, and the EDSS score had remained stable during this period. Seventy-one percent of patients were seropositive for the JC polyomavirus, and 65.2% of patients in the cohort had at least 2 risk factors for developing PML. The JC polyomavirus status was unknown for 22.1% of patients. The main reasons for stopping natalizumab were putative risk of PML, the patient’s decision, and a lack of natalizumab efficacy. Overall, 31.2% of patients stopped natalizumab because of tolerance or efficacy issues, and 69.1% were considered good responders. No compliance issue related to natalizumab use was reported. The distribution of reasons for stopping natalizumab with respect to PML risk stratification is shown in the Figure.

The mean WP was 17 weeks (range, 2–156 weeks). The WP was shorter than 3 months for 31.3% of patients, between 3 and 6 months for 47.0% of patients, and longer than 6 months for 21.7% of patients. Fifty-five percent of patients received no treatment during the WP, and other patients were treated with sequential methylprednisolone infusions (38.9%) or temporarily with an immunomodulatory drug (6.2%). Twenty-

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seven percent of patients relapsed during the WP. In the univariate analysis, no difference was found between patients with vs without relapse in terms of age, EDSS score, or the use of a rescue or planned treatment (methyldprednisolone or an immunomodulatory drug) during the WP. There were significantly more women in the group of patients that relapsed during the WP (32.4% vs 16.7%, P = .04). The risk of relapse was significantly higher for patients who had the longest MS duration and for patients who stopped natalizumab because of tolerance or efficacy issues compared with other patients (Table 2). A longer WP was the strongest risk factor for MS reactivation (P < .001). The percentages of patients who relapsed depending on the WP were 19.9% for less than 3 months, 31.3% for 3 to 6 months, and 59.1% for greater than 6 months. In the multivariate analysis, a WP shorter than 3 months was associated with a significantly lower risk of relapse (odds ratio, 0.23; 95% CI, 0.10-0.65; P = .001). Stopping natalizumab because of a lack of tolerance or efficacy was associated with a significantly higher risk of relapse (odds ratio, 3.20; 95% CI, 1.44-7.58; P = .05). The MS disease activity before natalizumab initiation and the reason for stopping natalizumab did not correlate with disease reactivation during the first months of fingolimod treatment.

**Discussion**

We collected data from one of the largest available samples to date of patients with MS switching from natalizumab to fingolimod. At the time of data collection, this cohort represented close to 100% participation of French MS tertiary care centers. Statistical analysis revealed 2 important findings that must be taken into consideration in clinical practice.

First, this study underlines the substantial risk of relapse during the WP. As expected, the risk correlated with MS disease activity before natalizumab initiation and with the duration of the WP. The risk increased significantly for patients with a WP of 3 months or longer. The use of a short-term rescue or planned treatment (methyldprednisolone or an immunomodulatory drug) did not mitigate the risk of relapse. Those findings have already been reported in multiple natalizumab withdrawal studies. Conversely, patients who had a short WP (<3 months) had a lower risk of relapse.

Second, our results demonstrate an early relapse during fingolimod therapy and a 3.0% rate of treatment withdrawal. This prevents our drawing any conclusions in terms of comparison of efficacy between natalizumab and fingolimod but is important to take into consideration, particularly for patients who were good responders to natalizumab. In a 22-patient cohort switching from natalizumab to fingolimod with a 9-month follow-up period, Rinaldi et al reported MS disease reactivation in 27% of patients, which is similar to our data. When including magnetic resonance imaging data, disease reactivation was present in 50% of patients in the cohort. We did not systematically collect radiologic data in our study.
The results of the ENIGM study suggest that switching from natalizumab to fingolimod can be an option for patients with tolerance or efficacy issues during natalizumab therapy. In this subgroup of patients, our results suggest that the MS disease activity was greater during the WP but not after fingolimod initiation.

If the switch was motivated by the risk of developing PML (slightly >1% for patients in the highest risk category according to the latest stratification data), the benefit-risk ratio between maintaining natalizumab therapy vs a switching strategy has to be carefully balanced. In all cases, our results suggest that the WP should be shorter than 3 months if a switch is chosen.

The main limitation of this study is the survey-based approach. Participants were asked to include all patients who switched from natalizumab to fingolimod, but there was no oversight to ensure that all possible individuals were enrolled in the survey and that all data time points were captured. Therefore, it would be relevant to confirm those results in a true prospective cohort study. It would also be germane to gather longer follow-up data about patients with a shorter WP to assess the safety and efficacy of this schedule.

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28th Congress of the European Committee for Treatment and Research Into Multiple Sclerosis, Ghezzi et al.11 presented similar results for a 32-patient cohort. In addition, some authors have reported isolated cases of patients treated with fingolimod after natalizumab discontinuation who manifested severe relapse and tumefactive magnetic resonance images.12,13

A more recent study reports data from 19 patients who stopped natalizumab after a mean period of 30 months. Patients were nonrandomly treated with fingolimod (n = 11), received an immunomodulatory drug (n = 4), or remained untreated (n = 4). The WP was 4 months for patients who switched to fingolimod. After a 34-week follow-up period, only 1 patient in the group that switched to fingolimod relapsed compared with 5 patients in the other groups. Comparable results were reported in a recent article from a group of 26 patients who switched to fingolimod compared with 10 patients who remained untreated after natalizumab discontinuation.14 In this cohort, the risk of disease reactivation during fingolimod therapy correlated with the duration of WP, which could not be confirmed in our sample. To date, no other published cohort study or registry is available among patients switching from natalizumab to fingolimod.

Table 2. Statistical Analysis Assessing the Risk of Relapse During the Washout Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>No Relapse</td>
<td>Relapse</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>41 (10)</td>
<td>40 (9)</td>
</tr>
<tr>
<td>EDSS score, mean (SD)</td>
<td>3.6 (1.5)</td>
<td>3.5 (1.6)</td>
</tr>
<tr>
<td>Natalizumab infusions, mean (SD), No.</td>
<td>31 (15)</td>
<td>30 (19)</td>
</tr>
<tr>
<td>Annualized relapse rate before natalizumab initiation, mean (SD)</td>
<td>1.6 (1.3)</td>
<td>2.1 (1.1)</td>
</tr>
<tr>
<td>Female to male ratio</td>
<td>1.73</td>
<td>4.30</td>
</tr>
<tr>
<td>Patients with washout duration ≥3 mo, %</td>
<td>72.8</td>
<td>100.0</td>
</tr>
<tr>
<td>Patients stopping natalizumab because of a tolerance or efficacy issue, %</td>
<td>20.1</td>
<td>47.8</td>
</tr>
<tr>
<td>Female sex</td>
<td>2.20 (1.03-4.63)</td>
<td></td>
</tr>
<tr>
<td>Washout period &lt;3 mo</td>
<td>0.23 (0.09-0.57)</td>
<td></td>
</tr>
<tr>
<td>Stopping natalizumab because of a tolerance or efficacy issue</td>
<td>3.20 (1.44-5.10)</td>
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Table 3. Statistical Analysis Comparing the Patients With vs Without Relapse After Fingolimod Initiation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Relapse</td>
<td>No Relapse</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>40.4 (9.7)</td>
<td>39.8 (10.4)</td>
</tr>
<tr>
<td>Female to male ratio</td>
<td>1.85</td>
<td>2.60</td>
</tr>
<tr>
<td>Annualized relapse rate before natalizumab initiation, mean (SD)</td>
<td>1.8 (1.5)</td>
<td>2.2 (1.1)</td>
</tr>
<tr>
<td>EDSS score at fingolimod initiation, mean (SD)</td>
<td>3.7 (1.7)</td>
<td>3.7 (1.8)</td>
</tr>
<tr>
<td>Patients relapsing during the washout period, %</td>
<td>48.6</td>
<td>32.9</td>
</tr>
<tr>
<td>Patients with washout duration ≥3 mo, %</td>
<td>68.0</td>
<td>44.6</td>
</tr>
<tr>
<td>Patients stopping natalizumab because of a tolerance or efficacy issue, %</td>
<td>22</td>
<td>32</td>
</tr>
<tr>
<td>Washout period &lt;3 mo</td>
<td>0.39 (0.08-2.10)</td>
<td></td>
</tr>
<tr>
<td>Stopping natalizumab because of a tolerance or efficacy issue</td>
<td>2.45 (0.30-21.70)</td>
<td></td>
</tr>
<tr>
<td>Relapse during the washout period</td>
<td>3.80 (1.26-7.58)</td>
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Abbreviation: EDSS, Expanded Disability Status Scale.
Conclusions

The ENIGM study gathered data from 333 patients with MS who switched from natalizumab to fingolimod in France. According to our data, switching can be an option for patients who develop tolerance or efficacy issues with natalizumab therapy. For patients who are good responders to natalizumab, the risk of MS reactivation should be taken into consideration. The WP should be shorter than 3 months.
Natalizumab vs Fingolimod in Multiple Sclerosis

Original Investigation Research

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