

Clinical Commentary

Switching from natalizumab to fingolimod: an observational study

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Background – Multiple sclerosis patients who discontinue using natalizumab are at risk of a rebound in disease activity. However, the optimal alternative therapy is not currently known. **Aims of the study** – We report on clinical and MRI data and patient safety in a group of relapsing–remitting multiple sclerosis patients who tested seropositive for the JC virus and who have switched from natalizumab to fingolimod because of concerns regarding PML risks. **Methods** – The test for JC virus antibodies was performed in 18 relapsing–remitting multiple sclerosis patients who were being treated with natalizumab for more than 1 year. Eight seropositive patients switched to fingolimod while the seronegative patients continued with natalizumab. **Results** – After switching to fingolimod, five of eight patients (63%) experienced clinical relapses, and MRI activity was detected in six of eight patients (75%). Neither clinical relapses nor MRI activity was observed in the patients who continued with natalizumab. No serious adverse effects were detected. **Conclusions** – Natalizumab is an effective treatment for relapsing–remitting multiple sclerosis, but its discontinuation continues to be a complex problem. All of the therapies tried thus far, including fingolimod, have been unable to control the reactivation of the disease. Further studies addressing alternative therapies after natalizumab discontinuation are necessary.

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Introduction

Natalizumab is an α 4-integrin antagonist that is approved for treating relapsing–remitting multiple sclerosis (RRMS). Natalizumab treatment is associated with an increased risk for progressive multifocal leucoencephalopathy (PML), an opportunistic brain infection that is caused by the JC virus. The estimated risk of PML is 0.57 per 1000 patients during the second year of treatment (13–24 infusions) and increases to 1.89 and 2.24 per 1000 patients during the third and fourth years of treatment, respectively (1). The risk of PML can be stratified based on three factors: the duration of natalizumab use, prior immunosuppression, and, of particular interest, seropositivity for the JC virus (2).

Currently, physicians and patients face the dilemma of a significant PML risk if therapy is continued or the risk of relapses and disability worsening if therapy is discontinued. If the patient chooses to discontinue natalizumab therapy, alternative therapies must be considered, despite the absence of sound, evidence-based information (3). Fingolimod is the most recently approved drug for treating multiple sclerosis. In Europe and Canada, fingolimod and natalizumab are reserved as second-line drugs for RRMS. Switching from natalizumab to fingolimod may be a reasonable option because both drugs are second-line therapies; however, little information is currently available concerning the efficacy and safety of fingolimod in this particular patient group.

We report on clinical and MRI data and patient safety in a group of RRMS patients who tested seropositive for the JC virus and who have switched from natalizumab to fingolimod because of concerns regarding PML risks.

Patients and methods

This observational study was performed in the MS Unit of the Hospital General Universitario de Alicante. All of the RRMS patients who were currently being treated with natalizumab for over a year were offered the JC virus antibody test (Stratify JCV™) to estimate their PML risk. If a patient tested negative, he was considered low risk and continued with natalizumab treatment. If, however, the patient tested positive, he was informed by the neurologist of his estimated risk for PML and the different therapeutic options were explained: continue with natalizumab or change to another drug, such as interferon beta, glatiramer acetate (GA) or fingolimod. The Spanish healthcare system provides all multiple sclerosis medication at no cost. Data concerning the efficacy and possible side effects were provided, as well as the possibility of relapses and worsening disability upon natalizumab withdrawal. Each patient signed an informed consent indicating his therapeutic choice.

The natalizumab treatment protocol included clinical visits every 3 months and an annual brain MRI during the first 2 years and every 6 months thereafter. After natalizumab withdrawal, the planned treatment protocol was 1000 mg intravenous methylprednisolone monthly for 3 months followed by daily doses of either oral fingolimod capsules (0.5 mg), GA or interferon beta. The patient follow-up included visits every 3 months and MRI studies at the time of natalizumab withdrawal and in months 3, 6 and 9. Follow-up visits included the evaluation of new relapses and Expanded Disability Status Scale (EDSS). A relapse was defined as a neurological disturbance that was similar to the type observed in MS and lasted a minimum of 24 h without a fever or an infection. The EDSS and neurological examination were performed by the same neurologist (APS).

The MRI studies were performed on a 1.5 T scanner (Phillips Healthcare, Eindhoven, the Netherlands; General Electric Medical Systems, Milwaukee, WI, USA). Contiguous, 3-mm axial sections, T2-weighted, FLAIR and gadolinium-enhanced T1-weighted scans through the whole brain were acquired. The MRI analyses were conducted by a neuroradiologist who was blinded to the patient's clinical details. The number of Gd-

enhancing lesions and new T2 lesions were determined.

The main objective of this observational study was to analyse the reactivation of MRI and clinical disease activity under fingolimod treatment and after natalizumab withdrawal. The clinical activity was evaluated by means of relapses. MRI activity was evaluated by the presence of new T2- or Gd-enhancing lesions. Another objective of the study was to examine the safety of fingolimod after initial treatment with natalizumab.

Results

Testing for antibodies to the JC virus (Stratify JCV™) was performed in 18 RRMS patients who were being treated with natalizumab for more than 1 year. Nine patients (50%) were seropositive, and the other nine were seronegative. One seropositive patient moved away and follow-up was lost. All of the seropositive patients chose to take fingolimod. These seropositive patients' clinical characteristics and clinical/MRI data while on natalizumab and after switching to fingolimod are summarized in Table 1. The eight patients who switched to fingolimod had a mean age of 34 years and received natalizumab for a mean treatment length of 29 months; six were women, one was Latin American and the rest of Caucasian origin. The mean disease duration was 11.1 years. For comparison, the nine seronegative patients who continued with natalizumab had a mean age of 31 years and received natalizumab for a mean of 27 months; seven were women and all were of Caucasian origin. The mean disease duration was 10.4 years. During the natalizumab treatment, 15 of 17 patients (88%) were free of relapses and 17 of 17 (100%) were free of MRI activity.

After switching to fingolimod, five of eight patients (63%) experienced clinical relapses, and MRI activity was detected in six of eight patients (75%). Brain MRIs showed Gd-enhancing lesions in 50% of the patients 6 months after the natalizumab withdrawal (3 months with fingolimod) and in 71% (5 of 7) at 9 months after natalizumab withdrawal (6 months with fingolimod) (Fig. 1). Most of the new lesions occurred in new brain areas. Patients received fingolimod for a mean of 9 months (range: 4–12 months). At the last clinical evaluation, the EDSS score worsened in three of eight patients.

The nine patients who were seronegative continued with natalizumab with a mean follow-up time of 13 months (Table 2). No patient suffered clinical relapses, and MRI activity was not

Table 1 Clinical characteristics of the MS patients who were seropositive to JCV and switched from natalizumab to fingolimod

Case	Sex	Age (y)	Previous treatments	Relapses year before NTZ	Time on NTZ (m)	Relapses during NTZ	New T2/Gd + lesions with NTZ	EDSS at NTZ end	Time on fingolimod (m)	Relapses during fingolimod	New T2/Gd + lesions at 3-m MRI	New T2/Gd + lesions at 6-m MRI	New T2/Gd + lesions at 9-m MRI	EDSS at end of observation period (T)
1	F	24	None	3	37	0	0/0	4	12	1 (m-2)	4/4	1/3	1/3	4.5 (m-15)
2	F	41	Interferon beta	2	34	1	0/0	6	9 (D)	1 (m-6)	0/0	0/0	1/1	6 (m-12)
3	F	29	Interferon beta	1	20	0	0/0	0	12	0	0/0	0/0	0/1	0 (m-15)
4	F	42	Interferon beta	2	38	0	0/0	2.5	4 (D)	1 (m-3)	4/4	4/3	ND	4 (m-12)
5	F	46	Interferon beta Glatiramer	2	20	0	0/0	4	9	0	0/0	0/0	0/0	4 (m-12)
6	M	32	Interferon beta	2	34	0	0/0	1	9	0	0/0	0/0	0/0	1 (m-12)
7	F	28	Interferon beta	1	15	0	0/0	3	10 (D)	1 (m-10)	0/0	6/3	2/2	5 (m-13)
8	M	30	Interferon beta Glatiramer	2	37	0	0/0	2.5	9	1 (m-7)	0/0	10/3	3/3	2.5 (m-12)

y: years, m: months, NTZ: natalizumab, ND: not done, (D): discontinued, (T) last observation after natalizumab withdrawal.

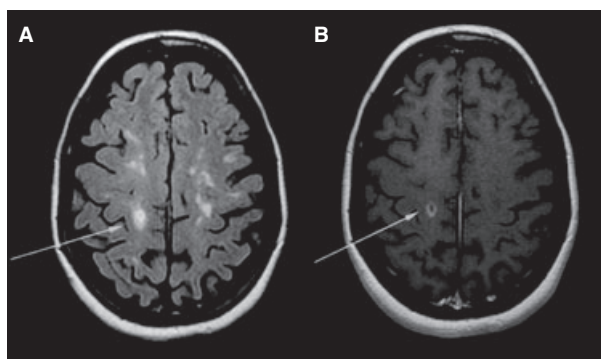


Figure 1. Patient 2. Brain MRI at 6 months with fingolimod shows a new lesion with rim enhancement.

detected in any of these patients. All of the EDSS scores remained stable.

Regarding adverse events, in the natalizumab group, the only recorded adverse event was a mild headache in two patients during natalizumab infusion. In the fingolimod group, the drug was well tolerated. One patient had an asymptomatic increase in his alanine aminotransferase level to four times the upper limit of the normal range.

Discussion

Several months after the interruption of natalizumab treatment, the risk of clinical and MRI subclinical activity returned (4). A number of small studies have also raised concerns that a

rebound effect may occur in some patients after the discontinuation of natalizumab (5–7). Considering that the recurrence of disease activity will emerge after discontinuing natalizumab, a panel of experts recommended initiation of another disease-modifying therapy (3). However, the optimal alternative therapy is not currently known (8).

Pulsed intravenous corticosteroids (one gram of IV methylprednisolone monthly) were used in 23 patients for a period of 90–150 days before restarting natalizumab. Even in this short period, however, MRI activity was detected in seven patients (30%), and four patients also had concomitant relapses (9).

Another study evaluated the monthly administration of one gram of oral methylprednisolone for 3 months, followed by GA; 55.5% (10/18) of patients showed contrast-enhancing lesions on brain MRIs at 6 months, and 50% (9/18) of patients experienced a clinical relapse during their follow-ups (10).

In a small observational study, five of seven MS patients who were treated with natalizumab and subsequently treated with GA relapsed; the mean time to the first relapse was 5.5 months (11). An open-label study tested treatment with GA after natalizumab in 40 MS patients: 62.5% of the patients were relapse free 12 months after the GA initiation, and the annualized relapse rate was significantly lower than before the natalizumab (12). At 6 months, MRI studies showed evidence of disease reactivation in 56% of the patients.

Table 2 Clinical characteristics of the MS patients who were seronegative to JCV and continued with natalizumab

Case	Sex	Age	Previous treatments	Relapses year before NTZ	Time on NTZ (m)*	Relapses during NTZ	New T2/Gd + lesions with NTZ	EDSS at the time of the serology test	Time on NTZ (m) after the serology test	Relapses on NTZ after the serology test	EDSS at end of observation period
9	M	32	Interferon beta, Glatiramer	1	38	0	0/0	1	12	0	1
10	F	27	Interferon beta	1	38	0	0/0	5.5	12	0	5.5
11	F	30	Interferon beta	1	20	0	0/0	1	12	0	1
12	F	38	Interferon beta	2	18	0	0/0	3.5	12	0	3.5
13	F	27	Interferon beta	2	36	1	0/0	3	15	0	3
14	F	31	Interferon beta	2	39	0	0/0	1	12	0	1
15	F	42	Interferon beta	1	17	0	0/0	3	15	0	3
16	F	23	Interferon beta	3	24	0	0/0	2	15	0	2
17	M	36	Interferon beta	2	15	0	0/0	4	12	0	4

y: years, m: months, NTZ: natalizumab, ND: not done.

*Time on natalizumab before the serology test for the JC virus.

Further information is provided by the RESTORE trial that evaluated the effect of a 24-week interruption in natalizumab treatment. This trial compared continued natalizumab treatment with a placebo or by switching to interferon beta-1a, glatiramer acetate or methylprednisolone as an alternative immunomodulatory therapy (13). The RESTORE trial confirmed a high rate of recurrence of the MRI and clinical MS disease activity, beginning at approximately week 12, despite treatment with GA or methylprednisolone. The authors note that this exploratory study was not powered to detect significant differences between the treatment groups.

Fingolimod is another potential treatment option, but little is known about its efficacy and safety following natalizumab therapy (14). In our series, no serious side effects have been observed thus far, but the administration of fingolimod did not prevent MS reactivation following natalizumab withdrawal. We used monthly pulses of methylprednisolone in the interim between natalizumab withdrawal and the start of fingolimod. It has been suggested that this regimen helps to prevent the early rebound of inflammatory activity (10).

Natalizumab is an effective treatment for relapsing–remitting multiple sclerosis, but its discontinuation continues to be a complex problem. All of the therapies tried thus far, including fingolimod, have been unable to control the reactivation of the disease. Further studies addressing alternative therapies after natalizumab discontinuation are necessary.

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None.

Conflict of interest

Angel Perez Sempere has received speaker honoraria from Biogen Idec, Bayer Schering Pharma, Merck Serono, Novartis, Sanofi-Aventis and Teva. Leticia Berenguer-Ruiz has received speaker honoraria from Novartis and Teva. Natalia Perez-Carmona has received speaker honoraria from Novartis and Teva. Patricia Martin-Medina, Rosa Sanchez-Perez, Josefa Polache-Vengud and Eloisa Feliu-Rey declare that there are no conflicts of interest.

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Sempere et al.

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