Severe multiple sclerosis reactivation under fingolimod 3 months after natalizumab withdrawal

L Daelman, A Maitrot, A Maarouf, MP Chaunu, C Papeix and A Tourbah

_Mult Scler_ published online 20 August 2012
DOI: 10.1177/1352458512458009

The online version of this article can be found at:
http://msj.sagepub.com/content/early/2012/08/16/1352458512458009
Severe multiple sclerosis reactivation under fingolimod 3 months after natalizumab withdrawal

L Daelman1,2, A Maitrot1, A Maarouf1, MP Chaunu1, C Papeix3 and A Tourbah1,2

Abstract
We report the case of a woman with multiple sclerosis who developed a severe neurological condition following natalizumab (NZB) withdrawal and soon after fingolimod (FTY) initiation. FTY was started 3.5 months after a two-year NZB treatment. Fifteen days later, she suffered partial repetitive seizures followed by a tonicoclonic seizure. This was associated with attention difficulties and an increased asthenia. Brain MRI follow-up disclosed large demyelinating active lesions in favour of disease reactivation. This case suggests that FTY introduction may occur less than three months after NZB withdrawal.

Keywords
Multiple sclerosis, relapsing–remitting, fingolimod, natalizumab, MRI

Date received: 4th June 2012; revised: 2nd July 2012; accepted: 17th July 2012

Introduction
Natalizumab (NZB), a humanized anti-alpha 4 integrin monoclonal antibody that decreases lymphocyte trafficking across the blood–brain barrier, has been approved for treatment of relapsing–remitting multiple sclerosis (RRMS). NZB interruption may reveal severe relapses associated with MRI reactivation of the disease.1–4 This rebound effect may be related to an immune reconstitution inflammatory syndrome (IRIS).5 Fingolimod (FTY), another approved treatment in Europe for active MS, is an orally administered disease-modifying drug that acts as a non-selective functional antagonist of the sphingosine-1-phosphate receptor, trapping B and T lymphocytes in secondary lymphoid tissues. FTY may be proposed to reduce relapse rate after NZB withdrawal. However, there are no recommendations concerning the delay that should be respected for this switch. Usually two to three months are proposed to avoid an hypothetic cumulative toxicity of these two drugs. Here we report the case of a young woman with RRMS who presented a severe reactivation of the disease, revealed by an epilepsy, 3.5 months after NZB withdrawal and 15 days after FTY initiation.

Case report
A 40-year-old Algerian woman was diagnosed as RRMS that started in 1988 with diplopia. The disease was following a benign course until 2004, when she complained of horizontal binocular diplopia with rotatory vertigo. MRI showed brain abnormalities consistent with the diagnosis. In 2007, she suffered left-sided numbness. A brain MRI revealed T2 weighted abnormalities (Figure 1(a)) and two T1-post-gadolinium active lesions. She was treated with IFNbeta-1a for seven months (from June to December 2007), which was stopped because of neutropenia. She was then treated with glatiramer acetate for one month (from February to March 2008), which was again stopped because of daily hyperthermia after injections. In 2009, she suffered two relapses, the first in June with regressive right-sided paraesthesia and hypoesthesia, and in September when she complained of persistent motor paresis in the left foot (Expanded Disability Status Scale, EDSS 2). A control brain MRI revealed new active lesions (Figure 1(b)).
Treatment with NZB was started in October 2009 and well tolerated. No relapse or MRI activity was noted for two years, and the EDSS was 1.5 at the last infusion. However, the patient decided to interrupt the treatment due to safety concerns, particularly the risk of progressive multifocal leukoencephalopathy (PML) (last infusion on 29 August 2011). She was readmitted in October because of a partial cervical Brown–Sequard syndrome with weakness and dysaesthesia in the right leg (EDSS 4). She was treated with a course of intravenous methylprednisolone (IVMP) and completely recovered. No active lesions were detected on a control brain MRI performed on 18 November 2011 (Figure 1(c)). Spinal cord MRI was not performed.

FTY was initiated on 13 December 2011 without cardiovascular concerns. Eleven days later the patient complained of paroxysmic aphasia (paraphasia and denomination) associated with unusual asthenia that led her to stop working. She was admitted as an emergency because of tonicoclonic seizure. Electroencephalography disclosed abnormal slow activity with spikes in the left temporal derivations. Brain MRI exhibited a large extension of previously known T2 lesions with gadolinium uptake (Figure 1(d) and (e)). She was treated with levetiracetam and she received another course of IVMP (1g/day for seven days) and FTY was interrupted on 28 December. Control brain MRI showed stability of lesion load (Figure 1(f)) and FTY was reintroduced on 19 January 2012. Ten days later, she complained of right temporal field visual defect with numbness in the right limb (EDSS 3). Her neurological examination confirmed a right inferior homonymous quadrantanopsia, and MRI exhibited a parietal cortical extension of the lesion with linear gadolinium enhancement (Figure 1(g)). Antibodies anti-JCV were positive in the blood, but PCR for JCV was negative in the CSF. Lymphocyte count showed 0.4 G/L and phenotyping showed the following: 92.10^6/L CD4 and 56.10^6/L CD8. Three additional grams of IVMP were administrated and FTY was continued. Visual field defect persisted (EDSS 2.5) and control MRIs showed the absence of active lesions (Figure 1(h)).

**Discussion**

This patient had an active disease that was stabilized for two years under NZB. She experienced an early relapse after NZB withdrawal, and a severe reactivation of the disease 3.5 months later despite 10 days of FTY therapy.
Withdrawal of NZB is known to be possibly followed by severe reactivation of the disease, which usually occurs three to four months or up to seven months later, consistent with the natural elimination of NZB, and corresponding to inflammatory rebound (which occurs especially in patients with short NZB treatment duration) or return of disease activity level before NZB. The delay of clinical and MRI efficacy of FTY is not known, and severe relapses occurring within the three months of treatment have been reported. There are no guidelines published for the use of FTY in relay with NZB, but a three-month interval free from treatment is commonly observed. During this period, our patient received monthly IVMP to avoid relapses.

The particular presentation of disease reactivation may have suggested the possibility of PML; however, negative PCR for JCV in the CSF and favourable clinical evolution argued against this hypothesis.

NZB blocks lymphocyte trafficking towards the CNS and may increase lymphocytes in the blood. FTY blocks T and B lymphocytes in secondary lymphatic tissue. IRIS usually occurs after plasma exchanges in the case of PML. Clinical and MRI inflammatory exacerbations are suggestive in our case of IRIS-like reaction, related to T-lymphocyte invasion of the CNS, despite FTY therapy and a decrease of CD4 count.

To our knowledge, this is the first case that reports such a reaction while switching from NZB to FTY. Two other cases of inflammatory reaction have been reported under FTY. The first case was described in a patient with neuromyelitis optica disorder spectrum, and the second in a MS patient while switching from IFN to FTY.

This observation raises the possibility of severe inflammation within the period of transition from NZB to FTY. This period should probably be shortened. IVMP preventive therapy may be used within this period; however, its efficacy has still to be confirmed.

Author contributions

All authors made a substantive intellectual contribution to the manuscript. L. Daelman analysed and interpreted the presented data and drafted the manuscript. A. Maitrot analysed the presented data and revised the manuscript for intellectual content. A. Maarouf interpreted the presented data and revised the manuscript for intellectual content. C. Papeix interpreted the presented data and revised the manuscript for intellectual content. A. Tourbah analysed and interpreted the data and drafted and revised the manuscript for intellectual content.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References