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Recurrent disease-activity rebound in a patient with multiple sclerosis after natalizumab discontinuations for pregnancy planning

Dear Editors,

Natalizumab discontinuation is a frequent clinical practice, mainly as part of the *progressive multifocal leukoencephalopathy (*PML) risk management strategy, but this approach has raised concerns about the possible consequences related to subsequent multiple sclerosis (MS) reactivation. Preliminary results of a randomized prospective trial[1] and observational studies yielded conflicting results (Table 1).[2-9]

We report the case of 16-year-old woman who in December 1996 developed relapsing–remitting MS with acute-onset lower limb paraesthesia followed by four relapses in the subsequent 10 months. Interferon-beta 1a therapy was initiated, but in the following years she had six new relapses and in July 2002 was enrolled in the SENTINEL study (natalizumab plus interferon beta 1a).[2]

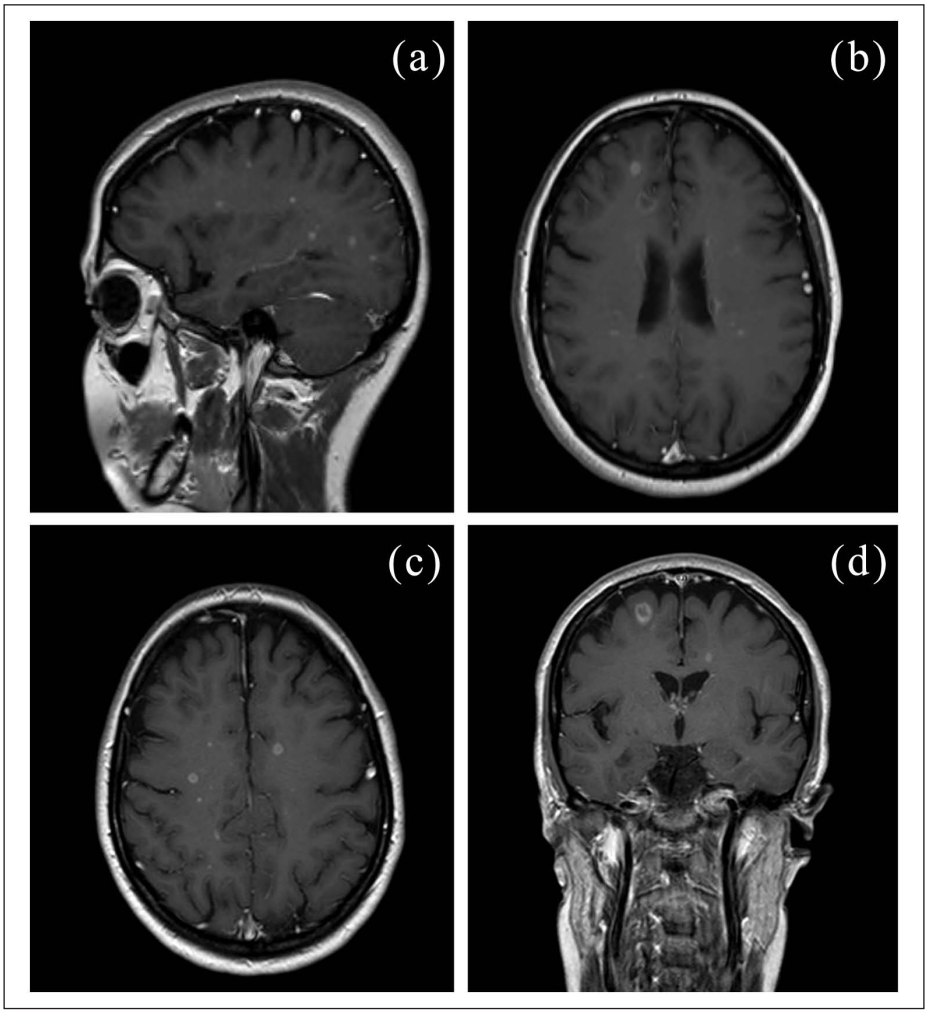

Figure 1. T1-weighted/gadolinium-enhanced lesions on sagittal and axial MR images performed after natalizumab discontinuation in May 2008 (a), (b). T1-weighted/gadolinium-enhanced lesions on axial and coronal MR images performed after natalizumab discontinuation in April 2010 (c), (d).

Table 1. Results of previous studies on clinical and MRI activity after natalizumab discontinuation.

	Number of subjects	ARR before treatment	T2 active lesions at baseline MRI	Gd-enhanced lesions at baseline MRI	Number of natalizumab infusions[a]	Follow-up after withdrawal[b]	DMD during follow-up[c]	ARR at follow-up	Number of patients with relapses during follow-up	T2 active lesions at follow-up MRI[d]	Gd-enhancing lesions at follow up MRI[d]	Unusual clinical or MRI disease activity
Miller et al.[5]	137	1.5		1.6	6	6		0.73	44/137 (32%)	2.6	2.5	No
Vellinga et al.[3]	21	1.2	3.4		(1–37)	15		0.73		10.3		Yes
Borriello et al.[6]	21	2.3		3.2	24	3.7	0/10	0.6	4/21 (19%)		2.3	Yes
Killestein et al.[4]	10	1.8	2.2	3.8	> 12	6	0/10	1.4	7/10 (70%)	11	10.7	Yes
West et al.[7]	68	1.9			> 12	6	4/68		19/68 (28%)		4.5	Yes
Miravalle et al.[8]	32	1.3		1.9	17.3	4	0/32	1	12/32 (38%)		3.6	Yes
O'Connor et al.[2]	1866			1.6	30 (1–41)	12	13%		(21%)		1.2	No
Kerbrat et al.[9]	27	2.3		3.7	12 (6–23)	6	0/27	1.8	18/27 (67%)		9.1	Yes

[a]Expressed as median (range).
[b]Expressed as mean number of months.
[c]Expressed as number of patients who undertook a disease modifying drug (DMD) (percentage).
[d]Values obtained at follow-up MRIs were combined.
Gd: gadolinium; ARR: total number of relapses experienced by the cohort divided by the person/years at risk.

At that time, she had mild disability (Expanded Disability Status Scale (EDSS) 2.0) and the pre-treatment brain MRI performed in June 2002 showed six gadolinium (Gd)-enhanced lesions. During natalizumab treatment, no clinical or radiological relapses occurred but in February 2005, after 31 infusions, natalizumab was stopped because of drug withdrawal from the market following the first two reported cases of PML. After three months, while still on interferon-beta 1a therapy, the patient experienced a new clinical relapse followed by another three clinical relapses in the subsequent 15 months and a marked worsening in her neurological disability (EDSS 4.0).

In November 2006, after reintroduction onto the market, natalizumab was restarted without any further evidence of clinical and MRI activity and with a mild improvement of her neurological disturbances (EDSS 2.0). In January 2008, after 14 infusions, she decided to stop treatment in order to commence pregnancy planning. After four months, she experienced subacute paraparesis (EDSS 4.0) and a brain MRI revealed >50 Gd-enhanced lesions (Figure 1(a) and (b)). A five-day steroid course was administered intravenously with clinical benefit and a brain MRI, performed one month later, did not show any Gd-enhanced lesions.

In July 2008, despite testing positive for anti-JC virus antibodies, the patient agreed to be rescheduled for natalizumab treatment and after six months her brain MRI was negative for Gd-enhanced lesions. In December 2009, after 16 drug infusions and improved clinical disability (EDSS 1.5), she again decided to stop natalizumab for pregnancy planning. Four months later, in April 2010, she reported mild hypoaesthesia of her left leg and a brain MRI scan showed 30 Gd-enhanced lesions (Figure 1(c) and (d)). High-dose steroids were administered intravenously and natalizumab restarted in July 2010. At present, the patient is still being treated with natalizumab with no clinical and MRI evidence of disease activity. In December 2012 EDSS was 2.0.

As our case highlights, the problem of the disease course after natalizumab discontinuation is apparent not only in the case of the PML risk management strategy but also in pregnancy planning. An increasing number of young women are on natalizumab therapy and are faced with the question of whether a drug holiday would be worthwhile for pregnancy planning. Natalizumab was rated with a pregnancy level C by the Food and Drug Administration, indicating a lack of adequate studies in humans, and is therefore recommended to be discontinued at least three months before conception. However, in a recent report,[10] no adverse event on pregnancy outcome, attributed to natalizumab exposure during early pregnancy, has been observed. In our patient, drug discontinuation led each time to a rebound activity that forced her to restart the treatment, without a successful pregnancy attempt.

Further studies are required to assess disease course after natalizumab discontinuation and to investigate alternative safe approaches for pregnancy planning.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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