Best practice in the use of natalizumab in multiple sclerosis

Óscar Fernández

Ther Adv Neurol Disord

(2013) 6(2) 69–79

DOI: 10.1177/
1756285612470401

© The Author(s), 2012.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Natalizumab is approved for the treatment of patients with relapsing–remitting multiple sclerosis who have failed first-line treatment with traditional disease-modifying therapies or who have highly active disease. The drug has proved highly effective, both in a clinical trial setting and in clinical practice, with marked reductions in the rate of clinical relapses and slowed disease progression. These clinical outcomes are mirrored by a marked reduction in disease activity as evidenced by magnetic resonance imaging of the brain. However, natalizumab treatment has been associated with a risk of progressive multifocal leukoencephalopathy (PML), a potentially fatal condition caused by JC virus (JCV) activation. When this condition was detected in a clinical trial shortly after approval, the drug was immediately and voluntarily withdrawn from the market. As a condition of its reinstatement, stringent pharmacovigilance measures and a risk management plan were enforced. The recent availability of a two-step enzyme-linked immunosorbent assay (ELISA) test for the presence of anti-JCV antibodies (free testing is available in a central laboratory for registered centers), along with an ever-improving understanding of other risk factors such as prior immunosuppressant use and duration of treatment, allow an increasingly refined stratification of the risk of PML. This improved stratification of risk can help guide decisions about treatment. This review will also deal with other topics of relevance to clinical practice such as the development of antinatalizumab antibodies and their negative implications in terms of hypersensitivity reactions and loss of efficacy, withdrawal of treatment, and compassionate pediatric use.

Keywords: multiple sclerosis, natalizumab, progressive multifocal leukoencephalopathy, risk stratification

Introduction

Natalizumab is a monoclonal antibody that targets the α_4 subunit of integrin $\alpha_4\beta_1$ (VLA-4), which is expressed on the surface of activated T-cells [Léger *et al.* 1997; Baron *et al.* 1993]. Antagonism of this target is thought to interfere with leukocyte adhesion to the vascular wall, thereby interfering with leukocyte trafficking across the blood–brain barrier and ultimately reducing the inflammation within the central nervous system considered responsible for manifestations of multiple sclerosis (MS), particularly during the relapsing–remitting phase (RRMS).

During the clinical development of natalizumab, randomized, controlled phase II and III studies showed that the agent was very effective at

reducing the annualized relapse rate (ARR) and other relapse-based endpoints [O'Connor *et al.* 2005; Polman *et al.* 2006]. In addition, significant improvements in imaging endpoints were seen [O'Connor *et al.* 2005; Miller *et al.* 2003]. Benefit in terms of slower disease progression (as measured by the Expanded Disability Status Scale [EDSS]) was also reported. However, during a phase III trial of combination therapy of natalizumab with interferon (IFN)-beta *versus* IFN-beta therapy alone, two cases were reported of progressive multifocal leukoencephalopathy (PML) [Rudick *et al.* 2006]. PML is a debilitating and often fatal neurological condition resulting from infection of the brain by the JC virus (JCV). On review of data from a clinical trial of natalizumab in the indication of Crohn's disease,

Correspondence to:
Óscar Fernández, MD, PhD
Instituto de Neurociencias
Clínicas, Servicio de
Neurología, Hospital
Regional Universitario
Carlos Haya, Avenida
Carlos Haya s/n, 29010
Málaga, Spain
oscar.fernandez.sspa@juntadeandalucia.es

another patient was diagnosed with PML [Van Assche *et al.* 2005]. Faced with these safety concerns, the manufacturer voluntarily withdrew the drug from the market in 2005. It was reinstated in 2006 on the condition that an extensive pharmacovigilance system and risk management program be implemented.

Given the concerns over the risks of therapy with natalizumab, the risk–benefit balance changed, and only patients who stood to benefit most from treatment are now considered appropriate for treatment. Thus, natalizumab, in the European Union, is indicated in patients with highly active disease and those who have failed therapy with first-line disease-modifying therapies (DMTs). Combination therapy with another immunomodulator is an absolute contraindication. One result of this change in indication is that the target population for natalizumab in clinical practice (high-risk patients) is very different from populations enrolled in the clinical trials (often treatment-naïve patients with relatively low disease activity). Studies of natalizumab in clinical practice are therefore particularly relevant.

Postmarketing studies and diligent pharmacovigilance are also very important given the concerns about PML. The condition is rare, so trends and risk factors can only really be detected with large patient numbers. A number of questions remain, particularly regarding the increase in risk with increasing duration of treatment. However, our understanding of the risk factors is improving and risk stratification algorithms are being applied. These can help avoid unnecessary administration of natalizumab to patients with a high risk of PML (that is, those where the benefits of natalizumab do not justify the risks) while not denying a highly effective treatment to others who are unlikely to experience such an event because they are afraid of the consequences.

Natalizumab in clinical trials

Efficacy

The efficacy of natalizumab was demonstrated in the pivotal AFFIRM trial, which randomized patients with a diagnosis of RRMS and who had had at least one medically documented relapse within the 12 months before the study began, a score of 0–5 on the EDSS and magnetic resonance imaging (MRI) with lesions consistent with multiple sclerosis to either natalizumab (627

patients) or placebo (315 patients) [Polman *et al.* 2006]. Of note, patients who had received more than 6 months of treatment with IFN-beta or glatiramer acetate were excluded from the study. The primary efficacy end points were clinical relapse rate (a measure of the inflammatory characteristics of the disease) at 1 year and cumulative probability of sustained progression of disability (EDSS) at 2 years. The majority of patients had one single relapse in the year prior to study entry and, at baseline the majority had an EDSS score between 1.0 and 2.5.

At 1 year, the ARR was 0.26 relapses/year in the natalizumab arm compared with 0.81 in the placebo arm ($p < 0.001$). The proportion of relapse-free patients in the year following treatment was higher in the natalizumab group than the placebo group ($p < 0.001$). These marked differences in terms of relapses were still apparent after 2 years. At 2 years, the cumulative probability of EDSS progression, sustained over 12 weeks, was 17% in the natalizumab arm and 29% in the placebo arm (hazard ratio [HR] 0.58; $p < 0.001$).

The results of this trial provided strong evidence that natalizumab is a very effective drug in patients with RRMS, reducing the inflammatory activity of the disease and ultimately slowing progression. Other trials in the clinical development program yielded similarly encouraging results, not only showing clinical benefit but also sharp reductions in disease activity measured by MRI [Miller *et al.* 2003; O'Connor *et al.* 2005; Rudick *et al.* 2006].

Safety

During the 2-year study period of the AFFIRM trial, 6% of the patients receiving natalizumab and 4% receiving placebo discontinued the study [Polman *et al.* 2006]. The rate of infections was not significantly higher in the natalizumab arm than the placebo arm (1.52 per patient-year *versus* 1.42 per patient-year; $p = 0.32$). Cancer was reported more frequently in the natalizumab group (three cases of breast cancer, one case of stage 0 cervical cancer, and one case of newly diagnosed metastatic melanoma) than the placebo group (one case of basal-cell carcinoma in the placebo group) but the low numbers precluded drawing any firm conclusions. In general, though, the safety profile of natalizumab in the AFFIRM trial appeared to be good. The SENTINEL trial of combination therapy of natalizumab with IFN-beta was terminated early

when two cases of PML were detected [Rudick *et al.* 2006]. With the exception of the cases of PML, there were no other major safety signals were detected during the trial.

Infusion reactions were reported in the AFFIRM trial [Polman *et al.* 2006]. In a subsequent analysis of the AFFIRM trial, the incidence of antinatalizumab antibodies was 9%, although persistently positive titers were observed in 6% [Calabresi *et al.* 2007]. The incidence of infusion reactions was found to be significantly higher in patients with positive titers.

Natalizumab in clinical practice

As mentioned earlier, in the European Union, natalizumab was approved for patients who have failed prior DMT or those with highly active disease, although the patients studied in the pivotal AFFIRM trial were generally treatment-naïve and did not have highly active disease. It is therefore comforting that a number of observational studies have confirmed the efficacy of natalizumab reported in clinical trials (Table 1). The duration of treatment was up to 50 months in one case [Fernández *et al.* 2012] and three studies included more than 1000 patients [Fernández *et al.* 2012; Mancardi *et al.* 2011; Piehl *et al.* 2011]. In these studies, the baseline EDSS ranged from 3.1 to 4.0 compared with 2.53 in the AFFIRM trial. Nevertheless, decreases in the ARR at 1 year with respect to year prior to natalizumab were generally greater in these studies than in the active-treatment arm of the AFFIRM trial. In most cases, a decrease in EDSS was observed after 1 year of treatment. These efficacy results are also in agreement with the findings to date of the Tysabri Observational Program (TOP) [Kappos *et al.* 2012]. Almost 3500 patients had been enrolled in this program as of June 2011. The mean ARR before starting treatment with natalizumab was 1.98 and 0.28 post-baseline ($p < 0.0001$). An analysis by subgroups showed the lowest post-baseline ARRs for treatment naïve patients (0.16) and highest postbaseline ARRs for patients who had received prior immunosuppressants (0.34).

One observational study has explicitly investigated the effect of baseline disability on efficacy outcomes [Fernández *et al.* 2011a]. The 78 patients included in the study were stratified according to baseline EDSS, and the impact on ARR was investigated. The authors found that the

difference between ARR before and after natalizumab treatment was 0.92 for patients with a baseline EDSS ≤ 3.5 ($p < 0.0005$), 0.70 those with EDSS 4.0–6.0 ($p < 0.007$) and 0.57 for those with EDSS ≥ 6 ($p = 0.386$). The authors concluded that benefit from natalizumab treatment in terms of reduced number of relapses could be expected for patients with EDSS scores up to 6. These results were confirmed in a much larger study [Fernández *et al.* 2012], showing that the reduction in ARR was maintained independently of the patients' EDSS at baseline even in patients with an EDSS score of over 6.

These observational studies also provide an indication of the safety of natalizumab. PML, the major concern with natalizumab treatment, which is reviewed at length in a later section. Here, we note that PML concerns aside, natalizumab is well tolerated. For the most part, the observational studies report discontinuation rates between 10% and 15% (Table 1). This is reasonable considering the long duration of follow-up in some of these studies.

The observational studies to date have also corroborated the presence of antinatalizumab antibodies, with an incidence as high as 14.1% in the study reported by Oliver and colleagues [Oliver *et al.* 2011], although only 9.3% were persistent at the second determination. That study examined the kinetics of antinatalizumab antibody development and concluded that most of the patients who develop antibodies will do so in the first 6 months of treatment. Antinatalizumab antibodies may be associated with the onset of late hypersensitivity reactions [Krumbholz *et al.* 2007] and reduced efficacy of the drug [Calabresi *et al.* 2007].

In summary, the findings of the observational studies reported to date provide support for the efficacy and safety of natalizumab in patients with more severe disease than those originally included in the pivotal trials. The major concern is, of course, PML.

Managing the risk of PML

The biggest issue facing the use of natalizumab in the clinic is how to deal with the risk of PML. This potentially life-threatening condition is caused by the JCV, which is widely present in healthy individuals but in certain circumstances can be an opportunistic infection of the brain,

Table 1. Overview of observational studies of natalizumab.

Study	Number of patients	Duration of treatment (months)	Mean annualized relapse rate prior to treatment	Decrease in annualized relapse rate at 1 year with respect to previous year (%) ^a	Decrease in mean Expanded Disability Status Scale after 1 year	Discontinuations	Hypersensitivity reactions	Neutralizing antibodies
Putzki <i>et al.</i> [2010a]	97	≥12	2.3	91	0.4	8 (8.2%)	2 (2.1%) ^b	4 (4.1%) ^c
Oturai <i>et al.</i> [2009]	234	Median 11.3 (range 3–21.5)	2.53	73	–	27 (12%)	9 (3.8%)	7 (2.9%)
Sangalli <i>et al.</i> [2011]	285	Up to 24	2.13	88	–	34 (12%)	18 (6.3%)	19 (6.6%)
Outteryck <i>et al.</i> [2010]	384	≥12	2.19	73	0.5	35 (9.1%)	15 (3.9%)	5 (1.3%)
Prosperini <i>et al.</i> [2011]	190	Median 15 (range 1–29)	20.0	90 ^d	0.2 ^e	31 (16.3%)	4 (2.1%) ^b	19 (10%)
Mancardi <i>et al.</i> [2011]	2971	–	–	–	–	–	–	–
Putzki <i>et al.</i> [2010b]	85	Median 17.2 (range 12–31.4)	2.0	87	0.2	10 (12%)	2 (2.4%) ^b	6 (7.1%) ^c
Piehl <i>et al.</i> [2011]	1115	Mean 22	–	–	0.48 ^f	116 (10.4%)	–	39 (3.9%)
Fernández <i>et al.</i> [2011a]	77	Mean 14.7	0.96	86	0.05	13 (16.8%)	1 (1.3%)	9 (11.7%)
Horga <i>et al.</i> [2011]	112	Mean 15.8	2.25	89	0.2	16 (14.4%)	5 (4.5%)	–
Fernández <i>et al.</i> [2012]	1415	Median 16 (range 1–50)	2.23	88	0.5	176 (14%)	46 (3.6%)	34 (3.1%)
AFFIRM/Polman <i>et al.</i> [2006]	627: natalizumab 315: placebo	24	1.53 (natalizumab) 1.50 (placebo)	83 (natalizumab) 54 (placebo)	–	3.8% (natalizumab) 4.8% (placebo)	9% (natalizumab) 4% (placebo)	57 (9%)

^aChange in median^bOnly reported if leading to discontinuation^cOnly reported if persistent and leading to discontinuation^dCalculated for entire follow-up period^eAt 15 months follow up^fFor 363 patients who completed 24 months of treatment

Figure 1. Risk of progressive multifocal leukoencephalopathy in natalizumab-treated patients, stratified according to duration of natalizumab use, prior immunosuppressant use and JCV-antibody status. (Based on Bloomgren *et al.* [2012].)

usually in patients with serious immune system disorders caused by, for example, HIV infection [Berger and Major, 2008] and immunosuppression [Mateen *et al.* 2011]. When natalizumab started to be administered to patients again following withdrawal from the market when the cases of PML had occurred in patients in clinical trials, an extensive risk management plan was implemented. We can now be fairly confident that all cases of PML resulting from administration of natalizumab are detected, and postmarketing programs are beginning to shed some light on the risk factors for developing PML and the best approaches to manage the risk.

The risk of PML can be stratified as shown in Figure 1. Three main risk factors have been identified: anti-JCV antibody positive status, duration of natalizumab treatment and prior use of immunosuppressants. According to a recent and comprehensive analysis based on extensive postmarketing data, as of 29 February 2012, 212 confirmed cases of PML had been reported in almost 100,000 natalizumab-treated patients, yielding a rate of 2.1 cases per 1000 patients [Bloomgren *et al.* 2012]. On investigating the impact of these factors on the risk of developing PML, on JCV-positive patients, duration of

therapy was found to be associated with an increased incidence of PML, thus the incidence (95% confidence interval [CI]) was 0.04 (0.01–0.10) for 1–12 months, 0.56 (0.40–0.77) for 13–24 months of therapy, 1.93 (1.55–2.38) for 25–36 months of therapy and 1.99 (1.52–2.58) for 37–48 months of therapy. Prior immunosuppressant use (regardless of timing) was identified in 34.5% of natalizumab-treated patients who developed PML compared with 20.3% of all natalizumab-treated patients [Bloomgren *et al.* 2012], further underlining prior immunosuppressant therapy as a risk factor. JCV antibody status is more difficult to assess as routine screening for JCV antibodies prior to natalizumab therapy has not been systematic. Nevertheless, among patients with a baseline JCV antibody status available who subsequently developed PML, all had a positive status suggesting that the presence of the JCV is a prerequisite for developing PML. The prevalence of the JCV in the population of natalizumab-treated patients with MS was reported to be 51% in a recent French study [Outteryck *et al.* 2012] and 59% in a recent German study [Trampe *et al.* 2012]. Prevalence does not seem to be affected by factors such as prior immunosuppressant therapy [Bozic *et al.* 2011].

Patients who had all three risk factors present have an estimated incidence of PML of 11.1 cases per 1000 patients (95% CI 8.3–14.5). Anti-JCV antibody assay has an estimated analytical false-negative rate between 2.5% and 2.7%, and an estimated incidence of PML among patients negative for anti-JCV antibodies of 0.09 cases or less per 1000 patients (95% CI 0–0.48), an incidence that is lower by a factor of at least 44 than the incidence among patients positive for anti-JCV antibodies ($p < 0.001$) [Bloomgren *et al.* 2012].

Follow-up of patients receiving natalizumab

Although careful selection of patients can help reduce the risk of PML, it cannot eliminate it. In addition, risk factors can change over the course of therapy. Obviously the duration of treatment will slowly increase and it is possible that patients will undergo conversion from JCV antibody negative to JCV antibody positive status. Current recommendation is to repeat the anti-JCV antibodies testing every 6 months in negative patients.

Patients should be monitored closely both clinically and by MRI to ensure that PML is detected as early as possible [Kappos *et al.* 2011]. MRI can be a very sensitive technique although not very specific, particularly with early PML lesions [Yousry *et al.* 2006; Hurley *et al.* 2003]. The recently published Spanish guidelines suggested examinations every 6 months for high-risk patients and every 12 months for medium- and low-risk patients [Fernández *et al.* 2011b]. Ideally, similar or preferably the same equipment should be used for MRI follow up to make it easier to detect subtle changes. PML on MRI show multifocal, asymmetric, subcortical white matter lesions, with little surrounding edema or mass effect. Hyperintense signals in subcortical white matter on T2-weighted and fluid-attenuated inversion recovery (FLAIR) are highly suggestive of PML. Gadolinium enhancement habitually is small, but sometimes can be more evident [Kappos *et al.* 2007].

In addition, the patients themselves and their families should be educated about the signs and symptoms to look out for. These signs and symptoms cannot easily be distinguished from an MS relapse. If the neurologist is reasonably certain that the patient is experiencing a relapse, treatment can continue; otherwise, treatment should be discontinued immediately until the

cause of the signs and symptoms has been established. MRI examination is essential in the event of clinical suspicion. Characteristics such as site, borders, and pattern of change of a lesion in a MRI examination can help distinguish PML lesions from those arising in a MS relapse [Coyle *et al.* 2009]. When PML is suspected, a study of JCV in CSF should help definitively confirm PML. Figure 2 summarizes the approach to take when PML is suspected.

JCV testing should be performed every 6 months as seroconversion of formerly negative status to positive status can occur (approximately 2% per year) and the test can give false negatives (estimated at 2.5%) [Gorelik *et al.* 2010].

After 24 months of treatment, the patient's situation should be carefully reassessed given the known association between duration of treatment and risk of developing PML. It is important that the patient is informed of the potential risks and that the decision about whether to continue or not is taken jointly by the patient and the treatment neurologist [Fernández *et al.* 2011b]. In a study of the decision about continuation with natalizumab treatment after receiving the results from JCV testing and subsequent stratification according to the known risk factors, Tur and colleagues reported that all JCV antibodies negative patients opted to continue [Tur *et al.* 2012]. Among those that were positive, 4/10 patients (40%) with all three risk factors present decided to continue. The authors also found a trend towards patients with a greater deterioration in EDSS being more likely to discontinue and, interestingly, that the treating neurologist also had an impact on the decision. These results highlight that the decision to continue is a complex one that involves an intricate balance of perceived risks and benefits and that neurologists can influence this perception.

Treatment of confirmed PML

The most appropriate treatment for PML is prevention by careful selection of patients according to the principles outlined above. Nevertheless, the risk associated with natalizumab treatment can never be fully eradicated. As favorable outcomes are more likely if the disease is detected early, constant vigilance is desirable, both on the part of the neurologist and that of the patients and their families. As mentioned earlier, natalizumab should be discontinued on suspicion of PML.

Figure 2. Recommended algorithm for action in the event of symptoms in the clinical course of patients treated with natalizumab. [Source: Fernández *et al.* [2011b].]

CSF, cerebrospinal fluid; JCV, JC virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.

The aim of treatment should be to eliminate the drug from the bloodstream as quickly as possible and thereby suppress its mechanism of action. This can be achieved by plasmapheresis and immune-adsorption techniques [Wenning *et al.* 2009; Kappos *et al.* 2011]. Other treatments such as antiviral agents, immunomodulatory and 5HT_{2A} receptor antagonists including psychoactive drugs (mirtazapine), have been tried, although there is no solid evidence of their usefulness.

On discontinuing natalizumab, care must be taken to avoid immune reconstitution inflammatory syndrome (IRIS) [Tan *et al.* 2009, 2011]. This condition appears several weeks after plasmapheresis or immune-adsorption. As yet, there is no consensus about how best to manage this condition, although by analogy with IRIS in patients with HIV infection, high-dose intravenous corticosteroids have been used with a certain degree of success.

It is encouraging to note that the mortality due to PML associated with natalizumab treatment has

decreased over the years, presumably due to a combination of earlier detection and better understanding of how to treat the disease. But there is still much work to be done.

Neutralizing antibodies

Like most biologic treatments, the development of neutralizing antibodies to natalizumab is an issue that needs addressing. Approximately 9% of patients have been reported to develop such antibodies, usually in the first 6 months of treatment. Positive antibody status is associated with allergic or hypersensitivity reactions, especially during the second infusion. If resources permit, it would be recommendable to monitor antinatalizumab antibodies in all patients after the first 6 months of treatment, because they have been shown to appear early during the treatment [Oliver *et al.* 2011; Fernández *et al.* 2011b]. Monitoring should, however, be mandatory in patients with allergic or hypersensitivity reactions and those with clinical relapse or new MRI findings indicative of disease activity. Patients

with persistent positive titers (that is, a positive result when the assay is repeated 4 weeks later) should be discontinued because the efficacy has been shown to decrease in such cases while the risk of hypersensitivity reactions is greater [Calabresi *et al.* 2007].

In view of the possibility of infusion reactions, every infusion should be monitored by trained nursing and/or medical staff who should be vigilant for possible infusion reactions such as tiredness, dizziness, headache, asthenia and nausea.

Withdrawal of natalizumab and 'drug holidays'

Given the increased risk of PML with time, at 2 years it is necessary to reassess treatment with the patients. A frank discussion of the risks and benefits should be held. Although the risk of PML increases with increasing duration of treatment, the negative effects of discontinuing treatment should also be presented.

On withdrawal, as the clinical and biological effects of the drug begin to wane, there will likely be a return of disease activity. There is however certain debate about whether a rebound effect is present. In a retrospective chart analysis of 68 patients with some form of dosage interruption, 19 (27.9%) had experienced a relapse within 6 months of interruption compared to none of the 16 with continuous treatment [West and Cree, 2010]. Moreover, of the 19 relapses, seven were severe, with a mean of 16 Gd⁺ lesions on brain MRI. The authors suggested that this was evidence of a possible rebound effect. In contrast, in a study of 23 patients enrolled in phase III clinical trials, Stüve and colleagues found little evidence of disease activity 14 months after discontinuation [Stüve *et al.* 2009]. In another analysis of the AFFIRM, SENTINEL and GLANCE studies, no rebound was apparent [O'Connor *et al.* 2011]. However, the patients included in those studies would have had lower disease activity prior to natalizumab treatment than is habitual in clinical practice.

The ongoing RESTORE study represents an attempt to provide a more definitive answer to the question of rebound of disease activity after discontinuation of natalizumab [Fox *et al.* 2011]. In total, 175 patients who had received 24 months of natalizumab therapy according to the labeling were randomized to continue

with natalizumab ($n = 45$), placebo ($n = 42$), or another DMT (intramuscular IFN β -1a, glatiramer acetate or corticosteroids), chosen at the discretion of the investigator ($n = 88$). Patients with MRI evidence of disease activity were considered as meeting the rescue criterion (whereupon natalizumab could be restarted or high-dose corticosteroids administered). During follow up, no patients who continued with natalizumab therapy presented with MRI evidence of disease and two had clinical relapse. This compared with 18/41 (44%) of patients on placebo with MRI evidence of disease and 7/41 (17%) with a clinical relapse. Most of these events occurred after week 12. These preliminary results suggest that natalizumab interruption is associated with a high rate of recurrence of MRI and clinical MS disease activity, mainly after week 12. For patients who switched to another DMT, intramuscular IFN β -1a seemed more effective than other treatments with regard to MRI activity (1/14 [7%] with MRI evidence of disease activity) although the clinical relapse rate was higher (4/14 [29%]). The RESTORE study was not designed or powered to answer questions about changes in the risk of PML with interruptions in dosing. Given the persistence of activity of the drug, it is recommended to continue monitoring for signs and symptoms of disease and PML. It is unclear how long such monitoring should continue although a recent analysis of the RESTORE study suggests that immune parameters had returned to expected pretreatment levels within 4 months of discontinuation [Cree *et al.* 2012].

Contraindications for natalizumab therapy

To determine eligibility for therapy, a detailed medical history of the patient should be taken into consideration. Before exposing patient to the risk of treatment, firm confirmation of MS diagnosis should be obtained and disease activity determined. The presence of concomitant diseases should be ascertained; HIV infection and history of immunodeficiency or lymphoproliferative diseases in particular can be considered contraindications for natalizumab. Similarly prior treatment with immunosuppressants should be considered with caution and considered for risk stratification. Baseline laboratory parameters should be examined for evidence of immunosuppression, which would be also be considered as a contraindication. Recently, a European program

for JCV antibody testing has been set up. Testing is done free by a central laboratory in Denmark for all centers that are registered with the program. The result in this test is now considered before initiating natalizumab therapy, permitting to stratify from the very beginning the risk associated with the therapy. Patients already on therapy who subsequently test positive for the JCV antibody may continue treatment if, on consultation between the neurologist and the patient, the potential benefit is considered greater than the potential risk.

Pediatric use

Natalizumab has not been tested formally in clinical trials in children and adolescents. Other DMTs, such as IFN have been used in children to treat MS and have generally been shown to be safe and so their labeling permits use of these DMTs in children, with the caveat that efficacy has not been demonstrated in well-designed and conducted studies in this population. However, failures of traditional DMTs have been reported [Appleton and Boggild, 2009] and, furthermore, childhood MS often follows an aggressive course. In view of this, there have been some reports of compassionate use of natalizumab in children, often with good results [Huppke *et al.* 2008]. The efficacy and safety profiles, as far as they could be assessed, appear to be similar to those in adults, or even better, given the lower prevalence of seropositivity for JCV in children [Yeh and Weinstock-Guttman, 2010] and the fact that no pediatric cases of PML have been reported after use of natalizumab. Clearly, though, further study is needed to establish, among other things, the optimal dose.

Conclusions

Natalizumab is a highly effective treatment for patients with RRMS. Our understanding of the risk factors for developing PML, the major safety concern with natalizumab treatment, is improving. Moreover, the widespread availability of JCV antibody testing should enable a much more precise stratification of the risk of PML. In patients who are anti-JCV antibody positive, another risk factor for PML is duration of treatment. With availability of antibody testing, it should be easier to make informed decisions about whether patients should continue treatment.

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 corresponding author (Oscar Fernández, MD, PhD) has received honoraria as consultant in advisory boards, and as chairman or lecturer in meetings, and has also participated in clinical trials and other research projects promoted by Biogen-Idec, Bayer-Schering; Merck-Serono, Teva, Novartis, Almirall and Allergan.

Acknowledgements

Editorial support was provided by Dr Gregory Morley, whose fees were paid by Biogen Idec Iberia, S.L.

References

- Appleton, R. and Boggild, M. (2009) Natalizumab in paediatric multiple sclerosis and service implication. *Dev Med Child Neurol* 51: 758–759.
- Baron, J., Madri, J., Ruddie, N., Hashim, G. and Janeway, C. (1993) Surface expression of alpha 4 integrin by CD4 T cells is required for their entry into brain parenchyma. *J Exp Med* 177: 57–68.
- Berger, J. and Major, E. (2008) Progressive multifocal leukoencephalopathy. *Semin Neurol* 19: 193–200.
- Bloomgren, G., Richman, S., Hotermans, C., Subramanyam, M., Goelz, S., Natarajan, A. *et al.* (2012) Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 366: 1870–1880.
- Bozic, C., Richman, S., Plavina, T., Natarajan, A., Scanlon, J., Subramanyam, M. *et al.* (2011) Anti-John Cunningham virus antibody prevalence in multiple sclerosis patients: baseline results of STRATIFY-1. *Ann Neurol* 70: 742–750.
- Calabresi, P., Giovannoni, G., Confavreux, C., Galetta, S., Havrdova, E., Hutchinson, M. *et al.* (2007) The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. *Neurology* 69: 1391–1403.
- Coyle, P., Foley, J., Fox, E., Jeffery, D., Munschauer, F., III, and Tornatore, C. (2009) Best practice recommendations for the selection and management of patients with multiple sclerosis receiving natalizumab therapy. *Mult Scler* 15(Suppl. 4): S26–S36.
- Cree, B., De Seze, J., Fox, R., Gold, R., Hartung, H., Jeffery, D., *et al.* (2012) Study: effects of a 24-week

- natalizumab treatment interruption on immune parameters and multiple sclerosis magnetic resonance imaging disease activity. Poster Presented at the *American Academy of Neurology 64th Annual Meeting*, New Orleans, LA.
- Fernández, O., Alvarenga, M., Guerrero, M., León, A., Alonso, A., López-Madróna *et al.* (2011a) The efficacy of natalizumab in patients with multiple sclerosis according to level of disability: results of an observational study. *Mult Scler* 17: 192–197.
- Fernández, O., García-Merino, J., Arroyo, R., Álvarez-Cermeño, J., Arbizu, T., Izquierdo, G. *et al.* (2011b) Spanish consensus on the use of natalizumab (Tysabri®) - 2011. *Neurologia (Barcelona, Spain)* [ePub ahead of print], PMID: 22078648.
- Fernández, O., Oreja-Guevara, C., Arroyo, R., Izquierdo, G., Pérez, J. and Montalban, X. (2012) Natalizumab treatment of multiple sclerosis in Spain: results of an extensive observational study. *J Neurol* [Epub ahead of print], PMID: 22289966.
- Fox, R., Kappos, L., Cree, B., Kaufman, M., Jeffery, D., Weinstock-Guttman, B., *et al.* (2011) Effects of a 24-week natalizumab treatment interruption on clinical and radiologic parameters of multiple sclerosis disease activity: The RESTORE study. In: *Late Breaking News. Presented at the European Committee for the Treatment and Research in Multiple Sclerosis 27th Annual Meeting*, Amsterdam, the Netherlands.
- Gorelik, L., Lerner, M., Bixler, S., Crossman, M., Schlain, B., Simon, K. *et al.* (2010) Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurol* 68: 295–303.
- Horga, A., Castillo, J., Rio, J., Tintore, M., Auger, C., Sastre-Garriga, J. *et al.* (2011) An observational study of the effectiveness and safety of natalizumab in the treatment of multiple sclerosis. *Rev Neurol* 52: 321–330.
- Huppke, P., Stark, W., Zürcher, C., Huppke, B., Brück, W. and Gärtner, J. (2008) Natalizumab use in pediatric multiple sclerosis. *Arch Neurol* 65: 1655–1658.
- Hurley, R., Ernst, T., Khalili, K., Del Valle, L., Simone, I. and Taber, K. (2003) Identification of HIV-associated progressive multifocal leukoencephalopathy: magnetic resonance imaging and spectroscopy. *J Neuropsychiatry Clin Neurosci* 15: 1–6.
- Kappos, L., Bates, D., Edan, G., Eraksoy, M., García-Merino, A., Grigoriadis, N. *et al.* (2011) Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. *Lancet Neurol* 10: 745–758.
- Kappos, L., Bates, D., Hartung, H., Havrdova, E., Miller, D., Polman, C. *et al.* (2007) Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. *Lancet Neurol* 6: 431–441.
- Kappos, L., Belachew, S., Butzkueven, H., Pellegrini, F., Trojano, M., Wiendl, H., *et al.* (2012) Long-term safety and efficacy and association between baseline treatment history and postbaseline relapses in multiple sclerosis patients treated with natalizumab in the TYSABRI® Observational Program (TOP). Poster 4.134 presented at the *American Academy of Neurology 64th Annual Meeting*, New Orleans, LA.
- Krumbholz, M., Pellkofer, H., Gold, R., Hoffmann, L., Hohlfeld, R. and Kümpef, T. (2007) Delayed allergic reaction to natalizumab associated with early formation of neutralizing antibodies. *Arch Neurol* 64: 1331–1333.
- Léger, O., Yednock, T., Tanner, L., Horner, H., Hines, D., Keen, S. *et al.* (1997) Humanization of a mouse antibody against human alpha-4 integrin: a potential therapeutic for the treatment of multiple sclerosis. *Hum Antibodies* 8: 3–16.
- Mancardi, G., Tedeschi, G., Amato, M., D'Alessandro, R., Drago, F., Milanese, C. *et al.* (2011) Three years of experience: the Italian registry and safety data update. *Neurol Sci* 31(Suppl. 3): 295–297.
- Mateen, F., Muralidharan, R., Carone, M., van de Beek, D., Harrison, D., Aksamit, A. *et al.* (2011) Progressive multifocal leukoencephalopathy in transplant recipients. *Ann Neurol* 70: 305–322.
- Miller, D., Khan, O., Sheremata, W., Blumhardt, L., Rice, G., Libonati, M. *et al.* (2003) A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 348: 15–23.
- O'Connor, P., Goodman, A., Kappos, L., Lublin, F., Miller, D., Polman, C. *et al.* (2011) Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis. *Neurology* 76: 1858–1865.
- O'Connor, P., Miller, D., Riester, K., Yang, M., Panzara, M., Dalton, C. *et al.* (2005) Relapse rates and enhancing lesions in a phase II trial of natalizumab in multiple sclerosis. *Mult Scler* 11: 568–572.
- Oliver, B., Fernández, O., Orpez, T., Alvarenga, M., Pinto-Medel, M., Guerrero, M. *et al.* (2011) Kinetics and incidence of anti-natalizumab antibodies in multiple sclerosis patients on treatment for 18 months. *Mult Scler* 17: 368–371.
- Oturai, A., Koch-Henriksen, N., Petersen, T., Jensen, P., Sellebjerg, F. and Sorensen, P. (2009) Efficacy of natalizumab in multiple sclerosis patients with high disease activity: a Danish nationwide study. *Eur J Neurol* 16: 420–423.

- Outteryck, O., Ongagna, J., Duhamel, A., Zéphir, H., Collongues, N., Lacour, A. *et al.* (2012) Anti-JCV antibody prevalence in a French cohort of MS patients under natalizumab therapy. *J Neurol* [ePub ahead of print], PMID: 22527227.
- Outteryck, O., Ongagna, J., Zéphir, H., Fleury, M., Lacour, A., Blanc, F. *et al.* (2010) Demographic and clinic characteristics of French patients treated with natalizumab in clinical practice. *J Neurol* 257: 207–211.
- Piehl, F., Holmén, C., Hillert, J. and Olsson, T. (2011) Swedish natalizumab (Tysabri) multiple sclerosis surveillance study. *Neurol Sci* 31(Suppl. 3): 289–293.
- Polman, C., O'Connor, P., Havrdova, E., Hutchinson, M., Kappos, L., Miller, D. *et al.* (2006) A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 354: 899–910.
- Prosperini, L., Borriello, G., Fubelli, F., Marinelli, F. and Pozzilli, C. (2011) Natalizumab treatment in multiple sclerosis: the experience of S. Andrea MS Centre in Rome. *Neurol Sci* [ePub ahead of print], PMID: 20535513.
- Putzki, N., Yaldizli, O., Bühler, R., Schwegler, G., Curtius, D. and Tettenborn, B. (2010a) Natalizumab reduces clinical and MRI activity in multiple sclerosis patients with high disease activity: results from a multicenter study in Switzerland. *Eur Neurol* 63: 101–106.
- Putzki, N., Yaldizli, O., Mäurer, M., Cursiefen, S., Kuckert, S., Klawe, C. *et al.* (2010b) Efficacy of natalizumab in second line therapy of relapsing–remitting multiple sclerosis: results from a multicenter study in German speaking countries. *Eur J Neurol* 17: 31–37.
- Rudick, R., Stuart, W., Calabresi, P., Confavreux, C., Galetta, S., Radue, E. *et al.* (2006) Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 354: 911–923.
- Sangalli, F., Moiola, L., Bucello, S., Annovazzi, P., Rizzo, A., Radaelli, M. *et al.* (2011) Efficacy and tolerability of natalizumab in relapsing–remitting multiple sclerosis patients: a post-marketing observational study. *Neurol Sci* [ePub ahead of print], PMID: 20544247.
- Stüve, O., Cravens, P., Frohman, E., Phillips, J., Remington, G., von Geldern, G. *et al.* (2009) Immunologic, clinical, and radiologic status 14 months after cessation of natalizumab therapy. *Neurology* 72: 396–401.
- Tan, I., McArthur, J., Clifford, D., Major, E. and Nath, A. (2011) Immune reconstitution inflammatory syndrome in natalizumab-associated PML. *Neurology* 77: 1061–1067.
- Tan, K., Roda, R., Ostrow, L., McArthur, J. and Nath, A. (2009) PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. *Neurology* 72: 1458–1464.
- Trampe, A., Hemmelmann, C., Stroet, A., Haghikia, A., Hellwig, K., Wiendl, H. *et al.* (2012) Anti-JC virus antibodies in a large German natalizumab-treated multiple sclerosis cohort. *Neurology* 78: 1736–1742.
- Tur, C., Tintoré, M., Vidal-Jordana, A., Castelló, J., Galán, I., Río, J. *et al.* (2012) Natalizumab discontinuation after PML risk stratification: outcome from a shared and informed decision. *Mult Scler* [ePub ahead of print], PMID: 22383232.
- Van Assche, G., Van Ranst, M., Sciot, R., Dubois, B., Vermeire, S., Noman, M. *et al.* (2005) Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 353: 362–368.
- Wenning, W., Haghikia, A., Laubenberger, J., Clifford, D., Behrens, P., Chan, A. *et al.* (2009) Treatment of progressive multifocal leukoencephalopathy associated with natalizumab. *N Engl J Med* 361: 1075–1080.
- West, T. and Cree, B. (2010) Natalizumab dosage suspension: are we helping or hurting? *Ann Neurol* 68: 395–399.
- Yeh, E. and Weinstock-Guttman, B. (2010) Natalizumab in pediatric multiple sclerosis patients. *Ther Adv Neurol Disord* 3: 293–299.
- Yousry, T., Major, E., Ryschkewitsch, C., Fahle, G., Fischer, S., Hou, J. *et al.* (2006) Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 354: 924–933.