

Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring



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Natalizumab, a highly specific $\alpha 4$ -integrin antagonist, is approved for treatment of patients with active relapsing-remitting multiple sclerosis (RRMS). It is generally recommended for individuals who have not responded to a currently available first-line disease-modifying therapy or who have very active disease. The expected benefits of natalizumab treatment have to be weighed against risks, especially the rare but serious adverse event of progressive multifocal leukoencephalopathy. In this Review, we revisit and update previous recommendations on natalizumab for treatment of patients with RRMS, based on additional long-term follow-up of clinical studies and post-marketing observations, including appropriate patient selection and management recommendations.

Introduction

Natalizumab—an $\alpha 4$ -integrin antagonist—was approved for treatment of patients with multiple sclerosis (MS) who have the active relapsing-remitting form of disease (RRMS) on the basis of its targeted mode of action and its positive effects on various clinical and MRI outcomes in the placebo-controlled clinical studies AFFIRM (Natalizumab Safety and Efficacy in Relapsing-Remitting MS),¹⁻⁸ SENTINEL (Safety and Efficacy of Natalizumab in Combination with Avonex [IFN β -1a] in Patients with Relapsing-Remitting MS),⁹ and GLANCE (Glatiramer Acetate and Natalizumab Combination Evaluation).¹⁰ Natalizumab is generally recommended for individuals who have not responded to currently available first-line disease-modifying therapy or who have very active disease.

Commercial and clinical trial dosing of natalizumab was suspended voluntarily in February, 2005, after three reports were made of progressive multifocal leukoencephalopathy (PML), an often fatal viral disease characterised by progressive inflammation and damage to the white matter, in patients treated with this agent. However, the drug was reintroduced in the USA and approved in the European Union (EU) in June, 2006, after no additional cases of PML were identified in previously treated individuals.¹¹

On the basis of additional analyses of AFFIRM, SENTINEL, and GLANCE, including long-term follow-up and post-marketing observations, we revisit our previous Review¹² of the position of natalizumab for treatment of patients with RRMS. We need to consider the conditions of use that are most likely to maintain or increase the therapeutic benefit of natalizumab while minimising patients' risk. Important factors to consider include appropriate patient selection, routine safety monitoring, and an understanding of both early recognition and timely management of PML. In this Review, we will provide general safety monitoring recommendations and a detailed update to our previous guidelines on the diagnosis and management of PML in

natalizumab-treated patients,¹² as developed by panels of experts in neurology and neuroradiology.

Natalizumab use and safety

In the 2-year, phase 3 AFFIRM study,¹ natalizumab monotherapy significantly decreased annual relapse rates by 68% ($p < 0.001$) in patients with MS and lowered disability progression rates (sustained for 3 months) by 42% ($p < 0.001$) compared with placebo. Additional analyses showed that over 2 years, natalizumab monotherapy elicited a 54% reduction in 6 months' confirmed disability progression, a 92% decline in the number of gadolinium-enhancing lesions during the second year ($p < 0.001$), an 83% decrease in the number of new or enlarging T2-hyperintense lesions over 2 years ($p < 0.001$), and a 76% fall in new T1-hypointense lesions. Natalizumab also reduced brain atrophy during the second year of treatment.^{1,2} In subgroup analyses, this drug was also effective in patients with more severe disease.^{3,4} Post-hoc investigations indicated that natalizumab substantially raised the probability that individuals were free of disease activity⁵ and that, in those with a baseline expanded disability status scale (EDSS) score of 2.0 or greater, treatment significantly increased the cumulative probability of 12-week confirmed improvement in disability.³ Natalizumab has also been shown to have beneficial effects on visual function⁶ and several aspects of quality of life.⁷ Finally, the AFFIRM researchers noted that natalizumab monotherapy was generally safe and well tolerated.^{1,8}

In the SENTINEL study,⁹ over 2 years, natalizumab plus interferon beta-1a significantly reduced the cumulative probability of 12-week confirmed disability progression by 24% ($p = 0.02$) and decreased annual relapse rates by 55% compared with interferon beta-1a alone ($p < 0.001$).⁹ In the phase 2 GLANCE study,¹⁰ a 74% lower number of new gadolinium-enhancing lesions ($p = 0.020$) and a 61% decline in new or newly enlarging T2-hyperintense lesions ($p = 0.029$) was recorded with the

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combination of natalizumab plus glatiramer acetate versus glatiramer acetate alone.

Safety data on natalizumab use in the post-marketing setting were available from spontaneous sources and through formal registries and observational studies. As of March 31, 2011, about 83 300 patients worldwide had been exposed to natalizumab in the post-marketing setting (representing 148 000 patient-years of exposure), including roughly 55 100 who were exposed for 12 months or longer, 44 900 for 18 months or more, 35 400 for at least 24 months, 27 400 for 30 months or longer, 18 700 for 36 months or more, and 10 700 for at least 42 months.¹³

On market reintroduction, patients from AFFIRM,¹ SENTINEL,⁹ and GLANCE¹⁰ were eligible to participate in an ongoing open-label study (STRATA [Safety of TYSABRI Re-dosing and Treatment])¹⁴ undertaken to assess the safety and efficacy of re-exposure to natalizumab after interrupted treatment. Although recurrence of MRI findings and relapse activity was seen during treatment interruption, 1094 patients re-exposed to natalizumab and included in the ongoing STRATA study had low annual relapse rates and either stable or improved EDSS scores over a 120-week treatment period.^{14,15} The STRATA study did not raise any immediate safety or tolerability concerns in individuals switching from interferons, glatiramer acetate, or chronic steroids to natalizumab, and no patients developed PML during the initial 24–48 weeks of evaluation.^{15–17} However, four cases of PML were recorded during the long-term treatment period of STRATA (after 33, 34, 44, and 46 cumulative doses of natalizumab), with three of the four patients having received previous immunosuppressive treatment.¹⁵ Serum samples available from these individuals, obtained 22–30 months before PML diagnosis, were analysed for the presence of antibodies against JC virus (JCV) with a novel two-step assay that combined standard ELISA with an immunosorbent step. All four patients were identified as being positive for anti-JCV antibodies.¹⁸ In STRATA, although overall incidence of infusion and hypersensitivity reactions was low (<1%), it was highest in individuals who had received only one to two natalizumab infusions before treatment interruption and who were also persistently positive for antibodies against natalizumab on subsequent entry into STRATA.¹⁵ As a whole, data from the AFFIRM open-label safety-extension study¹⁹ and the ongoing STRATA long-term extension study support the continued efficacy of natalizumab monotherapy over 3 years of treatment.¹⁴

Compared with the closely regulated conditions of clinical trials, the broader world of clinical practice could show greater variability in patients' characteristics. Whereas the AFFIRM¹ study population consisted largely of patients with MS who were treatment-naïve, people treated with natalizumab in the clinical practice setting generally have more severe disease at baseline

and most have received other disease-modifying therapies before natalizumab. Thus, to continue to assess the safety profile of natalizumab in clinical practice, a comprehensive risk-management plan was developed, including the TOUCH (Tysabri Outreach: Unified Commitment to Health) prescribing programme, mandatory in the USA, and the TYGRIS (Tysabri Global Observation Program in Safety) study. As of June 30, 2010, 42 587 patients with MS were enrolled and 37 048 had received natalizumab in TOUCH,²⁰ and as of May 23, 2010, 6467 patients were enrolled in TYGRIS,¹³ with 2203 in the USA and 4264 in the rest of the world. Several study groups have reported on their experience with natalizumab in clinical practice, with data from these observational studies and registries indicating similar efficacy and tolerability of natalizumab as have been reported for clinical studies.^{21–28}

The overall incidence of serious adverse events associated with natalizumab treatment seems to be low. Although spontaneous cases of serious liver injury (eg, strikingly raised amounts of hepatic enzymes or hyperbilirubinaemia) could potentially arise after natalizumab treatment, particularly in patients with pre-existing hepatic disorders, these adverse events have been recorded only rarely in the post-marketing setting.^{29,30} The rate of potentially serious liver events noted thus far has been similar in the placebo and treatment arms of clinical studies of natalizumab. Cases of melanoma have been seen in women with MS treated with natalizumab.^{31,32} However, a meta-analysis of safety data from clinical studies showed that the incidence of melanoma was similar in those who received natalizumab and placebo (0.07% vs 0.10%, corresponding to melanoma rates of 0.419 vs 0.823 per 1000 patient-years).³³ CNS lymphoma has also been reported;^{34–36} two patients diagnosed after one and three doses of natalizumab, respectively, had pre-existing disease that seems to have been unrelated to natalizumab.³⁵ Another case of CNS lymphoma that arose after 22 doses of natalizumab was reported in a patient negative for Epstein-Barr virus antibodies,³⁶ which are typically present in immunosuppression-related CNS lymphoma. Delayed infusion reactions (>2 h after natalizumab infusion), including type 3 serum sickness reactions managed with short courses of corticosteroids, are rare but have been noted.^{37,38} Finally, in clinical trials, herpes infections (varicella zoster and herpes simplex) occurred slightly more frequently in natalizumab-treated patients than in those receiving placebo. In post-marketing experience, rare reports have been made of serious herpes infections, including one fatal case of herpes encephalitis.^{29,30}

Background on PML

PML is an opportunistic infection of the CNS that, in cases unrelated to natalizumab, usually leads to death or severe disability.³⁹ Active replication of the human polyoma JCV in glial cells of the brain, causing lytic

death in oligodendrocytes, is the underlying pathobiology of PML. The infection typically arises in severely immunocompromised patients—eg, those with HIV infection, malignant disease, or transplanted organs. Development of PML is extremely rare in immunocompetent individuals.⁴⁰ People with autoimmune rheumatic diseases, especially systemic lupus erythematosus, are also at higher risk of PML.⁴¹ Administration of immunosuppressive treatments to any of these high-risk populations could further increase the likelihood of developing PML. In addition

to natalizumab, cases of PML have been reported in patients treated with various drugs, usually in combination with corticosteroids,⁴² including alkylating agents (eg, cyclophosphamide, carmustine, and dacarbazine),⁴³ purine analogues (eg, fludarabine, cladribine, and azathioprine), immunosuppressants (eg, ciclosporin, tacrolimus, sirolimus, and mycophenolate), and therapeutic monoclonal antibodies (eg, rituximab, infliximab, etanercept, basiliximab, daclizumab, efalizumab, alemtuzumab, and muromonab-CD3).^{39,44}

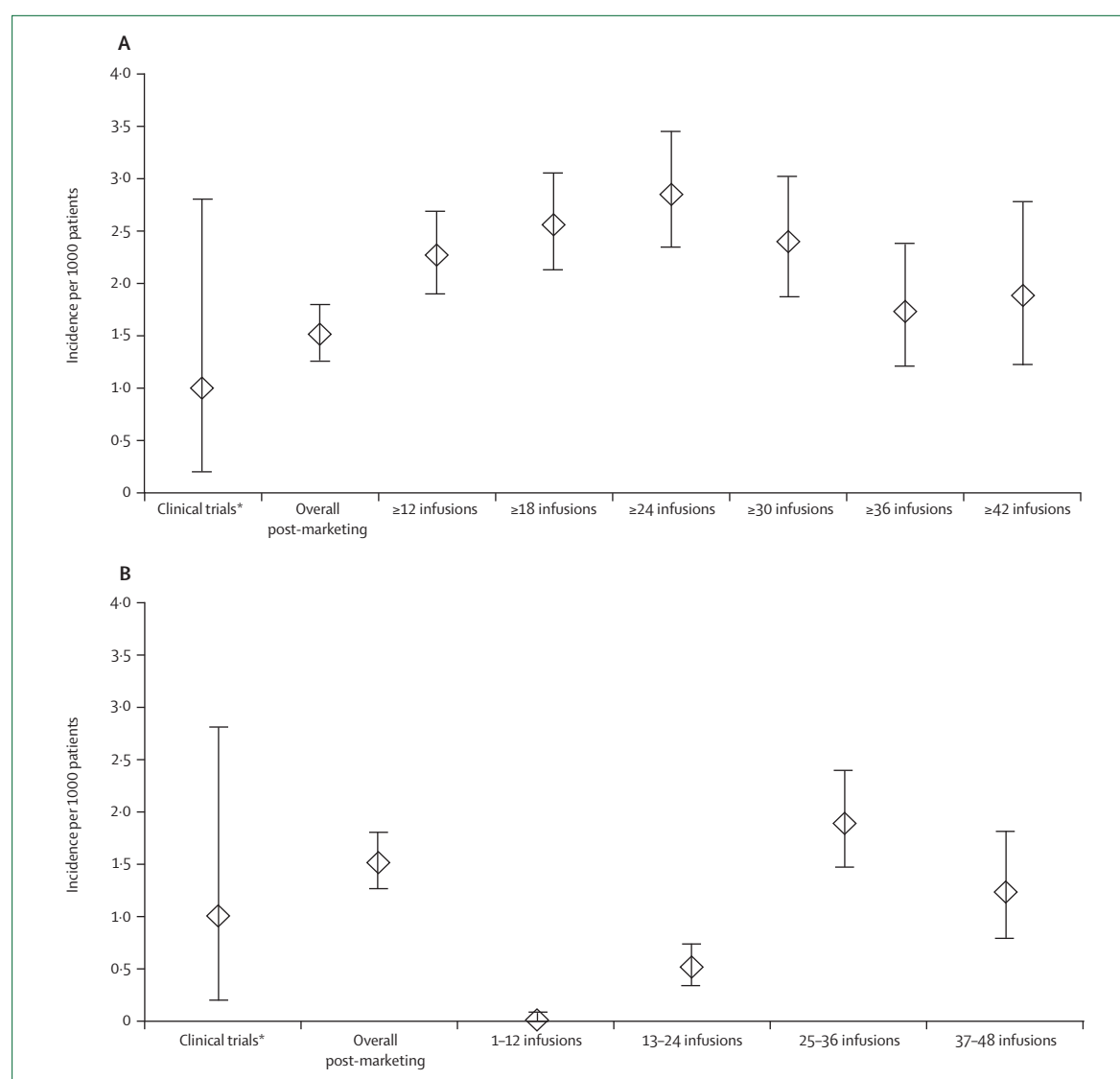


Figure 1: Estimated PML incidence by natalizumab treatment duration (A) and treatment epoch (B)

(A) Incidence by treatment duration was calculated from natalizumab exposure data up to May 31, 2011, and 133 confirmed cases as of June 1, 2011. Incidence for each period was calculated as number of PML cases arising after a defined minimum number of infusions divided by number of patients exposed to natalizumab (eg, for ≥24 infusions, all PML cases diagnosed after exposure to 24 infusions or more divided by the total number of patients ever exposed to at least 24 infusions). (B) Incidence for each treatment interval was calculated as number of PML cases arising during a treatment interval divided by number of patients exposed to natalizumab (eg, for 25–36 infusions, number of all PML cases diagnosed during this treatment interval divided by total number of patients ever exposed to at least 25 infusions). PML=progressive multifocal leukoencephalopathy. Error bars=95% CI. *Observed clinical trial rate in patients who received a mean of 17.9 monthly doses of natalizumab.

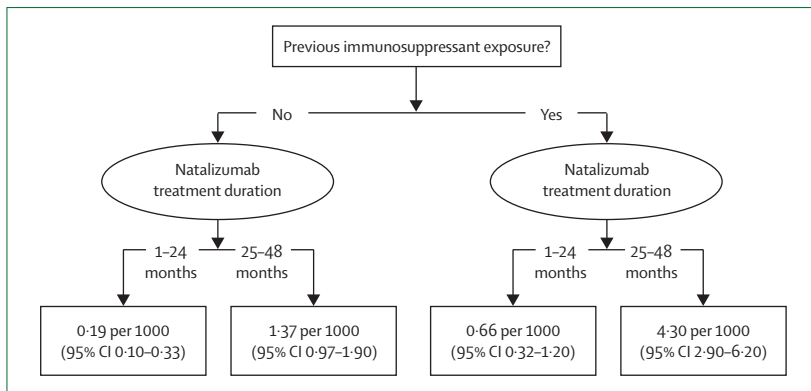


Figure 2: Approximate incidence of PML stratified by previous immunosuppressant use and duration of natalizumab treatment

Data are up to Feb 28, 2011. Data for PML incidence and previous immunosuppressant use are based on 102 patients with confirmed PML as of March 4, 2011, of whom only 93 have available data for immunosuppressant use. Data for previous immunosuppressant use are based on frequency of immunosuppressant use before natalizumab treatment in the TYGRIS observational study as of Nov 23, 2010. PML=progressive multifocal leukoencephalopathy.

PML in natalizumab-treated patients

PML was identified in three patients (two with MS and one with Crohn's disease) from pre-marketing clinical studies.⁴⁵⁻⁴⁷ As of June 1, 2011, all 133 reported cases of PML since relaunch of natalizumab (USA [n=50], European Economic Area [76], and rest of the world [7]) arose in people with MS who had received natalizumab monotherapy for more than 1 year.¹³ As of May 4, 2011, on the basis of post-marketing reports, the estimated overall risk of PML is 1.51 per 1000 patients (95% CI 1.27-1.79), which is generally similar to rates seen in clinical trials (figure 1).¹³

Analyses pertaining to the first 79 post-marketing cases (reported up to Dec 2, 2010)^{13,45-53} are outlined below. Overall recommendations, including presenting symptoms and management, are based on a cumulative review of 68 cases. 35 patients aged 27-59 years (mean 43.7) developed PML; 71% were women. Available details about the first 68 cases since relaunch are provided in the webappendix (pp 1-2). Mean number of doses of natalizumab received was 26.6 (range 12-44). At presentation, cognitive or behavioural symptoms were noted most usually, either alone or in association with motor, language, or visual symptoms. MRI findings at the time PML was suspected showed typical subcortical lesions. 43% of MRIs had some gadolinium enhancement, which was usually less intense and more granular or punctate than that typically seen with MS lesions. Nearly all cases were confirmed as PML on the basis of detection of JCV in the CSF. Levels of JCV detected were often low (<500 copies per mL, with 11 copies per mL the lowest detected level and 626 copies per mL the median).

Duration of natalizumab dosing before PML diagnosis ranged from about 1 year to more than 3.5 years (mean 2 years). Incidence of PML over time (figure 1) was very low in the first 12 months of treatment but thereafter

increased up to 36 months.¹³ Data currently available do not permit calculation of whether risk continues to rise after this period. If PML is more likely to develop after 12 months of treatment, the number of patients potentially at risk who have received natalizumab for 12 months or more (based on worldwide post-marketing data) is about 55 100.¹³ Risk of PML by treatment epoch (figure 1) rose in individuals with more than 24 months of natalizumab exposure, as calculated from cumulative exposure, including those receiving the drug in clinical trials (post reintroduction) and combined worldwide post-marketing exposure up to May 31, 2011.¹³

Patients with MS who developed PML were more likely to have been treated with an immunosuppressant before receiving natalizumab compared with the overall natalizumab-treated population. Immunosuppressant use at any time before initiation of natalizumab treatment increases risk of developing PML, despite there being no evidence for residual immune suppression when natalizumab treatment was initiated. As of March 4, 2011, 42% (39/93) of people with PML had been treated with an immunosuppressant before receiving natalizumab (previous use of an immunosuppressant was unknown for nine patients, who were excluded from analysis), but, at present, no specific pattern in type or duration of immunosuppressant use has been identified.¹³ By comparison, in TYGRIS, about 20% of natalizumab-treated patients (14% in the USA and 24% in Europe) had been treated with an immunosuppressant before receiving natalizumab.¹³ On the basis of these figures, individuals who have used immunosuppressants previously have about a 3-4-times greater risk of PML compared with those who have not used these drugs before.¹³ The increased risk of PML with previous immunosuppressant use seems to be independent of PML risk associated with duration of natalizumab treatment. As of Feb 28, 2011, PML risk for those who have not used immunosuppressants previously was estimated at 0.19 per 1000 patients (95% CI 0.10-0.33) with 1-24 months of natalizumab treatment and 1.37 per 1000 patients (0.97-1.90) exposed for 25-48 months. Risk of PML in individuals with previous exposure to immunosuppressants was 0.66 per 1000 patients (0.32-1.20) with 1-24 months of natalizumab treatment and 4.30 per 1000 patients (2.90-6.20) exposed for 25-48 months (figure 2).¹³ Estimates of PML risk in people with previous use of immunosuppressants have limitations; they are based, in part, on the proportion of patients in TYGRIS who have used immunosuppressants before, which is only a small subset of the overall natalizumab-treated population and, therefore, might not be representative of the entire population. Risk stratification by previous immunosuppressant use and treatment duration must be considered in a broader context that includes additional factors such as benefits of treatment, risks of inadequately treated MS, and the relative benefit-risk profiles of alternative treatments.

See Online for webappendix

Discontinuation of natalizumab is recommended on first suspicion of signs, symptoms, or MRI findings, or a combination, compatible with PML.^{13,20,29,30} Nearly all patients with PML have undergone plasma exchange or immunoadsorption to more rapidly remove natalizumab from plasma and to speed reconstitution of immune surveillance.

As of June 1, 2011, 24 of 133 (18%) natalizumab-treated patients with PML had died. The 109 surviving individuals have varying levels of disability, ranging from mild to severe.¹³ On the basis of preliminary data gathered from the first 79 cases of PML since relaunch of natalizumab, of people who were alive, had at least 6 months of follow-up after diagnosis of PML, and had Karnofsky scores⁵⁴ available (33 of 63 patients), 13% had mild disability, 50% had moderate disability, and 37% had severe disability.¹³ It is still too early to draw broad conclusions about outcomes in patients who developed PML while on natalizumab treatment.^{13,52} Data are currently insufficient to predict risk factors for PML survival and disability outcomes. Preliminary findings suggest that a delay in PML diagnosis and widespread changes typical of PML on MRI are associated with worse prognosis. High-dose steroid treatment, which is frequently used to combat the reversible inflammation associated with immune reconstitution inflammatory syndrome (IRIS), does not seem to be associated with increased mortality and is advocated by many experts.^{50,51} Outcomes of natalizumab-treated patients with PML are generally better than those recorded in clinical trials or reported in other settings (eg, HIV).⁵³ Overall, these data support heightened clinical vigilance, early PML diagnosis, and cessation of natalizumab treatment on suspicion of PML to optimise outcomes for patients with MS.

A laboratory marker that predicts the likelihood of PML development is needed urgently for selection of people most likely to benefit safely from natalizumab treatment and for early detection of PML. Despite one report of asymptomatic reactivation of JCV in a patient treated with natalizumab,⁵⁵ analysis of blood and urine samples from nearly 1400 individuals participating in clinical studies of natalizumab showed that JCV DNA was found rarely in blood. In the few cases in which JCV viraemia was recorded, no association was seen with natalizumab treatment or development of PML. Patients who developed PML related to natalizumab treatment also tested negative for JCV DNA in blood and peripheral blood mononuclear cells before onset of symptoms.⁵⁶ Blood analyses for raised amounts of CD34+ cells and JCV DNA have been suggested as useful for early detection,⁵⁷ but a recent publication casts some doubt on the robustness of this approach.⁵⁸

A two-step anti-JCV antibody assay that combines ELISA with an immunoadsorption step has been developed and is currently undergoing clinical evaluation. Preliminary assessments detected anti-JCV antibodies in 54% of patients with MS who were tested.¹⁸

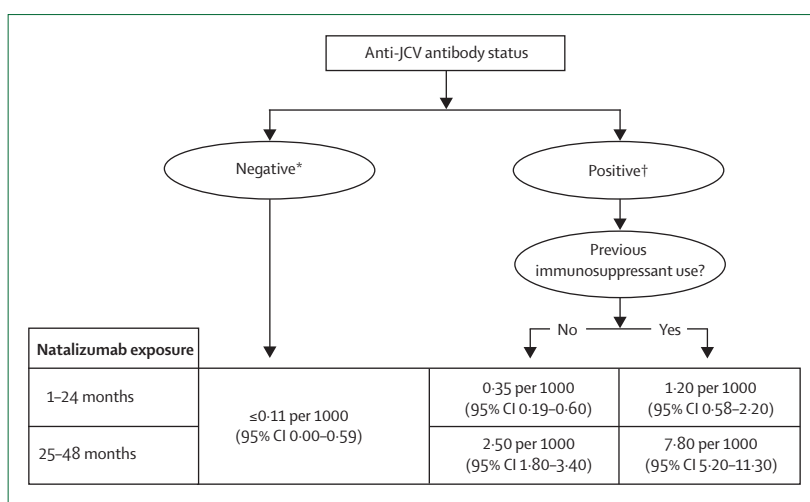


Figure 3: Estimated risk of PML based on anti-JCV antibody status, previous immunosuppressant use, and duration of natalizumab treatment

Patients who tested negative for anti-JCV antibodies represent the lowest risk group in the PML risk-stratification algorithm, whereas those at greatest risk of developing PML were treated with natalizumab for 25–48 months, received immunosuppressant drugs before initiation of natalizumab, and tested positive for anti-JCV antibodies. For patients who were positive for anti-JCV antibodies and had not used immunosuppressants before, irrespective of treatment duration, PML risk was consistent with risk in the overall natalizumab-treated population.⁶¹ *Estimate based on all patients negative for anti-JCV antibodies receiving at least one dose of natalizumab and one hypothetical PML case who was negative for anti-JCV antibodies at the time of PML diagnosis. †PML incidence in patients positive for anti-JCV antibodies calculated on the basis of the following assumptions: 55% of natalizumab-treated patients with multiple sclerosis are positive for anti-JCV antibodies, the proportion of natalizumab-treated patients with previous immunosuppressant use was 20% based on data from TYGRIS, and 100% of confirmed cases of PML were positive for anti-JCV antibodies before onset and diagnosis of PML. Data are risk per 1000 patients (95% CI). PML=progressive multifocal leukoencephalopathy. JCV=JC virus.

Anti-JCV antibody status seems to be stable over time, with an annual seroconversion rate that does not exceed 2–3%.⁵⁹ With this assay, assessment of anti-JCV antibodies in archived serum samples obtained from 31 natalizumab-treated patients 6–187 months before PML diagnosis showed that samples from all 31 patients tested positive for anti-JCV antibodies.⁶⁰ Therefore, detection of anti-JCV antibodies in plasma or serum, in combination with other known risk factors such as previous use of immunosuppressants and duration of natalizumab treatment, could serve as a method to stratify PML risk in patients with MS who are being treated with or are being considered for natalizumab treatment (figure 3). Large clinical studies are ongoing in which the potential clinical use of anti-JCV antibody testing is under assessment.

PML risk management

Plans for risk management of PML for patients with MS have been instituted in the EU, the USA, and elsewhere. In the EU, prescription of natalizumab is restricted to doctors skilled in the treatment of neurological diseases who have timely access to MRI facilities and have the ability to manage hypersensitivity reactions.³⁰ Specific education of doctors with respect to management of PML is needed for all prescribers, and

patients with MS are issued with a special card describing the possible symptoms of PML and other infections needing immediate investigation. In the

Panel: Clinical features indicative of MS relapse and PML

MS relapse

- Acute onset
- Occurs over several hours to days, reaches usually stable phase, and resolves spontaneously, even without treatment
- Clinical presentation includes diplopia, optic neuritis, and myelopathy (eg, paraparesis, discrete sensory level)

PML

- Subacute onset
- Occurs over several weeks and is progressive
- Clinical presentation includes aphasia, behavioural and neuropsychological alteration, retrochiasmal visual deficits, hemiparesis, and seizures

Features indicate the respective diagnosis without excluding the alternative.
MS=multiple sclerosis. PML=progressive multifocal leukoencephalopathy.

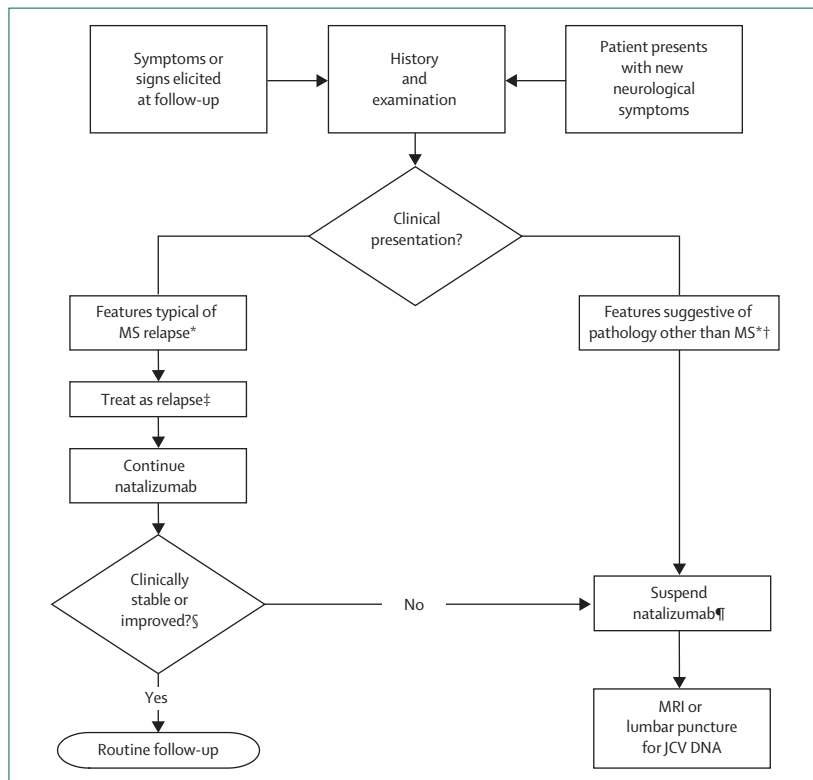


Figure 4: Clinical assessment of new or worsening neurological symptoms in patients with MS receiving natalizumab

*See panel. †Clinicians should consider other non-MS pathology in addition to PML, especially opportunistic infections. ‡Relapses should be managed according to usual clinical practice. A short course of steroids can be considered for patients in whom PML is unlikely to arise on clinical grounds. No response to steroids should trigger further investigation. §Clinical findings should be compared with those recorded at clinical presentation of this episode. ¶If non-MS pathology is suspected at clinical presentation or during follow-up, all future infusions should be postponed until PML or other opportunistic infections have been excluded definitively. MS=multiple sclerosis. PML=progressive multifocal leukoencephalopathy. JCV=JC virus.

USA, the TOUCH prescribing programme restricts distribution, prescription, and administration of natalizumab to registered pharmacies, doctors, and infusion centres, and provides guidelines for monitoring of patients with MS for PML and other potential serious adverse events.

Diagnostic algorithm

Clinical vigilance is the most important way to spot PML. The history and pattern of previous and current symptoms and signs will facilitate both patient management and assessment of potential PML (panel). If PML is suspected, neurologists should withhold natalizumab until this disease can be excluded. If a thorough neurological assessment cannot rule out PML, natalizumab must be suspended and not restarted until a disorder other than MS has been excluded with confidence. Natalizumab dosing can be resumed only if the diagnosis of PML is discounted.⁵² If PML is confirmed, permanent discontinuation of natalizumab is a key intervention.

Several PML diagnostic assessments in individuals treated with natalizumab are recommended.¹² First, a thorough neurological assessment should be undertaken at first presentation of new or worsening clinical signs or symptoms (figure 4). Second, if neurological assessment cannot rule out PML, cranial MRI with contrast should be done and compared with previous MRI scans; to optimise comparability, standardised high-quality imaging should be obtained at treatment start and at yearly intervals. MRI alone cannot be used to exclude PML (figure 5, table). If clinical symptoms or MRI lesions remain suggestive of PML, testing of CSF by PCR for JCV DNA—with an ultra-sensitive assay—should be done. Repeat MRI is recommended if clinical suspicion of PML remains. CSF can be negative for JCV DNA in early PML despite clinical and radiographic findings. If JCV is not detected but suspicion of PML persists, a repeat CSF test is recommended and—if it is again negative—a brain biopsy procedure should be considered (figure 6). Detection of JCV DNA in the CSF of a symptomatic patient confirms the diagnosis. However, a negative JCV PCR result should not exclude a possible diagnosis of PML. The JCV DNA assay should be based on quantitative real-time PCR to maximise sensitivity and specificity for detection, and an assay with a maximum lower limit of quantification of 50 DNA copies per mL should be used.

Patient management

At present, immune reconstitution (restoration of normal immune function or normal access to the brain for immune surveillance) is the only intervention that is effective for PML. Therefore, natalizumab-associated PML differs from PML associated with other disorders in that immune surveillance can be restored within a few weeks. Data from an open-label study in patients with

MS showed that plasma exchange rapidly reduced amounts of natalizumab in serum and restored leukocyte function, suggesting its potential value in facilitating immune reconstitution in cases of PML.⁶² Several courses of plasma exchange or immunoadsorption were used in post-marketing cases of PML to accelerate clearance of natalizumab from the circulation and to enhance immune surveillance of the CNS.^{48–50} Findings of small studies and retrospective observations show that anti-retroviral treatments, serotonin 5-HT_{2A}-receptor antagonists, and immunomodulatory therapies (interleukin 2 or interferon alpha or beta) for management of PML associated with HIV or transplantation are not effective.^{63–76} Mefloquine has been evaluated as a potential anti-JCV agent for treatment of PML and was administered to some patients with post-marketing natalizumab-associated PML, but to date, no clinical report has been published of demonstrable activity against JCV *in vivo*.^{13,48,49,77,78} Use of the investigational compound CMX001, an oral lipophilic nucleotide analogue of the antiviral cidofovir, in conjunction with plasma exchange, high-dose corticosteroids, intravenous immunoglobulin, and neurorehabilitation, was associated with stabilisation and recovery from PML that had developed in a natalizumab-treated MS patient.⁷⁹

Immune reconstitution inflammatory syndrome

PML develops in people with immunodeficiency but its characteristics can change with reconstitution of the immune system. IRIS^{62,78–83} arises with immune reconstitution, and is characterised by a striking lymphocytic response—usually with a predominance of CD8+ lymphocytes—and develops in correlation with control of JCV, tissue swelling, and breakdown of the blood–brain barrier, resulting in gadolinium contrast enhancement on scans.⁸⁴ PML in natalizumab-treated patients with MS has been particularly associated (more than previously seen with other diseases) with inflammatory transformation of brain lesions, probably because the immune system is intact, and the effects of the drug can be reversed. This inflammation results in an improved outlook for control of JCV while causing associated inflammatory damage in the brain. Effective immune reconstitution with minimum associated inflammatory neurological injury is necessary for management of PML in this setting, when an inflammatory reaction is typical.

In the post-marketing setting, nearly all patients with PML underwent plasma exchange or immunoadsorption to remove natalizumab from the plasma, to speed reconstitution of immune surveillance. IRIS developed about 2–12 weeks (mean 4.2 weeks) after cessation of natalizumab and earlier than this time (a few days to 8 weeks) in patients who underwent plasma exchange. With IRIS, affected individuals generally presented with striking deterioration of neurological symptoms, which in some was associated with new or

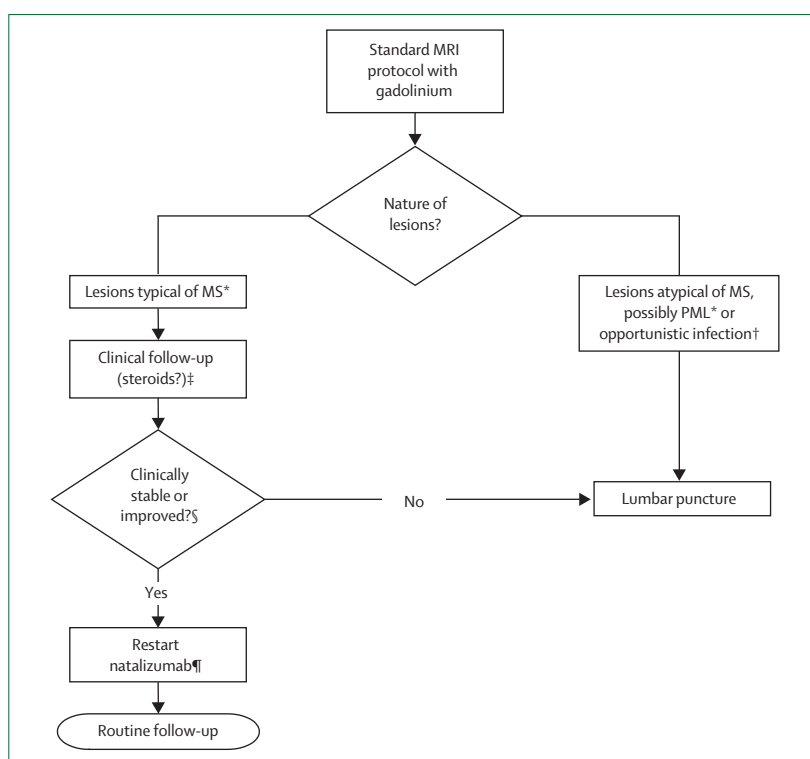


Figure 5: MRI assessment of new or worsening neurological symptoms in patients with MS receiving natalizumab

Natalizumab must be suspended and not restarted until non-MS pathology has been excluded confidently. If PML is suspected on the basis of clinical presentation and MRI is not readily available or inconclusive, laboratory investigations—eg, lumbar puncture to exclude PML—should not be delayed. *See table. Comparison with a baseline scan might assist with interpretation of MRI appearances. †Clinicians should consider other non-MS pathology in addition to PML, especially opportunistic infections. ‡Relapses should be managed according to usual clinical practice. A short course of steroids can be considered for patients in whom PML is unlikely to arise on clinical grounds. No response to steroids should trigger further investigation. §Clinical findings should be compared with those recorded at clinical presentation of this episode. ¶Resumption of natalizumab treatment must be considered only once PML or other opportunistic infections have been excluded definitively on the basis of clinical findings, further investigations, or both. MS=multiple sclerosis. PML=progressive multifocal leukoencephalopathy.

enhanced lesions on gadolinium-contrast MRI, brain swelling, or both. In most people in whom IRIS was diagnosed, treatment with high-dose steroids was initiated and led to improvements. For patients with MS who develop PML while on natalizumab, stopping this drug will reconstitute CNS immunity and will probably precipitate IRIS. If natalizumab is removed from the circulation by plasma exchange or immunoadsorption, the disorder will arise more rapidly and, by inference, PML will be brought under control more quickly. It is not clear whether IRIS becomes more manageable with use of plasma exchange or immunoadsorption. Corticosteroids could be useful for treatment of IRIS, particularly in severe or life-threatening cases of the disorder.⁸⁵ In support of this approach, early treatment with steroids in patients with HIV who developed IRIS improved prognosis, and steroids probably control the cerebral oedema associated with IRIS.^{1,58,82,83,85} However, diagnosis and management of

	MS	PML
Aspect and location of new lesions	Mostly focal; might affect entire brain and spinal cord, in white and possibly grey matter	Diffuse and asymmetric lesions (initially sometimes unifocal but usually multifocal or widespread), mainly subcortical and rarely periventricular, located almost exclusively in white matter, with occasional extension to deep grey matter; posterior fossa frequently involved (cerebellum, brainstem), rarely in spinal cord
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibres might be involved	Ill-defined edges; infiltrating; irregular in shape; confined to white matter, sparing grey matter; pushing against the cerebral cortex; U-fibres destroyed; typical spread along white-matter tracts
Mode of extension	Initially focal; lesions enlarge within days or weeks and decrease in size within months	Lesions extend homogeneously, continuously, and sometimes rapidly to contiguous (multifocal) and non-contiguous regions (widespread); confined to white-matter tracks, sparing the cortex
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex), apart from when inflammatory response is present
On T2-weighted sequence	Acute lesions have a hyperintense centre, isointense ring, and discrete hypointensity outside the ring structure; subacute and chronic lesions are hyperintense with no ring structure	Diffuse hyperintensity; slightly increased intensity of newly involved areas compared with old areas; little irregular signal intensity of lesions; sometimes granular appearance
On T1-weighted sequence	Acute lesions are densely hypointense (large lesions) or isointense (small lesions); increasing signal intensity over time in 80%; decreasing signal intensity (axonal loss) in about 20%	Slightly hypointense at onset, with signal intensity decreasing over time and along the affected area; no reversion of signal intensity
On FLAIR sequence	Hyperintense, sharply delineated	Preferred sequence for diagnosis because hyperintensity is most obvious; true extension of abnormality more clearly visible than on T2-weighted images, especially in coronal cuts
With gadolinium enhancement	Acute lesions have dense homogeneous enhancement and sharp edges, and contrast enhancement covers whole extension of the new lesion; subacute lesions have ring enhancement with eventual resolution over 1–2 months; chronic lesions show no enhancement	About half the cases to date have shown some enhancement, typically with a patchy aspect; some peripheral enhancement is possible; enhancement usually increases with inflammatory response or decreases with steroid administration
Atrophy	Focal atrophy is possible due to focal white-matter degeneration; no progression	Initially no focal atrophy; later in the course atrophy can arise

Findings suggest a typical target-like lesion pattern on diffusion-weighted images (DWI), with increased DWI contrast at margins and less in the centre where the apparent diffusion coefficient is raised. In some cases, PML lesions were wrongly thought to be infarcts on the basis of their DWI pattern. MS=multiple sclerosis. PML=progressive multifocal leukoencephalopathy. FLAIR=fluid-attenuated inversion recovery. *No MRI features are pathognomonic of MS or PML.

Table: MRI features for differential diagnosis of MS and PML*

IRIS remains controversial because data from controlled studies are sparse, but most experts—partly based on observations in case series—recommend rapid reconstitution of immune surveillance by plasma exchange (three to five sessions of 1.5 volume plasma exchange over 6–12 days)⁶² and anti-inflammatory treatment with steroids as soon as IRIS manifests.

Treatment interruption

In patients who developed PML while being treated with natalizumab, the duration of treatment before diagnosis ranged from about 1 year to more than 3.5 years (mean duration 2 years).^{45,46,50–52} As depicted in figure 1, risk of PML increases with longer treatment duration, at least up to 36 months.^{13,86} Up to now, interruption of natalizumab treatment has not been shown to reduce risk of PML, and event-driven studies to examine the effects of treatment interruptions on PML risk would be very difficult to undertake. Since PML is such a rare adverse event, such a study would need an unrealistically large population and long observation period. Risk of MS relapse after cessation of treatment is increased, although the extent to which disease activity recurs is assumed to depend largely on activity before initiation of any disease-modifying treatment together with disease activity before starting natalizumab.⁸⁷ Relapses were measured over an 8-month period in 1866 patients from clinical studies undertaken after voluntary suspension of natalizumab in February, 2005: gadolinium-enhancing lesions were analysed in 341 patients. Annual relapse rates and gadolinium-enhancing lesions both rose shortly after natalizumab interruption and peaked between 4 and 7 months. A rebound of relapse or gadolinium-enhancing lesion activity beyond placebo-treated levels from the clinical studies was not recorded in any analyses.¹⁴ None of the patients who had been on continuous treatment for more than 18 months developed de-novo antibodies to natalizumab after re-institution of treatment after interruption. Findings from a small study showed that clinical relapse or new lesions on MRI arose in seven of ten patients within 6 months of treatment discontinuation.⁸⁸ These authors concluded that alternative therapies should be considered during an interruption in natalizumab treatment to minimise resumption of disease activity. The RESTORE study (Randomized Treatment Interruption of Natalizumab)⁸⁹ is in progress to assess the rate of immune reconstitution after treatment interruption, the return of MS disease activity during interruption, and whether alternative therapies control the return of disease activity during interruption of natalizumab treatment. Additionally, efforts are underway to investigate the feasibility of alternative dosing regimens. However, at this time, neurologists treating patients with MS with natalizumab should expect and inform individuals that MS disease activity will return if an interruption period is initiated. When reviewing the collective body of data, treating doctors should also recognise that a patient's true baseline level of disease activity might not be known because of residual effects of treatments used before initiation of natalizumab.

Natalizumab treatment recommendations

Patient selection

In the USA, natalizumab is indicated as monotherapy for patients with relapsing forms of MS. Although this

agent is generally recommended for those who have had an inadequate response to—or cannot tolerate—an alternative MS treatment, the US label also allows use of natalizumab as first-line therapy in individuals with relapsing MS,²⁹ and as a result, US patients with progressive relapsing MS are more frequently treated with natalizumab. In a re-evaluation by the European Medicines Agency,³⁰ no reason existed to change current natalizumab indications as a monotherapy to delay accumulation of physical disability and reduce the frequency of clinical exacerbations in patients with RRMS not responding to first-line disease-modifying therapy or presenting with unusually high relapse and MRI activity. Although initial observations of PML arose in two patients with MS treated with a combination of interferon beta-1a and natalizumab, the fact that all subsequent cases of PML in the post-marketing setting occurred in people treated with natalizumab monotherapy suggests that PML risk is not due to interferon beta-1a. The increased risk of PML in immunosuppressed individuals means that natalizumab should not be given in combination with immunosuppressive treatment. However, as clearly shown by open-label PML cases,^{50,51} avoidance of natalizumab in combination with other disease-modifying treatments does not eliminate risk of PML.

Previous treatment with immunomodulators or immunosuppressants

Experience in pivotal studies and post marketing does not suggest an increased risk of complications—including PML—in patients who switch directly from interferons or glatiramer acetate to natalizumab.¹⁵ Individuals treated previously with interferon beta or glatiramer acetate might switch directly to natalizumab with no washout period as long as any signs of relevant treatment-related abnormalities are resolved. Patients who are HIV-positive and those with a history of immunodeficiency or haematological malignant disease should not receive treatment with natalizumab (data on file, Biogen Idec, MA, USA). Additional considerations for patient selection include other comorbidities, treatment history, and baseline laboratory values, particularly in those who have received previous immunosuppressants. The increased risk of PML emerging from post-marketing experience for patients exposed previously to immunosuppressive agents (eg, mitoxantrone, cyclophosphamide, cladribine, azathioprine, mycophenolate, methotrexate, or a combination) further underlines the need for careful assessment of those previously treated with immunosuppressive or antineoplastic agents for signs or symptoms of ongoing immune compromise before initiation of natalizumab. Such assessment should include normal leukocyte and differential counts, absence of signs of increased infection rate in the months preceding natalizumab treatment, and close clinical monitoring. A washout period of

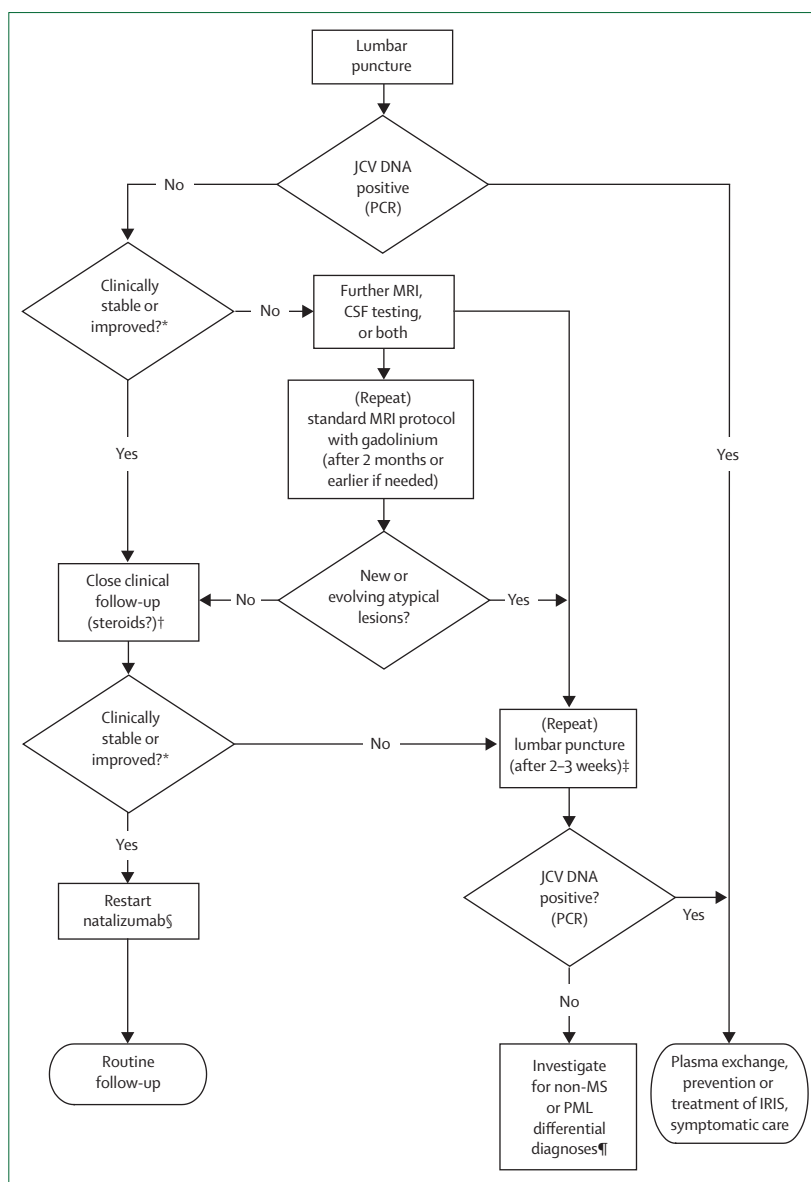


Figure 6: Laboratory differentiation of new or worsening neurological symptoms in patients with MS receiving natalizumab

Natalizumab must be suspended and not restarted until non-MS pathology has been excluded confidently.

*Clinical findings should be compared with those recorded at clinical presentation of this episode. †Close clinical follow-up consists of biweekly assessments. Relapses should be managed according to usual clinical practice. A short course of steroids can be considered for patients in whom PML is unlikely to arise on clinical grounds. No response to steroids should trigger further investigation. ‡Accelerate re-testing if aggressive clinical symptoms persist or progress. §Resumption of natalizumab treatment must be considered only once PML or other opportunistic infections have been excluded definitively on the basis of clinical findings, further investigations, or both. ¶Clinicians should consider other non-MS pathology in addition to PML, especially opportunistic infections, or consider brain biopsy to confirm or discount presence of JCV if CSF PCR is negative but if suspicion persists on the basis of clinical and MRI features. MS=multiple sclerosis. PML=progressive multifocal leukoencephalopathy. JCV=JC virus. IRIS=immune reconstitution inflammatory syndrome.

3–6 months has been proposed for people who have received immunosuppressants.⁸⁹ A longer washout period for mitoxantrone and cyclophosphamide is desirable, but the timeframe would need to be weighed

against the aggressiveness of active disease. Natalizumab probably should be used in patients with active relapsing MS before immunosuppressants, for which evidence of effectiveness is less well established. As of now, no consensus exists about how frequently laboratory testing needs to be done in individuals at increased risk of PML. In addition to thorough clinical assessment at each of the monthly infusions (by interview and as needed by clinical examination), more frequent MRI has been suggested (every 3–6 months).

Management of infusion and hypersensitivity reactions

Infusion centres should be prepared for appropriate management of infusion and hypersensitivity reactions that can arise with natalizumab treatment. Typical symptoms of infusion reactions include headache, dizziness, and nausea and are usually not a reason to stop natalizumab. These symptoms are usually managed by pretreatment with loratadine and paracetamol and by slowing the rate of infusion.^{90,91} In the AFFIRM study,¹ hypersensitivity reactions were defined as any report of hypersensitivity or allergic reactions, anaphylactic or anaphylactoid reactions, urticaria, allergic dermatitis, or hives. Symptoms of hypersensitivity reactions can also include fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnoea, or chest pain. By contrast with infusion reactions, current recommendations for hypersensitivity reactions are for natalizumab treatment to be discontinued and for the individual not to be retreated. Because of the effectiveness of natalizumab, this recommendation needs further investigation. Resumption of treatment after a hypersensitivity reaction is permitted for specific antibody treatments if they are administered in conjunction with pretreatment.⁹² A French cohort of 70 patients with MS who were pretreated with hydrocortisone and dexchlorpheniramine had no hypersensitivity reactions to natalizumab compared with another group of 384 people who were not pretreated and who had a hypersensitivity rate of 3–6%.⁸ Persistent antibodies against natalizumab were associated with an increase in infusion-related adverse events in the AFFIRM study.^{1,8} For patients having frequent infusion reactions or with reduced efficacy, testing for persistent antibodies could be useful when deciding whether to discontinue

natalizumab treatment, although testing before 3–6 months of treatment is not recommended. If patients test positive for antibodies they should be checked again 2–3 months thereafter. Natalizumab treatment does not need to be discontinued in the interim, but if both test results are positive for persistent antibodies against the drug, it should be discontinued. Patients who receive only one or two doses of natalizumab followed by an extended period without treatment might be at higher risk of hypersensitivity reactions on re-exposure,¹⁶ and consideration should be given to testing for the presence of antibodies before re-dosing in these individuals.

Delayed hypersensitivity reactions to natalizumab can occur up to 21 days after infusion.^{37,38,93} Not all reported cases were positive for neutralising antibodies and most people responded to short courses of oral prednisolone. Occurrence of a delayed reaction would warrant antibody testing. If delayed reactions happen in antibody-negative patients, these can be managed with steroids.

Pregnancy

As far as we know, no adequate and well controlled studies of natalizumab treatment have been done in pregnant women. Natalizumab is recommended during pregnancy only if the potential benefit justifies the potential risk to the fetus. The drug has been detected in human milk; the effects of exposure via breastmilk on infants are unknown.²⁹ TPER (Tysabri Pregnancy Exposure Registry) is a follow-up study of pregnant women with MS who were exposed to natalizumab within 3 months of conception or at any time during pregnancy. As of May 23, 2010, a total of 229 pregnant patients were enrolled prospectively into TPER; 172 known pregnancy outcomes were recorded.⁹⁴ Although pregnancy data are scant, interim analyses do not suggest any effect of natalizumab exposure on pregnancy outcome. Additional data are needed before a definite conclusion can be made.

Educational guidance

Doctors need to inform patients about the benefits and risks of natalizumab, provide them with a patient's alert card before initiation of treatment, and continue to counsel them on the risk of PML on a regular basis thereafter. Because of the increased risk of development of PML with prolonged treatment duration in JCV antibody-positive patients, the benefits and risks of natalizumab therapy should be reconsidered on an individual basis by the specialist doctor and the patient. The patient should be updated regularly about the risks of natalizumab, especially the amplified risk of PML, and, together with caregivers, should be reminded of early signs and symptoms of this adverse event. Patients should be instructed to contact their health-care provider should signs of liver injury (eg, jaundice, vomiting) arise, and they should be monitored regularly as appropriate for impaired liver function.

Search strategy and selection criteria

We searched Medline for articles published between 2007 and 2011 (last update May, 2011) and scanned references from relevant articles with the search terms: "natalizumab", "progressive multifocal leukoencephalopathy", "PML", and "JC virus and CNS". Papers published in English, German, and French were reviewed. The final reference list was generated on the basis of originality and relevance to topics covered in the Review.

Conclusions

Natalizumab has proven a highly effective treatment for patients with RRMS. The decision to prescribe this drug entails a benefit–risk assessment for each individual. The overall risk of PML still seems to be one case per 1000 individuals with MS; risk seems lower in patients who are seronegative for anti-JCV antibodies and higher in those who are JCV antibody-positive with previous immunosuppressive treatment. The clinician and patient must consider disease activity (both in terms of relapses with functional decline and MRI activity) and ascertain the likelihood of disability if natalizumab treatment is not started and balance these factors against the risk of developing PML with this drug. Once treatment is started, regular and comprehensive follow-up is essential. Early diagnosis and aggressive clinical management have probably led to the apparently better outcomes of post-marketing cases of PML compared with those noted in clinical trials or in the setting of systemic immunodeficiency. Ongoing studies and comprehensive, systematic post-marketing surveillance will continue to provide information that will help doctors make informed treatment decisions about natalizumab and further optimise its use in MS treatment.

Contributors

LK and JK interpreted and analysed data obtained in phase 3 core and extension studies and safety follow-up, reviewed published work, summarised discussions from expert groups, prepared a first draft of the Review, and reviewed and edited all drafts. DB, GE, ME, AG-M, NG, H-PH, EH, JH, RH, MK, OL-C, AM, CP, MR, TS, CS, and KV participated in the development of the guidelines and reviewed and approved drafts and the final version of the Review. DBC, SH, PWO'C, HLW, MC, RG, E-WR, and PSS reviewed and helped with final editing of the Review. EOM and HHH did laboratory assays for detection of JCV DNA in clinical samples of patients with multiple sclerosis relevant to the Review and edited and approved the final version.

Conflicts of interest

LK discloses that the University Hospital, Basel, has received research support from Actelion, Advancell, Allozyne, BaroFold, Bayer Health Care Pharmaceuticals, Bayer Schering Pharma, Bayhill, Biogen Idec, BioMarin, CLC Behring, Elan, Genmab, Genmark, GeNeuro SA, GlaxoSmithKline, Lilly, Merck Serono, MediciNova, Novartis, Novonordisk, Peptimmune, Sanofi-Aventis, Santhera, Roche, Teva, UCB, and Wyeth. LK has been principal investigator, member, or chair of steering committees or advisory boards on multiple sclerosis clinical trials sponsored by these companies, and has received lecture fees from one or more of these companies. Payments and consultancy fees have been used exclusively for support of research activities. DB has received honoraria and research support from Biogen Idec, Serono, Schering, and Teva Pharmaceuticals. GE has received honoraria for advisory board participation from Bayer, Biogen Idec, and LFB, and his institution has received grant support from Bayer, Merck Serono, and Teva. AG-M has received honoraria for consultancy and research support from Biogen Idec, Schering, Serono, and Teva Pharmaceuticals. NG has received honoraria and travel support from Biogen Idec, consultancy fees from Biogen Idec and Novartis, lecture fees from Biogen Idec and Merck Serono, and grants from Biogen Idec, Merck Serono, Sanofi-Aventis, and Genesis Pharma. H-PH has received honoraria and consultancy fees from Bayer Healthcare, Biogen Idec, Merck Serono, Novartis, and Genzyme and travel costs from Biogen Idec, Novartis, Merck Serono, and Bayer Schering with the approval of the Rector of the University of Düsseldorf. EH has received research funding from Biogen Idec, Novartis Pharmaceuticals, Octapharma, Schering, Serono,

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References

- 1 Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; **354**: 889–910.

- 2 Miller DH, Soon D, Fernando KT, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. *Neurology* 2007; **68**: 1390–1401.
- 3 Munschauer F, Giovannoni G, Lublin F, et al. Natalizumab significantly increases the cumulative probability of sustained improvement in physical disability. *Mult Scler* 2008; **14** (suppl 1): S167–68 (abstr P474).
- 4 Hutchinson M, Kappos L, Calabresi PA, et al, for the AFFIRM and SENTINEL Investigators. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. *J Neurol* 2009; **256**: 405–15.
- 5 Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. *Lancet Neurol* 2009; **8**: 254–60.
- 6 Balcer L, Galetta S, Calabresi P, et al. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. *Neurology* 2007; **68**: 1299–1304.
- 7 Rudick R, Miller D, Hass S, et al. Health-related quality of life in multiple sclerosis: effects of natalizumab. *Ann Neurol* 2007; **62**: 335–46.
- 8 Calabresi P, Giovannoni G, Confavreux C, et al. The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. *Neurology* 2007; **69**: 1391–403.
- 9 Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1 for relapsing multiple sclerosis. *N Engl J Med* 2006; **354**: 911–23.
- 10 Goodman AD, Rossman H, Bar-Or A, et al. GLANCE. Results of a phase II, randomized, double-blind, placebo-controlled study. *Neurology* 2009; **72**: 806–12.
- 11 Yousry T, Major E, Ryschewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 2006; **354**: 924–33.
- 12 Kappos L, Bates D, Hartung H-P, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. *Lancet Neurol* 2007; **6**: 431–41.
- 13 Biogen Idec MedInfo. <https://medinfo.biogenidec.com/medinfo/download?doc=Letter+Bodies%2FNatalizumab+Safety+Update.pdf&type=pml&doc&Continue=Continue> (accessed June 30, 2011).
- 14 O'Connor PW, Goodman A, Kappos L, et al. Disease activity return during natalizumab treatment interruption in multiple sclerosis patients. *Neurology* 2011; **76**: 1858–65.
- 15 O'Connor PW, Goodman AD, Kappos L, et al. Updated efficacy and safety of natalizumab in patients who participated in the STRATA study. *Mult Scler* 2010; **16** (suppl 10): S162 (abstr P483).
- 16 Polman CH, Goodman AD, Kappos L, et al. Safety and effectiveness of natalizumab re-dosing and treatment in the STRATA study. *Mult Scler* 2008; **14** (suppl 1): S173–74 (abstr P494).
- 17 O'Connor PW, Polman CH, Goodman AD, et al. Efficacy and safety of natalizumab in the STRATA study. *Neurology* 2009; **72** (suppl 3): A312–13 (abstr P06.127).
- 18 Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurol* 2010; **68**: 295–303.
- 19 O'Connor PW, Goodman A, Kappos L, et al. The efficacy of natalizumab monotherapy over 3 years of treatment in patients with relapsing multiple sclerosis. *Neurology* 2007; **68** (suppl 1): A275 (abstr P06.082).
- 20 Bozic C, Christiano LM, Hyde R, et al. Utilisation and safety of natalizumab in patients with relapsing multiple sclerosis. *Mult Scler* 2010; **16** (suppl 10): S315 (abstr P893).
- 21 Oturai AB, Koch-Henriksen N, Petersen T, et al. Efficacy of natalizumab in multiple sclerosis patients with high disease activity: a Danish nationwide study. *Eur J Neurol* 2009; **16**: 420–23.
- 22 Prosperini L, Borriello G, Fubelli F, Marinelli F, Pozzilli C. Natalizumab treatment in multiple sclerosis: the experience of S Andrea MS Centre in Rome. *Neurol Sci* 2011; **31** (suppl 3): 303–07.
- 23 Outteryck O, Ongagna JC, Zéphir H, et al. Demographic and clinic characteristics of French patients treated with natalizumab in clinical practice. *J Neurol* 2010; **257**: 207–11.
- 24 Belachew S, Phan-Ba R, Bartholomé E, et al. Natalizumab induces a rapid improvement of disability status and ambulation after failure of previous therapy in relapsing-remitting multiple sclerosis. *Eur J Neurol* 2011; **18**: 240–45.
- 25 Sangalli F, Moiola L, Bucello S, et al. Efficacy and tolerability of natalizumab in relapsing-remitting multiple sclerosis patients: a post-marketing observational study. *Neurol Sci* 2011; **31** (suppl 3): 299–302.
- 26 Piehl F, Holmén C, Hillert J, Olsson T. Swedish natalizumab (Tysabri) multiple sclerosis surveillance study. *Neurol Sci* 2011; **31** (suppl 3): 289–93.
- 27 Haas J, Mueller U, Asimiadou S. Experiences in the daily practice with natalizumab. *J Neurol* 2008; **255** (suppl 2): 207 (abstr P833).
- 28 Putzki N, Yaldizli O, Maurer M, et al. Efficacy of natalizumab in second line therapy of relapsing-remitting multiple sclerosis: results from a multi-center study in German speaking countries. *Eur J Neurol* 2010; **17**: 31–37.
- 29 Biogen Idec. Tysabri (natalizumab) injection: full prescribing information. March, 2011. http://www.tysabri.com/en_US/tysb/site/pdfs/TYSABRI-pi.pdf (accessed June 15, 2011).
- 30 European Agency for the Evaluation of Medicinal Products. Tysabri: EPAR—product information. May 27, 2011. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000603/WC500044686.pdf (accessed March 10, 2011).
- 31 Mullen JT, Vartanian TK, Atkins MB. Melanoma complicating treatment with natalizumab for multiple sclerosis. *N Engl J Med* 2008; **358**: 647–48.
- 32 Laroni A, Bedognetti M, Uccelli A, et al. Association of melanoma and natalizumab therapy in the Italian MS population: a second case report. *Neurol Sci* 2011; **32**: 181–82.
- 33 Panzara MA, Bozic C, Sandrock AW. More on melanoma with transdifferentiation. *N Engl J Med* 2008; **359**: 99–100.
- 34 Goebels N, Kappos L. Another complication of natalizumab treatment? Taking the challenge. *Ann Neurol* 2009; **66**: 264–66.
- 35 Bozic C, LaGuette J, Panzara M, et al. Natalizumab and central nervous system lymphoma: no clear association. *Ann Neurol* 2009; **66**: 261–62.
- 36 Schweikert A, Kremer M, Ringel F, et al. Primary central nervous system lymphoma in a patient treated with natalizumab. *Ann Neurol* 2009; **66**: 403–06.
- 37 Hellwig K, Schimrigk S, Fischer M, et al. Allergic and non-allergic delayed infusion reactions during natalizumab therapy. *Arch Neurol* 2008; **65**: 656–58.
- 38 Krumbholz M, Pellkofer H, Gold R, et al. Delayed allergic reaction to natalizumab associated with early formation of neutralizing antibodies. *Arch Neurol* 2007; **64**: 1331–33.
- 39 Weber T. Progressive multifocal leukoencephalopathy. *Neurol Clin* 2008; **26**: 833–54.
- 40 Berciano J, Leno C, Figols J, et al. Epilepsia partialis continua in progressive multifocal leukoencephalopathy: a motor cortex isolation syndrome. *Mov Disord* 2003; **18**: 1559–64.
- 41 Calabrese LH, Molloy ES, Huang DR, Ransohoff RM. Progressive multifocal leukoencephalopathy in rheumatic diseases. *Arthritis Rheum* 2007; **56**: 2116–28.
- 42 Warnatz K, Peter HH, Schumacher M, et al. Infectious CNS disease as a differential diagnosis in systemic rheumatic diseases: three case reports and a review of the literature. *Ann Rheum Dis* 2003; **62**: 50–57.
- 43 Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy: a national estimate of frequency in systemic lupus erythematosus and other rheumatic diseases. *Arthritis Rheum* 2009; **60**: 3761–65.
- 44 Carson KR, Focosi D, Major EO, et al. Monoclonal antibody-associated progressive multifocal leukoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project. *Lancet Oncol* 2009; **10**: 816–24.
- 45 Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N Engl J Med* 2005; **353**: 369–74.

- 46 Langer-Gould A, Atlas SW, Green AJ, et al. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med* 2005; **353**: 375–81.
- 47 Van Assche G, Van Ranst M, Sciot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 2005; **353**: 362–68.
- 48 Gold R, Wenning W, Haghighi A, et al. Treatment of PML unfolding during monotherapy with natalizumab. World Congress on Treatment and Research in Multiple Sclerosis; Sept 17–20, 2008; Montreal, ON, Canada.
- 49 Hartung H-P. New cases of progressive multifocal leukoencephalopathy after treatment with natalizumab. *Lancet Neurol* 2009; **8**: 28–31.
- 50 Wenning W, Haghighi A, Laubenberg M, et al. Treatment of progressive multifocal leukoencephalopathy associated with natalizumab. *N Engl J Med* 2009; **361**: 1075–80.
- 51 Linda H, von Heijne A, Major E, et al. Progressive multifocal leukoencephalopathy after natalizumab monotherapy. *N Engl J Med* 2009; **361**: 1081–87.
- 52 Clifford DB, DeLuca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol* 2010; **9**: 438–46.
- 53 Koralnik IJ. New insights into progressive multifocal leukoencephalopathy. *Curr Opin Neurol* 2004; **17**: 365–70.
- 54 Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, ed. Evaluation of chemotherapeutic agents. New York: Columbia University Press, 1949: p 196.
- 55 Chen Y, Bord E, Tompkins T, et al. Asymptomatic reactivation of JC virus in patients treated with natalizumab. *N Engl J Med* 2009; **361**: 1067–64.
- 56 Rudick RA, O'Connor PW, Polman CH, et al. Assessment of JC virus DNA in blood and urine from natalizumab-treated patients. *Ann Neurol* 2010; **68**: 304–10.
- 57 Major E. Re-emergence of PML in natalizumab-treated patients: new cases, new concerns. *N Engl J Med* 2009; **361**: 1041–43.
- 58 Warnke C, Smolianov V, Derhmel T, et al. CD34+ progenitor cells mobilized by natalizumab are not a relevant reservoir for JC virus. *Mult Scler* 2011; **17**: 151–56.
- 59 Gorelik L, Bixler S, Cheung A, et al. Assessment of the incidence of anti-JCV antibodies in a cohort of natalizumab-treated patients with multiple sclerosis. *Mult Scler* 2010; **16** (suppl 10): S306–07 (abstr P873).
- 60 Goelz SE, Gorelik L, Subramanyam M. Assay design and sample collection can affect anti-John Cunningham virus antibody detection. *Ann Neurol* 2011; **69**: 429–31.
- 61 Sandrock A, Hotermans C, Richman S, et al. Risk stratification for progressive multifocal leukoencephalopathy in MS patients using natalizumab. *J Neurol* 2011; **258** (suppl 1): S23 (abstr O212).
- 62 Khatri B, Man S, Giovannoni G, et al. Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. *Neurology* 2009; **72**: 402–09.
- 63 Giancola ML, Rizzi EB, Lorenzini P, et al. Progressive multifocal leukoencephalopathy in HIV-infected patients in the era of HAART: radiological features at diagnosis and follow-up and correlation with clinical variables. *AIDS Res Hum Retroviruses* 2008; **24**: 155–62.
- 64 Hall CD, Dafni U, Simpson D, et al, and the AIDS Clinical Trials Group 243 Team. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. *N Engl J Med* 1998; **338**: 1345–51.
- 65 Clifford DB, Yiannoutsos C, Glicksman M, et al. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. *Neurology* 1999; **52**: 623–25.
- 66 DeLuca A, Giancola ML, Ammassari A, et al. The effect of potent antiretroviral therapy and JC virus load in cerebrospinal fluid on clinical outcome of patients with AIDS-associated progressive multifocal leukoencephalopathy. *J Infect Dis* 2000; **182**: 1077–83.
- 67 DeLuca A, Giancola ML, Ammassari A, et al. Cidofovir added to HAART improved virological and clinical outcome in AIDS-associated progressive multifocal leukoencephalopathy. *AIDS* 2000; **14**: F117–21.
- 68 DeLuca A, Giancola ML, Ammassari A, et al. Potent anti-retroviral therapy with or without cidofovir for AIDS-associated progressive multifocal leukoencephalopathy: extended follow-up of an observational study. *J Neurovirol* 2001; **7**: 364–68.
- 69 Antinori A, Cingolani A, Lorenzini A, et al. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: data from the Italian Registry Investigative Neuro AIDS (IRINA). *J Neurovirol* 2003; **9** (suppl 1): 47–53.
- 70 Focosi D, Fazzi R, Montanaro D, et al. Progressive multifocal leukoencephalopathy in a haploidentical stem cell transplant recipient: a clinical, neuroradiological and virological response after treatment with risperidone. *Antiviral Res* 2007; **74**: 156–58.
- 71 Przepiorka D, Jaecle KA, Birdwell RR, et al. Successful treatment of progressive multifocal leukoencephalopathy with low-dose interleukin-2. *Bone Marrow Transplant* 1997; **20**: 983–87.
- 72 Re D, Bamborschke S, Feiden W, et al. Progressive multifocal leukoencephalopathy after autologous bone marrow transplantation and alpha-interferon immunotherapy. *Bone Marrow Transplant* 1999; **23**: 295–98.
- 73 Huang SS, Skolasky RL, Dal Pan GJ, et al. Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study. *J Neurovirol* 1998; **4**: 324–32.
- 74 Geschwind MD, Skolasky RI, Royal WS, McArthur JC. The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol* 2001; **7**: 353–57.
- 75 Nath A, Venkataramana A, Reich DS, et al. Progression of progressive multifocal leukoencephalopathy despite treatment with β -interferon. *Neurology* 2006; **66**: 149–50.
- 76 Kunschner L, Scott TF. Sustained recovery of progressive multifocal leukoencephalopathy after treatment with IL-2. *Neurology* 2005; **65**: 1510.
- 77 Brickelmaier M, et al. Identification and characterization of mefloquine efficacy against JC virus in vitro. *Mult Scler* 2008; **14** (suppl 1): S44 (abstr P53).
- 78 Clifford D, Nath A, Cinque P, et al. Mefloquine treatment in patients with progressive multifocal leukoencephalopathy (PML). *Neurology* 2011; **76** (suppl 4): A28 (abstr P01.023).
- 79 Frohman E, Remington G, Abraham T, et al. Management of natalizumab-associated progressive multifocal leukoencephalopathy (PML) with a complex regimen including the oral lipophilic nucleotide analogue CMX001. *Neurology* 2011; **76** (suppl 4): A246 (abstr P03.241).
- 80 Crum-Cianflone NF. Immune reconstitution inflammatory syndromes: what's new? *AIDS Read* 2006; **16**: 199–206.
- 81 Travis J, Varma A, duPlessis D, et al. Immune reconstitution inflammatory syndrome with PML in HIV: a case discussion and review of the literature. *Neurologist* 2008; **14**: 321–26.
- 82 Tan K, Roda R, Ostrow L, et al. PML-IRIS in HIV infection: clinical manifestations and treatment with steroids. *Neurology* 2009; **72**: 1458–64.
- 83 Perumal J, Hreha S, Bao F, et al. Post-natalizumab associated rebound or CNS immune reconstitution syndrome: clinical and MRI findings. *Mult Scler* 2009; **15** (suppl 2): S119 (abstr P418).
- 84 Vendrely A, Bienvenu B, Gasnault J, Thiebault JB, Salmon D, Gray F. Fulminant inflammatory leukoencephalopathy associated with HAART-induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy. *Acta Neuropathol* 2005; **109**: 449–55.
- 85 Egli A, Infanti L, Dumoulin A, et al. Prevalence of polyomavirus BK and JC infection and replication in 400 healthy blood donors. *J Infect Dis* 2009; **199**: 837–46.
- 86 Hyde R, Bozic C, Belcher G, et al. Utilization and safety of natalizumab in patients with relapsing multiple sclerosis in the post-marketing setting. *J Neurol Sci* 2009; **285** (suppl 1): S110.
- 87 Lenhard T, Biller A, Mueller W, Metz I, Schönberger J, Wildemann B. Immune reconstitution inflammatory syndrome after withdrawal of natalizumab? *Neurology* 2010; **75**: 831–33.
- 88 Killestein J, Vennegoor A, Strijbis EM, et al. Natalizumab drug holiday in multiple sclerosis: poorly tolerated. *Ann Neurol* 2010; **68**: 392–95.

- 89 Clinicaltrials.gov. Treatment interruption of natalizumab (RESTORE). Nov 18, 2010. <http://www.clinicaltrials.gov/ct2/show/NCT01071083?term=biogen+idec+restore&rank=1> (accessed March 10, 2011).
- 90 Stangel M, Sorensen PS, Petersen T, et al. Natalizumab utilization and safety in the TYGRIS program in the European Union and Canada. *Mult Scler* 2009; **15** (suppl 2): S234 (abstr P773).
- 91 Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 2007; **12**: 601–09.
- 92 Phillips T, O'Connor PW, Havrdova E, et al. Infusion-related hypersensitivity reactions during natalizumab treatment. *Neurology* 2006; **67**: 1717–18.
- 93 Berger E, Lavier A, Outteryck O, et al. Prevention of hypersensitivity reactions in natalizumab therapy. *Mult Scler* 2009; **15** (suppl 2): S120–21 (abstr P425).
- 94 Cristiano LM, Bozic C, Bloomgren G, Kooijmans-Coutinho M. Preliminary evaluation of pregnancy outcomes from the Tysabri (natalizumab) pregnancy registry. *Mult Scler* 2010; **16** (suppl 10): S294 (abstr P840).