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

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Natalizumab is a new treatment option for patients with active relapsing-remitting multiple sclerosis. In phase III studies, natalizumab was highly effective and well tolerated; however, three cases of progressive multifocal leucoencephalopathy (PML) were identified (estimated incidence of one per 1000; 95% CI 0·2–2·8; mean treatment period 17·9 months). In this Review we summarise the current information on PML, the three confirmed cases of PML, and the results of an extensive safety assessment of all patients treated with natalizumab. On the basis of these reviews, we make recommendations for appropriate selection of candidates for natalizumab and pretreatment assessments. In addition, a three-step diagnostic and management algorithm was developed to monitor natalizumab-treated patients with multiple sclerosis for PML and other opportunistic infections. The algorithm includes strategies for clinical, MRI, and laboratory assessments. Maintaining clinical vigilance allows for early suspension of natalizumab in potential cases of PML, thereby increasing the opportunity for immune reconstitution, which may improve prognosis if PML is confirmed.

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Introduction

Multiple sclerosis is a chronic, demyelinating disorder of the CNS that affects up to one million people worldwide.[1] About 80% of patients present with a relapsing course of the disease at diagnosis.[2] Disease-modifying therapies such as interferon beta-1a and glatiramer acetate can reduce relapse rates by about 30% and have an uncertain long-term benefit.[3–6] On the basis of the partial efficacy of these disease-modifying therapies, there is a substantial unmet need for more effective drugs for the treatment of multiple sclerosis.

Natalizumab (Tysabri; Biogen Idec and Elan Pharmaceuticals), an α4-integrin antagonist, is the most recent drug added to the collection of disease-modifying therapies available for patients with multiple sclerosis. α4-integrins are constitutively expressed on leucocytes and play an essential part in the migration of these cells into sites of inflammation within the CNS in patients with multiple sclerosis. In binding to α4-integrin, natalizumab prevents its ability to interact with ligands. It is thought that natalizumab prevents the adherence of activated leucocytes to inflamed endothelium, an important step in lesion formation in multiple sclerosis. In addition, by inhibiting interactions between α4-integrin and its ligands, natalizumab may reduce immune-cell activation and promote the apoptosis of lymphocytes.[7–11]

In a pivotal phase III study (the AFFIRM study[12]), natalizumab monotherapy significantly decreased the annual relapse rate by 68% ($p<0·001$) and the rate of disability progression, sustained for 3 months, by 42% ($p<0·001$) over 2 years compared with placebo; a sensitivity analysis showed that there was a 54% reduction in disability progression, sustained for 6 months. In addition, natalizumab significantly reduced the number of gadolinium-enhancing lesions during the second year by 92% ($p<0·001$) and new or enlarging T2-hyperintense lesions over 2 years by 83% ($p<0·001$).[12] In a second phase III study (the SENTINEL study[13]), the addition of natalizumab to intramuscular interferon beta-1a improved the clinical efficacy reported with intramuscular interferon beta-1a alone on multiple measures.[13] However, it is still unclear whether combination treatment with intramuscular interferon beta-1a improves the efficacy of natalizumab monotherapy.

Although natalizumab was well tolerated in pivotal studies, dosing was suspended on February 28, 2005, after the identification of two cases of progressive multifocal leucoencephalopathy (PML) in patients with multiple sclerosis who had received 28 and 37 doses, respectively, of natalizumab in combination with interferon beta-1a.[14,15] Later, a third case of PML was identified in a patient treated with natalizumab with Crohn's disease who was previously mistakenly diagnosed with astrocytoma. This patient received eight natalizumab infusions.[16] The occurrence of the rare but serious risk of PML in patients with multiple sclerosis has raised awareness in the community that as more highly effective therapies become available for the treatment of multiple sclerosis, it is likely that there will be risks that prompt the need for careful benefit–risk considerations when making treatment decisions. In addition, our current knowledge of risk associated with natalizumab and PML is only based on short-term drug treatment and whether longer treatment will result in an increased risk is not yet known. This type of issue is common in disease areas such as rheumatology, where risky, yet highly effective, therapies are typically used.

As physicians consider the benefits and risks of natalizumab treatment, it is important that they also consider conditions of its use that can maintain or increase benefit while minimising risk. Important factors are appropriate patient selection and the ability to recognise PML at its earliest stages, which would allow early diagnosis and intervention, and possibly improve outcome. In this Review we present an approach to selecting patients for natalizumab treatment and

guidelines on the diagnosis and management of PML in natalizumab-treated patients. These guidelines were developed by panels of experts in neurology, neuroradiology, and PML after the identification of PML in patients treated with natalizumab.

Background on PML

PML is a rare and progressive demyelinating disease of the brain that typically causes permanent disability or death. The classic presentation of PML is a triad of progressive dementia, motor dysfunction, and vision loss, but no pathognomonic signs or symptoms have been identified.[17–19] As PML progresses, dementia is reported, followed by coma and death;[20] mortality occurs in 30–50% of all PML cases during the first 3 months.[21] The disease is caused by infection of oligodendrocytes by the JC virus (JCV), a common and widespread human polyomavirus that is thought to be present in most healthy individuals. The seroprevalence of anti-JCV antibodies in healthy individuals ranges from 20% to 80%.[22,23]

PML predominantly occurs in immunocompromised individuals, including those immunocompromised due to HIV, haematological malignancies, organ transplants, and antineoplastic or immunosuppressive therapies. Although it is clear that systemic immunosuppression is a major risk factor for the development of PML,[24–26] the disease is uncommon even in this setting. The incidence of PML increased during the early years of the AIDS pandemic, occurring in up to 5% of patients,[21,24] which is less common than other opportunistic infections reported in AIDS patients (eg, *Pneumocystis carinii, Toxoplasma gondii, Mycobacterium avium* complex, and *Mycobacterium tuberculosis*).[27] Notably, the incidence of opportunistic infections decreased significantly with the introduction of highly active antiretroviral therapy, whereas the incidence of PML did not change substantially during this time.[28] Similarly, although PML has been described in the setting of treatment with immunosuppressive drugs such as methotrexate,[29–34] cyclophosphamide,[29,33,35–40] azathioprine,[29,34,41–47] and mitoxantrone,[48] this is also an uncommon occurrence. These results suggest that the development of PML is not solely dependent on infection with JCV; additional factors, including immunosuppression, are also required elements.

The mechanism by which PML develops is considered to be a stochastic process that involves multiple steps in the life-cycle of the JCV and its interactions with the immune system. The site of primary JCV infection is not known. However, detection of JCV in stromal cells and B lymphocytes isolated from tonsillar tissue suggests infection through the respiratory system or an oropharyngeal spread.[26] Alternatively, tonsillar infection may be the result of systemic dissemination from another site. JCV is also known to infect CD34+ haemopoietic precursor cells and kidney cell lines and is associated with these tissues. Hence, these data suggest that after primary infection of the tonsil with JCV, it may travel to sites of latency in the kidney and bone marrow via B cells.[17,49] This is supported by the identification of the JCV archetype, a virus that has not undergone genetic rearrangement, in the kidney and bone marrow; in contrast, virus isolated from PML patients contains a rearrangement of the regulatory region of the JCV genome.[26] The site of viral rearrangement and the mechanism by which JCV enters the brain from sites of latency and the kinetics of the virus leading to lysis of oligodendrocytes and transformation of astrocytes in the brain are not known.

MRI is a very sensitive method for the detection of neurological changes, particularly in the setting of clinical signs or symptoms; however, MRI does lack specificity for PML. On MRI, patients with PML show multifocal, asymmetric, subcortical white matter lesions that are indicative of demyelination.[50,51] White matter lesions are not typically surrounded by oedema, nor do they produce a mass effect.[52–55] Hyperintense signal abnormalities throughout the supratentorial subcortical white matter on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI, in the appropriate clinical setting, are highly suggestive of the disease.[52] The lesions typically affect the cerebrum, brainstem, or cerebellum, but are rarely found in the spinal cord.[56] Faint gadolinium enhancement on T1-weighted imaging has been reported in a small proportion of patients.[50,52] However, more pronounced gadolinium enhancement was reported during immune reconstitution after effective antiretroviral treatment in HIV and may indicate a better outcome.[14,57,58]

PCR analysis of cerebrospinal fluid for the presence of JCV DNA is a highly sensitive (60–80%) and specific (92–100%) test for the diagnosis of PML, particularly during late disease course.[25,59–61] JCV DNA has been reported in the blood and urine both in patients with PML and healthy immunocompetent individuals;[62–67] hence, the presence of JCV DNA in blood or urine is neither predictive nor diagnostic of PML. In instances where PML is suspected but JCV is not detected in the cerebrospinal fluid, a brain biopsy may be required to confirm diagnosis. Pathological features confirming PML diagnosis include enlarged, hyperchromatic oligodendroglial nuclei, atypically enlarged astrocytes, and lymphocytic inflammatory infiltrates.[17,68,69]

Several medications have been studied for the treatment of PML, including acyclovir, idoxuridine, vidarabine, amantadine, adenine arabinoside, cytarabine, cidofovir, interferon α, interleukin-2, zidovudine, camptothecin, and topotecan.[21,70–76] In most cases, such treatments have been unsuccessful in improving patient prognoses. Immune reconstitution appears to be the most effective intervention for improving outcomes in patients with PML. For example, in transplant patients with PML, early discontinuation or dose reduction of immunosuppressive therapy was associated with favourable clinical outcomes.[41,45] Some patients were left with residual

neurological deficiencies but improving symptoms over time, whereas others experienced no residual neurological damage or symptoms.

Assessment of natalizumab-treated patients for additional PML cases

After the identification of PML in three natalizumab-treated patients and subsequent suspension of natalizumab dosing, an extensive safety study was done.[51] In this study, all patients who received natalizumab on clinical protocols had a detailed medical history, a physical examination, a neurological assessment, an MRI scan of the brain, and, if possible, cerebrospinal fluid testing for JCV DNA. All patients suspected of PML were assessed by an independent adjudication committee (IAC), which was composed of experts in neurovirology, neuroradiology, and clinical neurology, to determine whether a diagnosis of PML was confirmed, indeterminate, or ruled out. Of 3417 patients with multiple sclerosis, Crohn's disease, or rheumatoid arthritis who had received natalizumab in clinical trials, 3116 (91%) patients were assessed for PML, with a mean treatment duration of 17·9 months. 97% of patients with multiple sclerosis and 91% of patients with Crohn's disease were assessed within 3 or 6 months of their last natalizumab dose, respectively. 44 of the 3116 patients assessed were referred for an IAC review. PML was ruled out in 43 of 44 patients; PML could not be ruled out in one patient with multiple sclerosis because cerebrospinal fluid and follow-up MRI data were not available. There were no patients with detectable JCV DNA in the cerebrospinal fluid of the 396 samples available to test. Thus, despite this exhaustive search, no additional cases of PML in natalizumab-treated patients were identified. A "subclinical" occurrence of PML seemed unlikely.

The biological effects of natalizumab persist for about 3 months,[77] and treatment-associated changes in the number and distribution of cerebrospinal fluid cells have been described for up to 6 months after stopping treatment.[78–80] If there was immune reconstitution, the increased inflammation would probably be associated with transiently more active clinical symptoms and more notable changes on MRI, particularly gadolinium enhancement. On the basis of these data, the risk of PML associated with natalizumab was estimated to be 1 in 1000 patients (95% CI 0·2–2·8 per 1000) over a mean treatment period of 17·9 months.[51] To date, the risk of PML with natalizumab treatment for longer than this period is unknown.

In the safety study, an exploratory analysis was done to test for the presence of JCV DNA in plasma using PCR analysis with both a high-throughput automated method and a more sensitive low-throughput manual method.[81] Five of 2370 (0·2%) patients tested positive for JCV viraemia with the automated method; three of these patients were never treated with natalizumab.[82] These results were confirmed using the manual method. In a random subset of 209 patients who were tested with the manual method, an additional five (2·4%) patients had detectable JCV DNA. None of the patients who tested positive for JCV DNA had clinical features or MRI findings suggestive of PML. All of the three confirmed cases of PML had available plasma samples before and after diagnosis of PML. Only one of the three patients (the patient with Crohn's disease) had consistently detectable JCV DNA in plasma before onset of PML symptoms.[81]

The presence of concomitant immunomodulators and altered immune function from chronic immunosuppression were the only discernible additional risk factors for PML in natalizumab-treated patients.[14–16] In the patient with Crohn's disease and PML, immunocompromise due to azathioprine may have been a contributory factor in the development of PML as indicated by persistent leucopenia and bone marrow suppression even following discontinuation of azathioprine.[16] In addition, both patients with multiple sclerosis and PML were receiving concomitant interferon beta-1a and natalizumab; however it is unclear whether combination treatment increased the risk of developing PML given the small number of cases. To date, interferon beta has never been associated with PML.

On reintroduction of natalizumab for commercial dosing, each country initiated a risk-management programme (called the TOUCH [Tysabri Outreach: Unified Commitment to Health] Prescribing Program in the USA). These programmes will allow for ongoing assessment of the incidence of and risk factors for PML in natalizumab-treated patients.

Suggested diagnostic and management algorithm

As physicians consider the benefits and risks of natalizumab treatment, it is important that they also consider the conditions for use that will maintain or increase benefit while minimising risk. After the identification of PML in patients treated with natalizumab, a panel of experts in JC virology, neurology, and neuroradiology (see acknowledgments) was consulted in an effort to identify guidelines for the appropriate use of natalizumab. On the basis of systematic assessment of signs, symptoms, MRI, or laboratory evidence of PML used in the safety assessment, as well as current information on PML, the following guidelines on the management of natalizumab-treated patients were developed. The panel recommendations, based on our current understanding of multiple sclerosis, PML, and natalizumab, are intended to complement the appropriate use of natalizumab as recommended in the product labelling, and should be considered in association with the physician's interpretation of each individual case. These recommendations will be updated as new data become available on the association between natalizumab and PML.

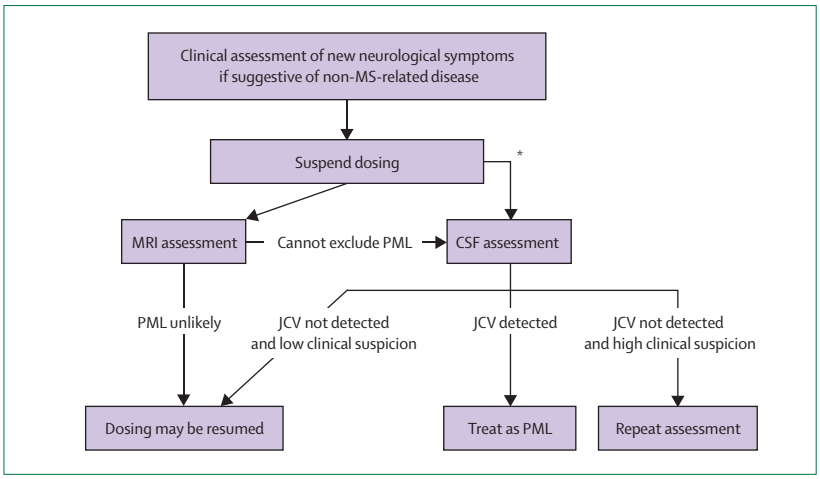

Figure 1: **Suggested diagnostic algorithm for natalizumab-treated patients with new or worsening neurological clinical signs and symptoms**
MS=multiple sclerosis. CSF=cerebrospinal fluid. *If PML is suspected on the basis of clinical presentation and MRI is not readily available, CSF assessment to exclude PML should be considered before MRI.

Pretreatment risk management guidelines

Patient-selection considerations

The specific risk factors for PML, other than altered immune function, are not currently known. Furthermore, there is not enough information to adequately assess theoretical risk factors for PML when being treated with natalizumab, such as degree and type of immunocompromise or duration of treatment with natalizumab. However, there are certain factors independent of natalizumab that physicians should consider before initiating treatment. These include considering the medical history of each patient such as confirmed diagnosis of relapsing multiple sclerosis, disease activity, comorbidities, treatment history, and baseline laboratory values, particularly in patients who have received immunosuppressants in the past. In general, immunosuppression can increase a patient's risk of developing opportunistic infections such as PML. Being HIV positive and having a history of immunodeficiency or haematological malignancy should be regarded as contraindications to natalizumab treatment. In addition, patients previously treated with immunosuppressive or antineoplastic drugs should be carefully assessed for signs or symptoms of ongoing immune compromise before starting natalizumab therapy. The availability and documentation of disease history, including the pattern of signs and symptoms at presentation and during any subsequent relapses, will ease the future assessment of patients who develop symptoms indicative of PML over the course of therapy.

A pretreatment cranial MRI scan is also strongly recommended and should be done within 3 months of starting natalizumab therapy. This scan will be useful to compare with subsequent scans that may be done to investigate the cause of new or worsening neurological symptoms once on natalizumab therapy.

Identifying patients who are likely to benefit

The pivotal studies of natalizumab showed the efficacy and tolerability of therapy in two patient populations: treatment-naive patients with mild to moderate disability (Expanded Disability Status Scale [EDSS] score 0 to 5) with active clinical disease (ie, relapse) within the year before study enrolment, and patients with mild to moderate disability (EDSS score 0 to 5) who had continued disease activity within the year before study despite treatment with intramuscular interferon beta-1a.[12,13] Subgroup analyses showed that patients who fulfilled the inclusion criteria benefited from natalizumab treatment, regardless of baseline disease activity. Nevertheless, patients with highly active disease at baseline (defined by a high number of prestudy relapses and the presence of gadolinium-positive lesions on MRI) showed reductions in annual relapse rate and sustained disability progression greater than those with lesser degrees of disease activity.[83] Therefore, patients with relapsing forms of multiple sclerosis with high disease activity, particularly those on active treatment with disease-modifying drugs, may be considered as preferred candidates for natalizumab treatment. However, currently there are not sufficient data on the efficacy and safety of natalizumab in patients with progressive forms of multiple sclerosis. Therefore, at this stage, patients with secondary progressive or primary progressive multiple sclerosis should not be treated with natalizumab.

Use as monotherapy

Although it is not clear whether the addition of immunomodulatory or immunosuppressant therapy to natalizumab increases the risk of PML, given that the two confirmed cases of PML in multiple sclerosis occurred in combination treatment, it seems reasonable that natalizumab should be indicated as monotherapy.[84] In addition, the lack of data to determine whether natalizumab in combination with other drugs is more effective than natalizumab alone also suggests it would be prudent to use natalizumab only as monotherapy at this time.

Wash-out period

The suggestion that natalizumab should be used as monotherapy immediately leads to the question of whether wash-out periods are required after treatment with immunomodulators or immunosuppressants. Currently, for interferon beta and glatiramer acetate, it is unclear whether a wash-out is needed or will have any impact on the risk of PML.

Although there are no clinical data on wash-out periods after the use of immunosuppressive drugs, a wash-out period seems reasonable. The duration of the wash-out period must be based on the drug used, the duration of treatment, and the possible sequelae of the treatment. For example, for such agents as azathioprine,

methotrexate, mycophenolate mofetil, mitoxantrone, and cyclophosphamide a wash-out period of 3 months, or even longer for the latter two drugs, should be considered to allow for recovery of immune function. Minimum requirements would be that the leucocyte and neutrophil counts are within the normal range and that there is no recent indication of increased frequency of infections. Again, this requirement must be balanced against the risks of withholding therapy in a patient with active multiple sclerosis.

Diagnosis of PML in natalizumab-treated patients

An overview of the recommended algorithm for the diagnosis and management of PML is shown in figure 1. This algorithm should be used as a guide for assessing new or worsening neurological symptoms in natalizumab-treated patients through clinical vigilance, the use of MRI, and laboratory testing. Details of the individual components of the algorithm are presented in the following sections.

Clinical assessment

The clinical picture of the early PML course can be difficult to distinguish from a multiple sclerosis relapse. Although pathognomonic signs discerning multiple sclerosis relapses and PML do not exist, the two may be differentiated on the basis of factors including course of onset, development of symptoms, and clinical presentation (table 1). Multiple sclerosis relapses are typically discrete events that develop over hours to days, stabilising or improving even in the absence of treatment. Conversely, PML is a subacute disease that develops over weeks and progressively worsens. Presenting symptoms favouring multiple sclerosis relapses include diplopia, optic neuritis, and myelopathy, whereas those favouring PML include changes in behaviour and cognitive ability, visual and motor difficulties, and hemiparesis. Although it is possible that PML may present differently in the setting of natalizumab, the three cases of PML identified during natalizumab clinical studies were all aggressive in development, as expected; the time from first symptoms to death for the two fatal cases was 3–6 months.[14–16]

On the basis of the current information on natalizumab and PML, clinical vigilance by neurologists is the most important method of monitoring for PML and should allow for early recognition of PML. Indeed, it is important to have a low threshold for clinical changes to withhold natalizumab and investigate such changes for possible PML to allow diagnosis as early as possible. A thorough neurological assessment should be done at the first presentation of new or worsening clinical signs or symptoms (figure 2). If the presenting features and development are suggestive of multiple sclerosis, symptoms may be treated as a relapse and managed according to usual clinical practice. A clear optic neuritis or myelopathy can be common in multiple sclerosis yet very rare in the setting of PML. However, if there is any doubt about the cause of clinical symptoms, natalizumab should be discontinued immediately and an appropriate work-up should be done. On the basis of the pharmacodynamics of natalizumab, temporary suspension of the drug (ie, for days or a few weeks) is not expected to compromise its effectiveness.[85]

The fact that natalizumab is given monthly by health-care professionals at an infusion centre readily allows for

	Multiple sclerosis relapse	PML
Onset	Acute	Subacute
Evolution	Over hours to days Normally stabilizes Resolves spontaneously or with treatment	Over weeks Progressive
Clinical presentation	Diplopia Optic neuritis Incomplete myelopathy or partial myelitis	Cortical signs and symptoms Behavioural and neuropsychological alterations Retrochiasmal visual deficits Hemiparesis

Table 1: **Clinical features that can help to distinguish between multiple sclerosis relapse and PML**

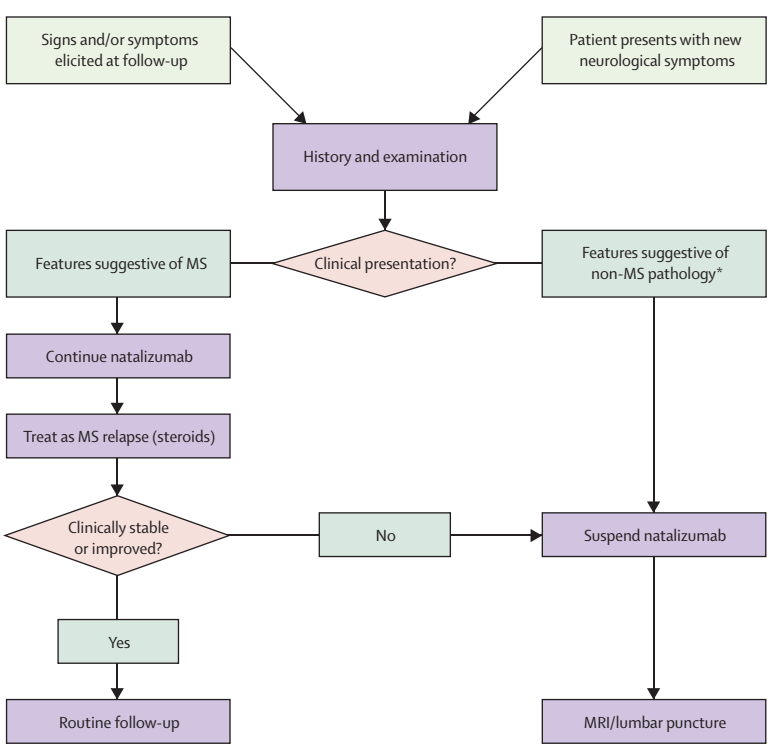

Figure 2: **Clinical assessment guidelines for new or worsening neurological symptoms in natalizumab-treated patients**

If presenting features and development are suggestive of multiple sclerosis, symptoms may be treated as a relapse and managed according to usual clinical practice. A single course of corticosteroids may be considered if PML is unlikely on the basis of clinical findings and/or subsequent patient assessment. If corticosteroids are used, the patient should be monitored clinically for signs of stabilisation and improvement. A lack of response to corticosteroids should immediately indicate further investigation. If the patient's presenting symptoms do not unequivocally suggest multiple sclerosis, or if the patient does not stabilise or improve clinically despite treatment, natalizumab should be immediately suspended. After stopping treatment, an MRI assessment should be done. If MRI is not easily available or there is a high clinical suspicion of PML, then lumbar puncture should be done (only in the absence of the usual contraindications). *see Table 2. MS=multiple sclerosis.

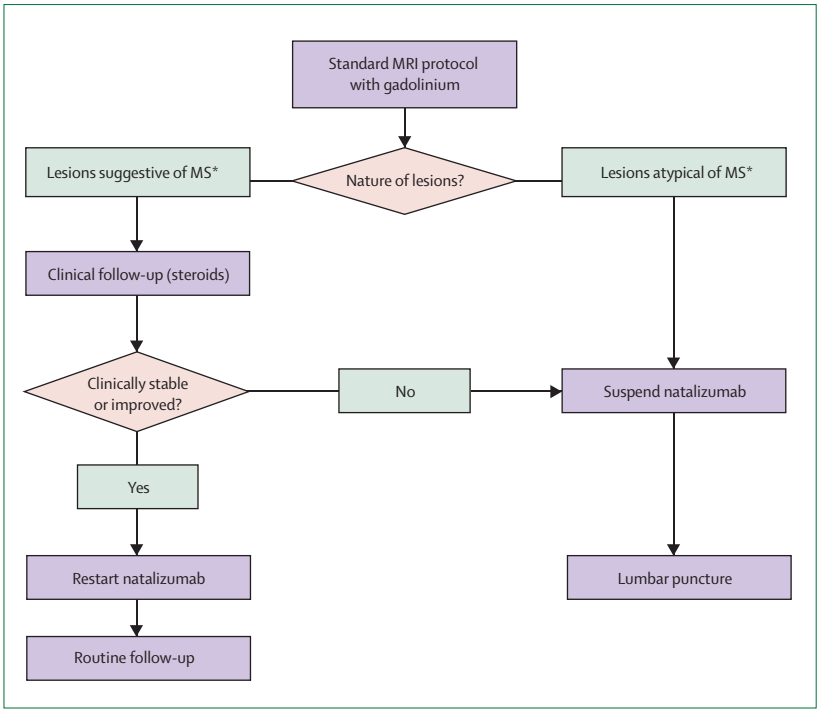

Figure 3: **MRI assessment guidelines for natalizumab-treated patients with new or worsening signs or symptoms that are not obviously associated with multiple sclerosis**
An MRI scan should be done and compared with a pretreatment MRI scan to differentiate PML lesions from multiple sclerosis lesions. Patients with lesions typical of multiple sclerosis should be treated appropriately and closely followed for further clinical exacerbations or abnormalities. A follow-up MRI should be considered after 1–2 months to assess lesion changes over time. If the symptoms or signs stabilise or improve during close clinical follow-up, natalizumab may be reinitiated and the patient routinely monitored. It is important to note that all decisions regarding continued natalizumab treatment should be made in the context of benefit–risk considerations. If MRI-detectable lesions are suggestive of PML, or the patient is unresponsive to typical treatment for a presumed relapse or experiences a worsening of signs and symptoms, lumbar puncture should be done (only in the absence of the usual contraindications). *see Table 2.

frequent patient monitoring. The three patients who developed PML while receiving natalizumab each presented with clinical signs and symptoms that were unusual for multiple sclerosis and were recognised by their families or health-care providers. Patients should be advised to remain proactive in reporting any unusual disease activity at the onset of symptoms. As such, initial patient counselling should include a briefing on possible "red flag" symptoms and provision of educational documents such as a patient medication guide or patient alert card.

In view of the mode of action of natalizumab it is possible that other non-multiple sclerosis pathologies, such as opportunistic infections, could occur. This alternative should be considered in the differential diagnosis of any unusual symptoms, and appropriate investigations should be done.

MRI assessment

If PML cannot be ruled out in a patient with new or worsening signs or symptoms on clinical assessment, a standard cranial MRI scan with gadolinium should be done (figure 3) and this should be compared with the pretreatment MRI scan to differentiate PML from multiple sclerosis. In a safety assessment of natalizumab-treated study patients, when lesions from a recent MRI scan had indeterminate abnormalities, a comparison with an early MRI scan was successful in excluding a diagnosis of PML in all but one case.[51] Certain features of brain lesions, including location, borders, and patterns of change, help distinguish between multiple sclerosis and PML (table 2). Lesions typical of multiple sclerosis are generally focal, widespread, periventricular, can be found in the spinal cord and in the posterior fossa early on, and typically have round or finger-like sharp edges with occasional U-fibre involvement. In addition, multiple sclerosis lesions enlarge within days or weeks, eventually decreasing in size, and mass effect may be observed in acute lesions. By contrast, lesions typical of PML are generally diffuse and subcortical, can be found in white matter tracts, are cortex sparing, and typically have ill-defined and irregularly shaped borders, with destruction of U-fibres. PML lesions continuously progress and mass effect is rarely reported, even in large lesions. Despite these features, although MRI is a highly sensitive test for suspected lesions of PML, particularly in the setting of clinical signs or symptoms, it still lacks specificity. Lesions in multiple sclerosis and other demyelinating processes, oedema, and glioma can be difficult to distinguish from early PML lesions.[50,86,87] Figure 4 shows typical lesions on MRI scans in a patient with multiple sclerosis and a patient with PML.

A suggested brain MRI protocol for the detection of PML should include proton density/T2, FLAIR and both unenhanced and contrast-enhanced T1-weighted sequences. These sequences can best help to distinguish PML lesions from those characteristic of other inflammatory CNS disorders, including multiple sclerosis, at early stages of disease.[51,52,57,58] Importantly, the consistent use of a standard MRI protocol and positioning on similar anatomical landmarks will facilitate comparison with a pretreatment brain MRI scan and aid in the detection of early alterations.

Although MRI is important diagnostically, it is a poor screening test for routine monitoring; MRI is very sensitive for detecting CNS pathology, but it is non-specific for PML in the setting of multiple sclerosis lesions, and there is no practical scanning frequency for use as a screening test given the sudden onset and fast progression of PML.

Laboratory assessment

The integration of laboratory investigations into the diagnostic plan for PML is outlined in figure 5.[88] Although the analysis of cerebrospinal fluid for JCV DNA is very specific for the diagnosis of PML,[51] current information suggests that in early PML cerebrospinal fluid is usually negative for JCV DNA despite clinical and radiographic findings.[59] The low

	Lesions typical of multiple sclerosis	Lesions typical of PML
Location	Mostly focal Widespread in brain and spinal cord Periventricular Posterior fossa lesions often seen early	Diffuse, mainly subcortical White matter tracts, sparing cortex
Borders	Sharp edges, round or finger-like Confluent with other lesions U-fibres may be involved	Ill-defined, irregular shape, infiltrating U-fibres destroyed
Mode of extension	Lesions initially focal Enlarge within days or weeks Eventually decrease in size over months	Diffuse/asymmetrical/homogenous lesions No confluence with other lesions Continuous progression
Mass effect	May be seen in acute lesions	Rare, even in large lesions
T2-weighted imaging	Acute lesions: hyperintense centre, isointense ring, discrete hyperintensity outside ring structure reflecting oedema Subacute/chronic lesions: hyperintense, no ring structure	Diffuse hyperintensity Slightly increased intensity of newly involved areas compared with old areas Little irregularity in signal intensity
T1-weighted imaging	Acute lesions: densely hypointense (large lesions) or isointense (small lesions) Subacute/chronic lesions: increasing signal intensity over time (80% of cases); decreasing signal intensity over time due to axonal loss (20% of cases)	Slightly hypointense at onset Signal intensity decreasing over time and along the affected area No reversion of signal intensity
FLAIR sequence	Hyperintense Sharply delineated	Hyperintensity and extension more clearly visible than on T2-weighted sequence
T1-weighted imaging + gadolinium	Acute lesions: dense, homogenous enhancement; sharp edges Subacute lesions: ring enhancement Chronic lesions: no enhancement	Usually no enhancement, even in large lesions*
Atrophy	Focal atrophy possible No or slow progression of generalised atrophy	Focal atrophy generally not observed

*Some peripheral enhancement reported in HIV-positive patients, particularly during therapy (partial reconstitution of immune function). Adapted with permission from the Massachusetts Medical Society.[51]

Table 2: **MRI features favouring multiple sclerosis versus PML**

sensitivity in early PML and the invasive nature of the test make it a poor screening tool. Hence, cerebrospinal fluid testing for JCV by PCR should be used for diagnosis only in patients with neurological symptoms or MRI lesions suspicious for PML. In general, lumbar puncture for obtaining a cerebrospinal fluid sample should take place only if the underlying pathology of MRI lesions atypical of multiple sclerosis remains unresolved. It is important to note that a negative cerebrospinal fluid sample does not exclude PML.

Blood testing for JCV DNA is an attractive option for monitoring because it is less invasive than cerebrospinal fluid testing, and it stands to reason that the presence of JCV DNA in the blood would be a risk factor for PML. However, results from the safety study done by Yousry and colleagues[51] and the current information on HIV suggest that this is not the case[25,62,67,89] and that the test has a low sensitivity and predictive value. Therefore, this test requires further development before it can be of diagnostic value.

Conclusion

Multiple sclerosis is a serious disease for which there is a substantial unmet need for more efficacious therapies. The magnitude and breadth of effects displayed by natalizumab in clinical studies confirm its place as a highly effective therapy for active relapsing-remitting multiple sclerosis. However, as with other therapies used to treat other immune diseases with significant efficacy, there are risks associated with natalizumab. The

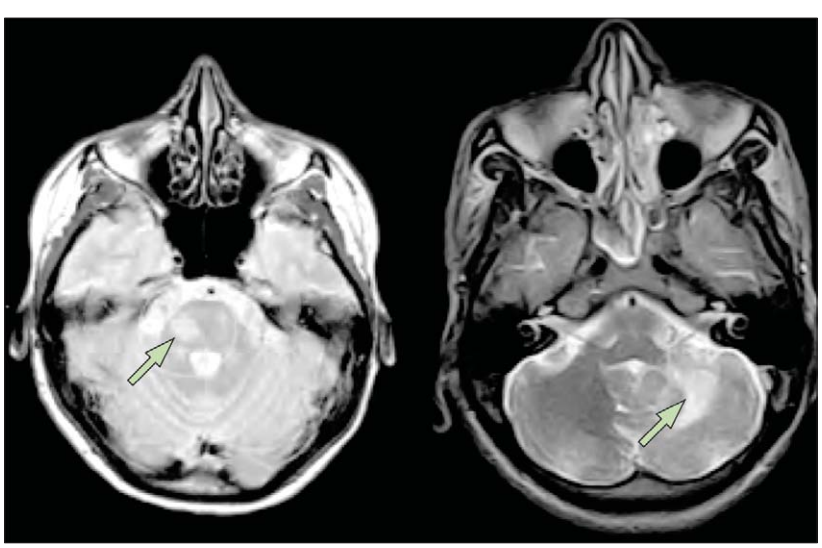

Figure 4: **Typical lesion in the posterior fossa in a case of multiple sclerosis (left) and a lesion depicted in a case of PML (right) on T2-weighted scans**

Note that the more diffuse hyperintense pattern with poorly delineated borders is indicative of PML but may also occur at certain stages of lesion development in multiple sclerosis.

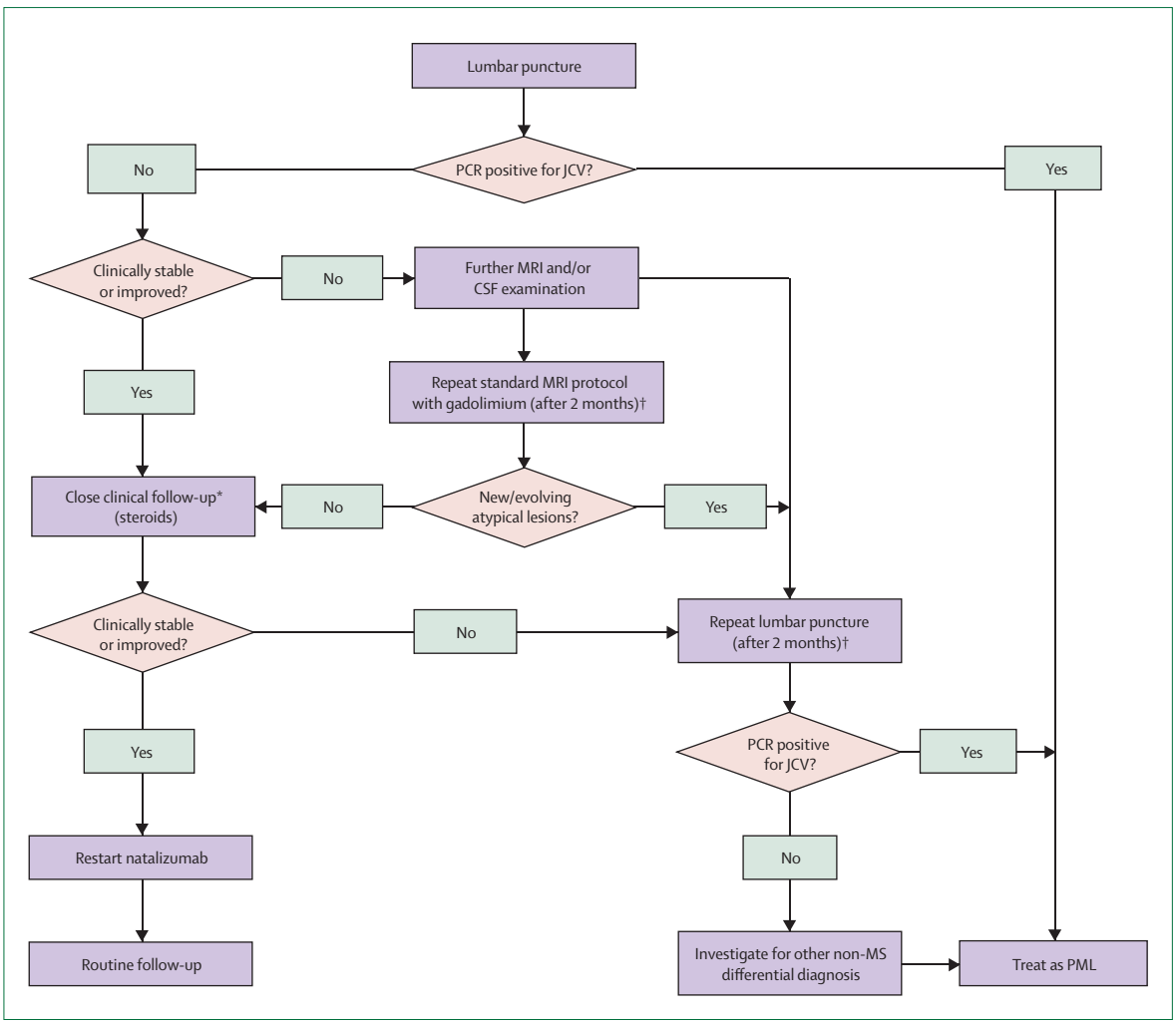

Figure 5: **Laboratory assessment guidelines for natalizumab-treated patients with clinical signs/symptoms and MRI lesions suggestive of PML**
A lumbar puncture and PCR analysis of CSF for JCV DNA should be performed in patients with clinical signs/symptoms and MRI lesions suggestive of PML. If cerebrospinal fluid has detectable JCV DNA by PCR, a diagnosis of PML is confirmed. If no JCV DNA is detected, the patient should be continuously monitored for worsening symptoms. If clinical stability or improvement does not occur, a repeat MRI should be done as indicated after 2 months; a follow-up MRI should be done earlier than 2 months in patients with aggressive clinical changes. Should the repeat MRI reveal new or developing atypical lesions, a further cerebrospinal fluid analysis should be done. An inability to exclude PML should prompt consideration of a brain biopsy, particularly if clinical suspicion of PML remains high. If PML is ruled out after retesting, a non-multiple sclerosis differential diagnosis should be considered and the underlying pathology should be investigated further. Under all circumstances, it is critical that natalizumab not be reinitiated until a diagnosis of either PML or another opportunistic infection is definitively excluded and continuation of natalizumab is deemed appropriate for ongoing multiple sclerosis treatment after a consideration of benefit versus risk. Because the utility of blood and urine testing for the diagnosis of PML has not been confirmed,[25,72,88] such tests are not recommended for the screening or monitoring of patients for the presence of JCV. *Close clinical follow-up is considered to be a minimum of biweekly assessments. †Evaluation should be accelerated in patients with aggressive clinical changes.

identification of PML in association with natalizumab raises the need for careful consideration by both physicians and patients of this rare but serious risk before starting treatment. As with other immunomodulatory drugs, physician and patient education is an important part of managing serious adverse events.

As there is no known treatment or cure for PML, rapid recognition and diagnosis and early discontinuation of natalizumab are key interventions. The suggested diagnostic algorithm for PML in patients with multiple sclerosis treated with natalizumab is intended to heighten awareness and assist in the appropriate work-up when PML is suspected. In the three cases of confirmed PML, patients, their families, or their health-care providers recognised clinical signs of PML that prompted concern. Previously, such changes would have been diagnosed as associated with multiple sclerosis rather than a rare disease like PML. Now, such clinical changes should be considered as PML until proven otherwise, prompting rapid suspension of natalizumab dosing and an appropriate work-up. Current information suggests that early recognition can improve outcomes, although it is not known whether this will be the case with natalizumab. However, it is hoped that the use of

Search strategy and selection criteria

References for the review on PML were identified by searching MEDLINE between 1969 and 2006 (last update October 2006) and references from relevant articles; numerous articles were also identified through searches of the extensive files of the authors. The search terms "progressive multifocal leukoencephalopathy", "PML", "JC virus and CNS" were used. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the topics covered in the Review.

natalizumab in accordance with appropriate conditions, clinical vigilance, and knowledge of how to diagnose and manage PML will provide a means of minimising risk while permitting patients with multiple sclerosis who need more effective medication access to this important new therapy.

Contributors

LK took the initiative of creating the manuscript, participated in interpretation and analysis of data collected in the phase III studies and their safety follow-up, reviewed literature, summarised discussions from expert groups, and reviewed all drafts. DB participated in the development of the guidelines and reviewed and approved drafts and the final version of the manuscript. H-PH participated in the conception, design, collection, and interpretation of data, and reviewed drafts of the manuscript. EH participated in the development of the guidelines and in the review of all drafts of the manuscript. DM participated in the development of the guidelines and editing drafts of the manuscript. CHP participated in the development of the guidelines and review of drafts of the manuscript. MR participated in the development of the guidelines and writing of the manuscript. SLH participated in the review and editing of the manuscript. RAR participated in the writing of the manuscript. HLW reviewed and approved drafts and the final version of the manuscript. PWO participated in data generation, analysis, and manuscript preparation. JK participated in meetings to develop the diagnostic algorithm and reviewed preliminary and final drafts of the manuscript. EWR reviewed and approved drafts and the final version of the manuscript. TY participated in the development of the guidelines and editing drafts of the manuscript. EOM participated in laboratory assays for detection of JCV DNA in clinical samples of patients with multiple sclerosis relevant to the manuscript. DBC participated in the development of the guidelines, review of natalizumab toxicity, background regarding PML, and editing drafts of the manuscript.

Conflicts of interest

The authors disclose the following conflicts of interest: LK discloses that the University Hospital, Basel, has received research support from Biogen Idec, GlaxoSmithKline, Novartis Pharmaceuticals, Sanofi-Aventis, Schering, Serono, Teva Pharmaceuticals, and Wyeth Pharmaceuticals. LK has been principal investigator, member, or chair of steering committees or advisory boards in multiple sclerosis clinical trials sponsored by Abbott Laboratories, Bayer, Bayhill, Berlex, Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Centocor, Eisai, Elan Pharmaceuticals, Genzyme, GlaxoSmithKline, Immune Response, Neurocrine, Novartis Pharmaceuticals, Sanofi-Aventis, Schering, Serono, Roche, Teva Pharmaceuticals, UCB Pharma, and Wyeth, and has received lecture fees from one or more of these companies. Payments and consultancy fees were exclusively used for the support of research activities. DB has received honoraria and research support from Biogen Idec, Serono, Schering, and Teva Pharmaceuticals. H-PH has received honoraria and consultancy fees from, and participated as an investigator in phase II and III trials for, Biogen Idec, Bayer Vital, Schering, Serono, and Teva Pharmaceuticals. H-PH has received research grant support from Biogen Idec. EH has received clinical study research funding from Biogen Idec, Novartis Pharmaceuticals, Octapharma, Schering, Serono, and Teva Pharmaceuticals. She has received honoraria for symposium lectures from Biogen Idec, Pfizer, Schering, and Teva Pharmaceuticals. DM has received grant support from Biogen Idec, Elan, Schering, and GlaxoSmithKline for performance of MRI analyses in clinical trials, as well as honoraria for advisory or consultancy work, lectures, and related travel expenses from Aventis, Biogen Idec, Bristol Myers Squibb, GlaxoSmithKline, Schering, Serono, UCB Pharma, and Wyeth. CHP has received consultancy fees from Biogen Idec, Schering AG, Teva Pharmaceuticals, Serono, Novartis Pharmaceuticals, GlaxoSmithKline, and Antisense Therapeutics, lecture fees from Biogen Idec, Schering AG, and Teva Pharmaceuticals, and grant support from Biogen Idec, Schering AG, Wyeth, Novartis Pharmaceuticals, and GlaxoSmithKline. MR has received travel grants and consultancy fees from Aventis, Biogen Idec, Coloplast, and Schering. SLH has received a research grant from Biogen Idec for neurodegenerative disease research. RAR discloses that the Cleveland Clinic has received research support from Biogen Idec. RAR was principal investigator for the SENTINEL trial, which was supported by Biogen Idec. HLW has received consultancy fees from Autoimmune, Biogen Idec, Pepgen, Pfizer, Serono, Teva Pharmaceuticals, and Vascular Biogenics. PWO has served as a consultant for and received research trial grant support from Biogen Idec. JK has received honoraria and consultancy fees from Biogen Idec, Sanofi-Aventis, Schering, and Serono. EWR has received grant support from Biogen Idec, Schering, Novartis, Sanofi-Aventis, and GlaxoSmithKline for assessment of multicentre multiple sclerosis studies. Payments for advisory board and steering committee membership as well as speaker honoraria by the above mentioned companies to EWR were exclusively used for research projects at the Department of Neuroradiology. TY received support to perform MRI analyses through a research grant from Biogen Idec to the Institute of Neurology. EOM has no relationships to disclose. DBC has received payment as a consultant by Biogen Idec, Genzyme, Millennium, Pfizer, and Schering-Plough, and as a speaker by Boehringer-Ingelheim and Bristol-Myers Squibb. DBC has received research support from Bavarian Nordic, NeurogesX, Pfizer, Roche, Savient Pharmaceuticals, and Tibotec.

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