Recommendations for the Selection, Treatment, and Management of Patients Utilizing Natalizumab Therapy for Multiple Sclerosis

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Abstract

Natalizumab is an integrin receptor antagonist indicated for the treatment of multiple sclerosis (MS). Natalizumab is indicated as monotherapy in patients who have had an inadequate response to other forms of MS treatment and is not recommended as first-line treatment because of the potential for serious adverse events associated with its use. It is critical for both physicians and patients to understand the benefits as well as the potential risks of treating MS with natalizumab. One of the serious adverse events associated with treatment with natalizumab is the possibility of developing progressive multifocal leukoencephalopathy (PML). Physicians and patients must weigh the benefits of treatment against the possibility of developing PML before undergoing treatment. Proper clinical vigilance, via the Tysabri Outreach: Unified Commitment to Health (TOUCH) Prescribing Program, is currently the best method to minimize the risk of PML, associated with natalizumab therapy.

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Natalizumab (Tysabri; Biogen Idec, Inc, Elan Pharmaceuticals, Inc) is an integrin receptor antagonist indicated for the treatment of relapsing multiple sclerosis (MS).[1] Natalizumab binds to the α_4 subunit of $\alpha_4\beta_1$- and $\alpha_4\beta_7$-integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α_4-mediated adhesion of leukocytes to specific receptors (ie, vascular cell adhesion molecule-1 on vascular endothelial cells and connecting segment-1 and/or osteopontin expressed by parenchymal cells).[1]

The exact mechanism by which natalizumab exerts its effects in MS is unknown. However, it is postulated that by binding to the α_4-integins, natalizumab reduces the migration of lymphocytes into the central nervous system (CNS) of patients with MS and inhibits further recruitment of immune cells into inflamed tissue, thus reducing the formation of MS lesions.[2]

Natalizumab is indicated as monotherapy for the treatment of patients with relapsing forms of MS to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. Natalizumab is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy.[1]

Advanced MS is a serious condition requiring an assertive stance to therapy. Natalizumab is an effective option to delay progression of advanced MS but it is also associated with a risk of developing progressive multifocal leukoencephalopathy (PML), which is a demyelinating disease of the CNS caused by lytic infection of oligodendrocytes by the papovavirus JC that causes death or severe disability. Consequently, patients and clinicians need to understand the risks and benefits of natalizumab therapy and compare them against the effects of not treating the disease. Below is a review of the efficacy and safety of natalizumab monotherapy for the treatment of MS.

Efficacy of Natalizumab and the AFFIRM Trial

The AFFIRM (Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis) trial[3] established natalizumab as an effective therapy for patients with relapsing MS. This 2-year phase 3 trial compared natalizumab (300 mg every 4 weeks; n = 627) to placebo (n = 315) in patients with relapsing MS. The primary end points were the rate of clinical relapse at 1 year and the rate of

Table 1. Recommendations on Patient Selection for Natalizumab Therapy

1. Suboptimal response to interferon beta or glatiramer acetate, defined as:
Two or more relapses within 1 year
One significant relapse in the past year or a mild relapse accompanied by significant MRI changes
Significant MRI changes at 1 year in the absence of clinical symptoms; continued MRI activity on serial MRIs
2. Patients who cannot tolerate interferon beta or glatiramer acetate
3. Patients fitting into poor prognosis category
Devastating relapse at onset
Early high relapse rate
High lesion activity/lesion load on brain MRI at first attack
Rapid onset of disability (eg, cognitive, physical, activities of daily living)
High-risk populations with historically more malignant forms of multiple sclerosis

MRI indicates magnetic resonance imaging.
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3-month sustained progression of disability at 2 years. Results from this study were impressive. Natalizumab reduced the rate of clinical relapse at 1 year by 68% (P <.001) and reduced the risk of 3-month sustained progression of disability by 42% over 2 years (hazard ratio [HR], 0.58; 95% confidence interval [CI], 0.43-0.77; P <.001). The sensitivity analysis for 6-month sustained progression of disability was a 54% risk reduction in the natalizumab group (HR, 0.46; 95% CI, 0.33-0.64; P <.001).[3]

Patients receiving natalizumab also had 83% fewer new or enlarging T2 hyperintense lesions detected by magnetic resonance imaging (MRI) over 2 years compared with those given placebo (1.9 ± 9.2 lesions [mean ±SD] vs 11.0 ± 15.7, respectively [P <.001]) and reduced the mean number of lesions as detected by gadolinium-enhanced MRI by 92% as compared with placebo at both 1 year and 2 years (P <.001).[3]

In a post hoc subgroup analysis of data from the AFFIRM trial, natalizumab was effective in patients with highly active MS (2 or more relapses within a year and 1 or more gadolinium-enhancing [Gd+] lesions at study entry). Natalizumab, compared with placebo, reduced the risk of disability progression by 64% (vs 39%; P <.0001) and relapse rate by 81% (0.28 vs 1.46, respectively; P <.001).[4]

Safety of Natalizumab, the SENTINEL Trial, and Patient Selection

Natalizumab is associated with an increased risk of PML. This condition was first reported during a second phase 3 trial, the SENTINEL (Safety and Efficacy of Natalizumab in Combination with Interferon beta-1a) trial.[5] This trial randomly assigned 1171 patients on interferon (IFN) beta-1a therapy who had at least 1 relapse to receive either continued IFN-beta therapy plus natalizumab (n = 589) or IFN beta plus placebo (n = 582) for up to 116 weeks. Results from this trial showed that the combination of IFN beta and natalizumab was efficacious (ie, combination therapy had a lower annualized rate of relapse over a 2-year period compared with IFN beta alone [0.34 vs 0.75, respectively; P <.001]) and was associated with fewer new or enlarging lesions on T2-weighted MRI (0.9 vs 5.4; P <.001). However, the trial was terminated early when 2 cases of PML, 1 fatal, were diagnosed in natalizumab-treated patients.

As of May 6, 2010, a total of 49 cases of PML were identified among approximately 67,700 patients who have received natalizumab worldwide.[6]

Patient Selection

Due to the seriousness of PML, an expert panel was recently assembled to develop best practice recommendations for the use of natalizumab in patients with MS.[7-9] The panel determined that natalizumab should only be given to patients who (1) have had a suboptimal response to standard treatment (eg, IFN beta or glatiramer acetate [GA]), (2) cannot tolerate standard treatment, or (3) have a poor prognosis (Table 1).[9] For patients switching from IFN beta or GA to natalizumab, no washout period is necessary.

The expert panel further noted that a poor response to IFN beta or GA should be defined as 2 or more relapses within a year of treatment, 1 significant relapse in the past year, a single relapse accompanied by new MRI activity (eg, new Gd+ lesions, new or enlarging T2 hyperintense lesions, or new T1 black holes) within 1 year, or a significant increase in MRI activity even in the absence of clinical activity.[9]

Table 2. Factors That May Be Considerations for Not Initiating Natalizumab Therapy

Inappropriate for therapy	Current immunocompromise Active malignancy that requires treatment, or that brings about an immune deficiency state Active viral hepatitis; jaundice Inability to obtain magnetic resonance imaging
Concerns	Prior radiation therapy History of melanoma Prior immunosuppressive therapy (duration is an important factor) Current or prior liver dysfunction Age (immunosenescence)
Indications to hold therapy	Suspicion of progressive multifocal leukoencephalopathy Active infection Unexplained fever or other significant medical issues requiring further testing and intervention

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Natalizumab can also be given to patients who cannot tolerate IFN beta or GA (ie, those who develop flulike symptoms or injection-site reactions). Finally, patients fitting into a poor prognosis category may also benefit from natalizumab (Table 1). In these groups of patients, natalizumab as first-line therapy can be considered. For example, first-line therapy with natalizumab is recommended for patients with a devastating first relapse, or accompanying poor prognosis MRI activity (eg, T1 black hole formation, high number and volume of Gd+ lesions).[9]

Natalizumab is not appropriate for some patients (Table 2).[9] Patients who are immunocompromised should not receive natalizumab because they may be at increased risk for developing PML. Therefore, patients suspected of having a compromised immune system due to previous long-term use of immunosuppressive agents, chronic medical comorbidities, and/or recurrent or a recent history of opportunistic infection should be screened for immune competency prior to receiving natalizumab.[9] The package insert for natalizumab does not require or recommend a washout period prior to initiation of therapy; however, the panel recommended that patients previously given immunosuppressants, such as azathioprine, mycophenolate mofetil, cyclophosphamide, mitoxantrone, and methotrexate, should undergo a 3- to 6-month washout period before beginning treatment with natalizumab. The panel felt that no washout period is necessary following IFN beta, GA, or corticosteroid treatment.[9]

The panel also stated that since MRI at baseline is essential for monitoring treatment efficacy, natalizumab should only be given as a last option in patients who cannot receive an MRI.[9]

Monitoring Patients Using Natalizumab

In order to assess efficacy of natalizumab therapy, the panel recommended that prior to beginning therapy, baseline clinical (physical exam, medical history, cognitive function), laboratory (human immunodeficiency virus and CD4 counts [if appropriate], complete blood count; liver function tests), and image testing (MRI with contrast) should be performed. After initiating treatment, routine follow-up should include a neurologic exam and MRI at 6 months, with subsequent exams and MRIs every 12 months thereafter. These recommendations are related to assessing symptoms and status of MS; monitoring for PML, as outlined below, differs slightly but generally overlaps with this schedule. Additionally, other tests may be performed if necessary (Table 3).[9]

Some patients show hypersensitivity to natalizumab infusions, which may be the result of the patient developing antibodies to natalizumab. If persistent antibody positivity is suspected (ie, reduced treatment efficacy and an increased incidence of infusion reactions such as pruritus, nausea, flushing, dyspnea), antibody testing should be performed. It should be noted that antibodies detected within the first 6 months of treatment may be transient and disappear with continued dosing. Repeat testing at 3 months after the initial positive result is recommended to confirm that antibodies are persistent. If persistent antibody positivity is confirmed, clinicians should discontinue natalizumab therapy.[1,9] Patients developing antibodies after 6 months of initial treatment most likely have persistent antibody positivity.[9]

Managing Adverse Events

Short-Term Events

Two short-term adverse events associated with natalizumab are hypersensitivity reactions and infusion-related reactions. Hypersensitivity reactions are allergic reactions that usually occur within 2 hours of the start of the infusion; typical symptoms manifest as urticaria with or without sys-

Table 3. Panel Recommendations for Initial Testing and Follow-Up for Natalizumab Therapy

Type of Testing	Test at Screening/First Visit	Routine Management
Blood work	Complete blood cell count Liver function test HIV[a] CD4 count[a]	
Routine and esoteric	Full neurologic examination Cognitive testing History for risk factors and contraindications	Full neurologic examination at 6 months and every subsequent 12 months Cognitive testing as indicated by neurologic examination Neutralizing antibodies (as indicated by infusion reaction or MS activity)
MRI	Brain MRI with contrast at baseline	At 6 months and every 12 months after initiation *or* As needed based on clinical symptoms
Lumbar puncture		JCV antibody upon suspicion of PML not differentiated with MRI or clinical examination

HIV indicates human immunodeficiency virus; JCV, John Cunningham virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.
[a]Depending on risk level, as is CD4:CD8.
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temic signs and symptoms (eg, changes in airway, breathing, circulation, and vital signs). If a patient shows any symptoms indicative of a hypersensitivity reaction, natalizumab should be discontinued.[1,9]

In contrast, an infusion-related reaction generally does not warrant discontinuation. An infusion-related reaction is defined as any adverse event that occurs within 2 hours of infusion[1] but is not considered to be immunoglobulin E–mediated. Common infusion-reaction symptoms include headache, dizziness, fatigue, nausea, sweats, and rigors.[1] These symptoms can be treated symptomatically, and patients with a history of infusion reactions can be pretreated with H1 and/or H2 blockers and/or acetaminophen.[9]

Progressive Multifocal Leukoencephalopathy

As discussed earlier, the most serious long-term adverse event associated with natalizumab is the development of PML. Although PML is rare, it is a very serious condition without an effective treatment.

While symptoms of PML are dependent on the location of the lesion, the 3 most common presenting symptoms associated with PML are motor weakness, visual disturbance, and altered mental status.[10] Aphasias, cerebellar signs, seizures, headaches, and vertigo have also been associated with PML.[11] Because PML is rare and can affect different brain areas and pathways, it is unfortunately difficult to diagnose. Generally, if a patient shows the above-listed symptoms, or if other non–MS-related symptoms appear, it is advised that natalizumab therapy be discontinued until PML can be ruled out (**Figure**).[12] While most non-MS symptoms are unlikely related to PML, it is important to distinguish PML from relapsing MS.[12]

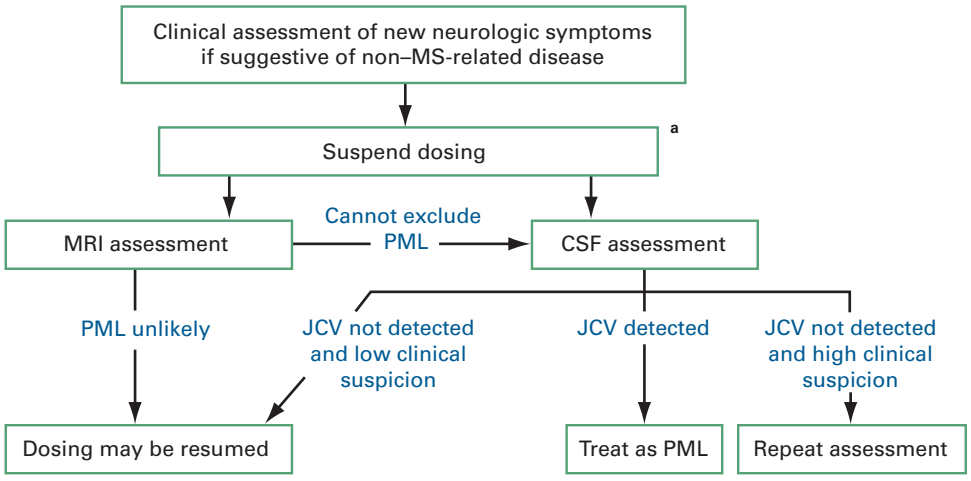
Patients at Risk for PML

As discussed, immunosuppression from any cause is associated with development of PML, and could predispose patients receiving natalizumab to the condition. Aside from this and treatment duration, there are no other known patient characteristics that make one more susceptible to PML. Since the risk of PML increases with longer duration of natalizumab treatment and is something that can be managed directly, some physicians believe that a natalizumab "holiday" may be beneficial; however, currently there are no data to indicate that a drug holiday reduces the risk of PML.

Patients With PML

If any new signs or symptoms suggestive of PML are observed, natalizumab dosing should be immediately withheld. If PML is confirmed, natalizumab should not be reinstated. Furthermore, natalizumab can be removed more quickly by plasma exchange therapy. Khatri et al[13] showed that 3 sessions of plasma exchange therapy over a period of 1 week reduced plasma concentrations of natalizumab by 92%. Immune reconstitution inflammatory syndrome (IRIS) has been reported in the majority of patients using natalizumab who developed PML and subsequently discontinued natalizumab. In almost all cases, IRIS occurred after plasma exchange was used to eliminate circulating natalizumab.[1]

■ **Figure.** Diagnostic Algorithm for Suspected PML



CSF indicates cerebrospinal fluid; JCV, John Cunningham virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.
[a]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.
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The use of antiviral agents to treat patients with PML has been investigated. To date, however, all evidence is anecdotal, and until properly performed trials have been developed, there are no available treatment options for PML.

The TOUCH Prescribing Program

At present, the most effective method to monitor for PML is clinical vigilance. To help physicians monitor for PML, a restricted distribution plan is in place for natalizumab. Natalizumab is available in the United States *only* through a restricted distribution program called the Tysabri Outreach: Unified Commitment to Health, or TOUCH, Prescribing Program.[1] Only prescribers and patients enrolled in the TOUCH Prescribing Program can prescribe and receive natalizumab, and only pharmacies and infusion centers authorized by the TOUCH Prescribing Program can dispense and infuse natalizumab. All prescribers, pharmacists, infusion center staff, and patients must be educated about the TOUCH program and the risks associated with natalizumab therapy, including PML and other opportunistic infections.

Infusion personnel are mandated to ask patients questions regarding their health status prior to every natalizumab infusion as part of the TOUCH Prescribing Program. These questions screen for new neurologic problems, medical conditions that can weaken the immune system, and use of medicines that can weaken the immune system. Some physicians add more specific questions to the mandatory list to enhance long-term management and surveillance of health-related issues. Prescribers must (1) ensure that the patient receives the medication guide; (2) review the TOUCH Prescriber/Patient Enrollment form with the patient and answer all questions; and (3) obtain consent from the patient as part of the initial prescription process.[1] Also, prescribers must (1) report any serious opportunistic and atypical infections in patients given natalizumab to Biogen Idec or Elan; (2) evaluate patients at 3 months and 6 months following the first infusion, and every 6 months thereafter; and (3) determine every 6 months whether patients should continue on treatment and, if so, reauthorize treatment every 6 months.

Patients are instructed to promptly contact their physician if they develop any new or worsening symptoms that persist over several days, particularly neurologic symptoms.[14] Symptoms that may indicate PML include behavioral and neuropsychological alterations, homonymous hemianopsia, cortical blindness, hemiparesis, acute or subacute cognitive dysfunction, aphasia, seizures, ataxia, and tremor.[9]

To ensure implementation of the TOUCH Prescribing Program is appropriate and effective, the manufacturer regularly evaluates the effectiveness of the program and reports health outcomes data (eg, PML rate, overall safety) and systems/process data and quality and compliance metrics to the US Food and Drug Administration.[15]

Conclusion

MS is a serious, debilitating disease and, as the disease progresses, treatment decisions must balance the inherent risks

of the disease with the risks of more aggressive treatment. One such treatment option is natalizumab, which has shown powerful efficacy in patients with MS. However, the risk of developing PML following natalizumab therapy outweighs the benefits for some patients. Proper clinical vigilance is the best method to help reduce the risk of PML, and adherence of the TOUCH Prescribing Program can reduce the risk of serious adverse events in patients treated with natalizumab.

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REFERENCES

1. Tysabri [prescribing information]. Cambridge, MA: Biogen Idec Inc; 2009.

2. Rice GP, Hartung HP, Calabresi PA. Anti-alpha4 integrin therapy for multiple sclerosis: mechanisms and rationale. *Neurology.* 2005;64(8):1336-1342.

3. Polman CH, O'Connor PW, Havrdova E, et al; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med.* 2006;354(9):899-910.

4. Hutchinson M, Kappos L, Calabresi PA, et al. The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. *J Neurol.* 2009;256(3):405-415.

5. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med.* 2006;354(9):911-923.

6. PML incidence in patients receiving Tysabri. https://medinfo.biogenidec.com/ [registration required]. Accessed May 10, 2010.

7. Munschauer FE, Benedict RHB, Granger CV, Niewczyk PM. Introduction to best practice recommendations for the selection and management of patients with MS on natalizumab. *Mult Scler.* 2009;15(4 suppl):S1-S6.

8. Coyle PK, Jeffrey DR. Clinical efficacy and benefit of natalizumab. *Mult Scler.* 2009;15(4 suppl):S7-S15.

9. Coyle PK, Foley JF, Fox EJ, et al. Best practice recommendations for the selection and management of patients with multiple sclerosis receiving natalizumab therapy. *Mult Scler.* 2009;15(4 suppl):S26-S36.

10. Tornatore C, Clifford DB. Clinical vigilance for progressive multifocal leukoencephalopathy in the context of natalizumab use. *Mult Scler.* 2009;15(4 suppl):S16-S25.

11. Weber T. Progressive multifocal leukoencephalopathy. *Neurol Clin.* 2008;26(3):833-854.

12. Kappos L, Bates D, Hartung HP, et al. Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring. *Lancet Neurol.* 2007;6(5):431-441.

13. Khatri BO, Man S, Giovannoni G, et al. Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. *Neurology.* 2009;72(5):402-409.

14. Tysabri (natalizumab) Medication Guide. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM089809.pdf. Accessed April 23, 2010.

15. Tysabri risk minimization action plan: summary of TOUCH. http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM107197.pdf. Accessed April 23, 2010.