First-line natalizumab in multiple sclerosis: rationale, patient selection, benefits and risks

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Abstract: Natalizumab (NTZ) is a highly effective disease modifying therapy for the treatment of relapsing forms of multiple sclerosis (MS). Despite evidence to support its use as first-line therapy, risk of NTZ-associated progressive multifocal leukoencephalopathy (PML) has largely contributed to it being relegated to a second-line position. Recent preliminary data may allow for a more accurate analysis of JC virus (JCV) risk stratification of a given patient's PML risk. Herein we propose an algorithm to help guide clinicians through this decision-making process. We recommend that NTZ be considered for first-line use in JCV antibody negative MS patients, JCV 'low positive' MS patients without prior exposure to immunosuppression and for a limited period (12–24 months) in JCV 'high positive' MS patients with an aggressive disease course. We caution against first-line use in JCV antibody 'high positive' patients beyond 12–24 months and any JCV antibody positive patient with a history of prior immunosuppression.

Keywords: JC polyomavirus, multiple sclerosis, natalizumab, progressive multifocal leukoencephalopathy, treatment algorithm

Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disorder of the central nervous system (CNS) characterized by inflammatory lesions in the brain and spinal cord that result in varying degrees of neurological impairment. Self-reactive lymphocytes that target myelin antigens are believed to play an important role in the pathogenesis of MS [Lassmann *et al.* 2007]. To access the CNS and initiate damage of the myelin sheath, these cells must cross the blood–brain barrier by first binding to adhesion molecules present on vascular endothelial cells. Thus, inhibiting the ability of these inflammatory cells to enter the CNS by interfering with the molecules involved in vascular adhesion became an attractive therapeutic target for treatment of MS. One such drug, natalizumab (NTZ), is a humanized monoclonal antibody that targets the $\alpha 4$ subunit of $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins, which are molecules involved in transmigration of T cells into the CNS through interaction with ligands in the extracellular matrix. NTZ blocks the interaction of these molecules with their receptors, vascular cell adhesion

molecule 1 (VCAM-1) and mucosal addressin cell adhesion molecule 1, present on the vascular endothelium resulting in decreased migration of inflammatory cells from the peripheral circulation into the target tissues [Rice *et al.* 2005; Steinman, 2005].

NTZ development

NTZ was first studied in the experimental autoimmune encephalomyelitis (EAE) model and subsequently in MS patients [Sheremata *et al.* 2005]. It successfully passed through phase I trials and was then examined as a therapeutic agent for the treatment of MS in several larger trials. The AFFIRM trial, was a randomized, 2-year, double-blind, placebo-controlled, phase III study which evaluated the efficacy and safety of NTZ in patients with relapsing remitting multiple sclerosis (RRMS) [Polman *et al.* 2006]. Sustained 12-week and 24-week progression of disability at year 2 was reduced by 42% and 54%, respectively, with NTZ compared with placebo ($p < 0.001$). Annualized relapse rate was decreased by 68% at one year with NTZ ($p <$

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0.001). New or enlarging T2 lesions were reduced by 83% ($p < 0.001$) and gadolinium enhancing lesions were reduced by 92% on brain magnetic resonance imaging (MRI) ($p < 0.001$). Efficacy of NTZ was further confirmed by the SENTINEL trial, which studied the combination of NTZ and interferon (IFN)- β 1a in RRMS patients [Rudick *et al.* 2006].

While NTZ was shown to be clinically effective in patients with RRMS in two phase III clinical trials [Polman *et al.* 2006; Rudick *et al.* 2006], it was unexpectedly associated with a serious complication, progressive multifocal leukoencephalopathy (PML). This was initially observed in two patients from the SENTINEL trial in which NTZ and IFN β were combined [Kleinschmidt-Demasters and Tyler, 2005; Langer-Gould *et al.* 2005]. An additional PML case was seen in a NTZ treated Crohn's disease patient [Van Assche *et al.* 2005]. PML is a potentially fatal CNS opportunistic infection caused by reactivation of a clinically latent JC polyomavirus (JCV) that infects and destroys oligodendrocytes, leading to multifocal areas of demyelination and associated neurologic dysfunction [Berger and Koralnik, 2005]. In addition to latent or chronic infection with JCV, rearrangement of this virus into the neurotropic strain (found in the brain tissue of patients with PML) must occur if a patient was originally infected with the archetypal strain [Berger, 2011]. PML invariably occurs in the context of impaired cell-mediated immunity, most frequently observed in individuals with compromised immune systems, such as human immunodeficiency virus (HIV) patients and those receiving prolonged treatment with immunosuppressive drugs. One mechanism suggested to contribute to the development of PML in NTZ treated patients is that, by blocking α 4 integrin and thus decreasing lymphocyte trafficking to the brain, the normal immune surveillance in the brain becomes reduced, allowing reactivation of latent viruses present in the nervous system [McFarland and Jacobson, 2006; Stuve *et al.* 2006]. In addition, further studies suggest that JCV may replicate within B lymphocytes located within bone marrow and lymphoid tissue which may cross the blood-brain barrier passing infection to astrocytes at the vessel border and setting the stage for infection of oligodendrocytes [Berger, 2011]. As of June 2013, there have been 372 cases of NTZ-associated PML reported in MS patients [Biogen Idec, 2013]. Because of concern for PML risk

associated with NTZ, this therapy is often reserved for 'second-line' use. In this paper we intend to challenge this practice and revisit the use of NTZ first-line in the treatment of relapsing MS patients.

Rationale and efficacy data supporting first-line NTZ use

The efficacy of NTZ on clinical and MRI outcomes has been well defined in phase III, double-blinded, placebo-controlled trials such as AFFIRM and SENTINEL [Polman *et al.* 2006; Rudick *et al.* 2006]. Of important note, 90% of all RRMS patients enrolled into AFFIRM were treatment-naïve [Polman *et al.* 2006], which likely contributed to the US Food and Drug Administration (FDA) approval of this product and did not restrict its use to second-line therapy. Subgroup analysis of the AFFIRM study in treatment naïve patients with highly active relapsing MS (≥ 2 relapses in the year prior to study initiation and ≥ 1 gadolinium enhancing lesion on MRI at time of study entry) also demonstrated prominent efficacy. These patients experienced a 53% reduction in 12-week sustained disability progression compared with placebo ($p = 0.029$) and there was a 64% reduction in 24-week sustained disability progression at 2 years ($p = 0.008$) [Hutchinson *et al.* 2009]. The annualized relapse rate (ARR) over the 2-year study in highly active, treatment-naïve patients was reduced by 81% compared with placebo ($p < 0.001$). These patients also had a 75% decrease in cumulative probability of relapse over 2 years ($p < 0.001$) [Hutchinson *et al.* 2009]. Based on its high level of efficacy, NTZ should be considered in patients with aggressive MS disease courses at least for the first 12–24 months regardless of JCV serum antibody status.

Therapies that have been traditionally considered 'first-line therapies' including the interferons and glatiramer acetate are only partially effective in preventing disease progression in MS. In clinical practice, these agents are often positioned first line due to their well-documented safety profile, not because of superior efficacy. Recently, with the increased number of options for MS disease-modifying therapies, the bar for treatment success has shifted from partial protection from relapses and MRI disease activity to complete freedom from disease activity as measured by MRI and clinical examination. A post-hoc analysis of the AFFIRM trial demonstrated that 64% of patients

on NTZ were free of clinical disease activity ($p < 0.0001$), 58% were free of radiographic disease activity ($p < 0.0001$) and 37% were free of combined clinical and radiographic activity throughout the two year study ($p < 0.0001$) [Havrdova *et al.* 2009].

Results from the multinational Tysabri® Observational Program (TOP) which included 3976 MS patients, demonstrated that ARR were lower in patients who were treatment naïve and had a lower baseline Expanded Disability Status Scale (EDSS) (<3.0) at the time of NTZ initiation [Kappos *et al.* 2012]. These results were adjusted for baseline EDSS, gender, relapse status in the past year, prior disease modifying therapy, disease duration and treatment duration. Mean ARRs on NTZ according to baseline EDSS were: EDSS 0.0–2.0 [ARR: 0.18; 95% confidence interval (CI): 0.16–0.21], EDSS 2.5–4.0 (ARR: 0.22; 95% CI: 0.20–0.24) and EDSS 4.5–9.5 (ARR: 0.24; 95% CI: 0.22–0.27), $p = 0.0004$. ARRs on NTZ therapy were lower in treatment-naïve patients (ARR: 0.16; 95% CI: 0.13–0.20) compared with those on prior therapy, 1 prior therapy (ARR: 0.21; 95% CI: 0.19–0.23) and >1 prior therapy (ARR: 0.29; 95% CI: 0.26–0.31) $p < 0.0001$ [Kappos *et al.* 2012]. This suggests that treatment-naïve patients may achieve a greater benefit if NTZ is used as a first-line option. Additionally, since patients with lower EDSS scores are more likely to be earlier in the course of their disease, these data also suggest that using NTZ first line in patients with less disability may result in better clinical outcomes.

Application of NTZ first line is also supported by recent work by Sargento-Freitas and colleagues, who reported on clinical predictors of optimal response to NTZ in a small sample ($n = 47$) of MS patients [Sargento-Freitas *et al.* 2013]. Optimal response to NTZ was defined as a sustained reduction in EDSS by ≥ 1 point or reduction in annualized relapse rate by more than 1 point. Interestingly, favorable characteristics for optimal response to NTZ included younger age at time of treatment, less disability (EDSS of 4.5 or less), shorter disease duration (9.5 years or less) and higher ARR in the year prior to NTZ initiation which may encourage MS clinicians to use NTZ as a first-line therapy.

NTZ has also been shown to be highly effective in MS patients with aggressive phenotypes such as in African American MS patient populations. African American MS patients often have a more aggressive

disease course, characterized by increased frequency of relapses, less recovery from relapses, faster disability accumulation and a faster progression from RRMS to secondary progressive multiple sclerosis (SPMS) [Kaufman *et al.* 2003; Cree *et al.* 2004, 2009]. Evidence has demonstrated that African American MS patients have a diminished response to interferon β -1a [Cree *et al.* 2005]. However, a post hoc analysis of African American MS in the AFFIRM and SENTINEL trials demonstrated that NTZ treatment is highly effective in this population. African American patients on NTZ experienced a 60% reduction in ARR compared with placebo ($p = 0.02$). Results were also significant for these patients on MRI outcomes including a 79% reduction in mean gadolinium enhancing lesions ($p = 0.03$) and a 90% reduction in mean new or enlarging T2 lesions ($p < 0.008$) [Cree *et al.* 2011]. Considering African American MS patients as an example of patients with aggressive phenotypes, clinicians may opt to consider NTZ first-line in such patient populations.

Patient selection, benefits and risks

Above we have reviewed robust data supporting the efficacy of NTZ in RRMS, along with evidence for its use as a first-line therapy. The risk of PML, however, has largely contributed to reservation of NTZ for second-line use. In January 2012, the FDA approved use of the JCV antibody test. Patients who are found to be JCV antibody negative carry a negligible risk for PML. Patients with JCV antibody positivity have prior viral exposure and therefore an increased risk of NTZ associated PML [Gorelik *et al.* 2010].

Among JCV antibody positive patients, two other factors have been found to further stratify NTZ-associated PML risk: prior immunosuppressive exposure and time on therapy. A recent study of JCV antibody testing provides encouraging preliminary data which may allow immunosuppression-naïve JCV antibody positive patients to be further stratified into a 'high positive' (JCV antibody index >1.5) and 'low positive' (JCV antibody index ≤ 1.5) categories, although the use of these data is currently off-label.

A patient's high or low JCV antibody index status is obtained by measuring the patient's serum for the JCV antibody. Amongst JCV antibody positive MS patients, the JCV antibody index can be used to determine each patient's specific titer. The serum antibody titer is typically listed on the

Figure 1. Algorithm to help guide clinicians in the consideration of natalizumab (NTZ) first-line in relapsing remitting multiple sclerosis (RRMS).

AB, antibody; DMT, disease-modifying therapy; JCV, JC polyomavirus; MRI, magnetic resonance imaging; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.

laboratory result form for a JCV serum antibody test in any patient whose result is positive. However, some laboratories may not automatically report the index and it may need to be requested by the ordering clinician. This result is available to all clinicians.

If proven, this study demonstrates that ‘low positive’ JCV antibody patients are at substantially lower NTZ associated PML risk compared with ‘high positive’ patients, allowing a more precise assessment of a given patient’s risk [Plavina *et al.* 2013]. Using these data, we have constructed a preliminary algorithm to help guide clinicians in the consideration of NTZ first-line in relapsing MS, although we caution against using the antibody titer data to clarify exact risk at this time (Figure 1).

The decision to start a patient on disease-modifying therapy with NTZ begins with assessing the individual’s JCV antibody status. If a patient is determined to be JCV antibody negative, and as such at only a theoretical risk of developing PML (<1:10,000) [Biogen Idec, 2013], any such patient may be considered to start NTZ first line. The false negative rate of the JCV serum antibody test is 2.5% [Gorelik *et al.* 2010]. A recent small

study ($n = 67$) examined urine and serum for detection of JCV levels to evaluate the JCV serum antibody test and determined the false negative rate to be 37% [Berger *et al.* 2013]. Further studies are needed in larger numbers of patients to determine the significance of these findings. Monitoring of these patients should include periodic (most often every 3–6 months) rescreening of their antibody status as there is a 2–3% seroconversion rate annually for these patients [Gorelik *et al.* 2010]. In addition to evaluation of JCV antibody status, the risk of rebound of MS disease activity following NTZ discontinuation should be discussed with the patient prior to treatment initiation since a patient may later decide to stop therapy due to desire to become pregnant or if they seroconvert to be JCV antibody positive. There is not strong evidence to suggest that disease activity returns more aggressively than a patient’s previous baseline level of disease. However, small studies have shown that even with steroid pulses during treatment discontinuation, approximately 30–50% of patients will suffer a relapse within 6 months [Magraner *et al.* 2011; Borriello *et al.* 2012].

If an individual considering NTZ is found to be JCV antibody positive and has never been exposed

to prior immunosuppression, then evaluation of the JCV antibody index is quite helpful in guiding treatment decisions. 'Low positive' patients (index 0.9–1.5) are at much lower risk for PML. Patients with an index of 0.9 carry a 1:10,000 PML risk in the first 24 months on therapy, 3:10,000 for months 25–48 and 4:10,000 for months 49–72. Patients with an index of 1.5 carry a 1:10,000 in the first 24 months on therapy, 1.2:1000 in months 25–48 and 1.3:1000 for months 49–72. The PML risk is much higher amongst 'high positive' JCV patients with index >1.5. For these patients, PML risk is 1:1,000 for months 1–24, 8.1:1000 for months 25–48 and 8.5:1000 for months 49–72 [Plavina *et al.* 2013]. Again, the use of JCV antibody index data for risk stratification should be used with caution as these data are preliminary.

Given these differences in PML risk, 'low positive' and 'high positive' JCV antibody patients may be stratified differently. 'High positive' patients may not be appropriate candidates for NTZ as first-line therapy long term, but for patients who are 'high positive' with a more aggressive disease course, use may be considered for 1–24 months where the risk remains relatively low (1/1000), whereas 'low positive' patients might be considered for long-term use with proper monitoring. For patients who are JCV antibody positive on therapy, the JCV serum antibody index test should be repeated every 3–6 months. This allows for the risk of PML to be more accurately predicted over time. It is possible that the index could increase and result in a higher risk of PML. If a previously high JCV antibody index value decreases, it is unclear how to interpret these data. We recommend that, once a patient has been classified as 'high positive', their risk should be considered as such regardless of whether the JCV antibody index decreases on subsequent testing. Longitudinal data have shown that patients index values do not typically fluctuate over time [Plavina *et al.* 2013]. Of note, JCV antibody index risk stratification does not apply to patients with prior exposure to immunosuppression [Plavina *et al.* 2013]. We would not recommend starting a JCV antibody positive patient with a history or prior immunosuppression on NTZ first line.

There are emerging lines of evidence to support the recommendation of frequent (every 3–4 months) brain MRI scans to screen for asymptomatic PML in JCV antibody positive patients.

Several recent investigations suggest that MRI evidence of PML often precedes clinical symptoms by 2–3 months [Clifford *et al.* 2010 Bloomgren *et al.* 2012]. One could therefore 'catch' presymptomatic PML by careful attention to new MRI lesions on scans performed every 3–4 months. This is particularly encouraging given PML data from January 2013 suggest important differences in outcomes of patients diagnosed with symptomatic PML (clinical symptoms) *versus* asymptomatic PML (MRI findings only). As of January 2013, there were 319 confirmed NTZ associated PML cases, of which 21 (6.6%) presented asymptotically (MRI only) compared with 298 who presented symptomatically [Dong-Si *et al.* 2013]. At that time, 100% of the asymptotically presenting patients were alive compared with 76.5% of the symptomatic presentation group. Among PML survivors, asymptotically presenting patients demonstrated lower EDSS (3.6 *versus* 5.3) [Dong-Si *et al.* 2013]. Based on these data, we recommend that JCV antibody positive patients benefit from close monitoring with brain MRIs performed on a quarterly basis. To decrease costs associated with frequent MRI testing, clinicians may consider ordering a limited cerebral MRI for monitoring of PML using T2 flair sequences every 3–4 months after the first year.

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References

- Berger, J. (2011) The pathogenesis of progressive multifocal leukoencephalopathy. *Discovery Med* 12: 495–503.
- Berger, J., Houff, S., Gurwell, J., Vega, N., Miller, C. and Danaher, R. (2013) JC virus antibody status underestimates infection rates. *Ann Neurol* 74: 84–90.
- Berger, J. and Koralnik, I. (2005) Progressive multifocal leukoencephalopathy and natalizumab—unforeseen consequences. *N Engl J Med* 353: 414–416.
- Biogen Idec (2013) PML incidence in patients receiving Tysabri® (natalizumab). Available at: <https://medinfo.biogenidec.com>
- Bloomgren, G., Richman, S., Hotermans, C., Subramanyam, M., Goelz, S., Natarajan, A. *et al.* (2012) Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 366: 1870–1880.
- Borriello, G., Prosperini, L., Mancinelli, C., Gianni, C., Fubelli, F. and Pozzilli, C. (2012) Pulse monthly steroids during an elective interruption of natalizumab: a post-marketing study. *Eur J Neurol* 19: 783–787.
- Clifford, D., De Luca, A., Simpson, D., Arendt, G., Giovannoni, G. and Nath, A. (2010) Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol* 9: 438–446.
- Cree, B., Al-Sabbagh, A., Bennett, R. and Goodin, D. (2005) Response to interferon β -1a treatment in African American multiple sclerosis patients. *Arch Neurol* 62: 1681–1683.
- Cree, B., Khan, O., Bourdette, D., Goodin, D., Cohen, J., Marrie, R. *et al.* (2004) Clinical characteristics of African Americans vs. Caucasian Americans with multiple sclerosis. *Neurology* 63: 2039–2045.
- Cree, B., Reich, D., Khan, O., De Jager, P., Nakashima, I., Takahashi, T. *et al.* (2009) Modification of multiple sclerosis phenotypes by African ancestry at HLA. *Arch Neurol* 66: 226–233.
- Cree, B., Stuart, W., Tornatore, C., Jeffery, D., Pace, A. and Cha, C. (2011) Efficacy of natalizumab therapy in patients of African descent with relapsing multiple sclerosis: analysis of AFFIRM and SENTINEL data. *Arch Neurol* 68: 464–468.
- Dong-Si, T., Richman, S., Bloomgren, G., Wenten, M., Philip, G., Datta, S. *et al.* (2013) Natalizumab-associated progressive multifocal leukoencephalopathy (PML) in multiple sclerosis patients: survival and functional outcome when asymptomatic at diagnosis. 65th Annual Meeting of the American Academy of Neurology, San Diego, CA.
- Gorelik, L., Lerner, M., Bixler, S., Crossman, M., Schlain, B., Simon, K. *et al.* (2010) Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurol* 68: 295–303.
- Havrdova, E., Galetta, S., Hutchinson, M., Stefoski, D., Bates, D., Polman, C. *et al.* (2009) 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* 8: 254–260.
- Hutchinson, M., Kappos, L., Calabresi, P., Confavreux, C., Giovannoni, G., Galetta, S. *et al.* (2009) The efficacy of natalizumab in patients with relapsing multiple sclerosis: subgroup analyses of AFFIRM and SENTINEL. *J Neurol* 256: 405–415.
- Kappos, L., Butzkueven, H., Pellegrini, F., Trojano, M., Wiendl, H., Zhang, A. and Hotermans, C. (2012) Long-term safety and efficacy and association between baseline treatment history and postbaseline relapses in multiple sclerosis patients treated with natalizumab in the TYSABRI® Observational Program (TOP). *Neurology* 78(Meeting Abstracts 1): P04.134.
- Kaufman, M., Johnson, S., Moyer, D., Bivens, J. and Norton, H. (2003) Multiple sclerosis: severity and progression rate in african Americans compared with whites. *Am J Phys Med Rehabil* 82: 582–590.
- Kleinschmidt-Demasters, B. and Tyler, K. (2005) Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon β -1a for multiple sclerosis. *N Engl J Med* 353: 369–374.
- Langer-Gould, A., Atlas, S., Green, A., Bollen, A. and Pelletier, D. (2005) Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med* 353: 375–381.
- Lassmann H., Bruck W., Lucchinetti C.F. (2007) The immunopathology of Multiple Sclerosis: An Overview. *Brain Pathol* 17(2): 210–218.
- Magraner, M., Coret, F., Navarre, A., Bosca, I., Simo, M., Escutia, M. *et al.* (2011) Pulsed steroids followed by glatiramer acetate to prevent inflammatory activity after cessation of natalizumab therapy: a prospective, 6-month observational study. *J Neurol* 258: 1805–1811.
- McFarland, H. and Jacobson, S. (2006) Natalizumab and immune cells. *Arch Neurol* 63: 1366–1367.
- Plavina, T., Bloomgren, G., Richman, S., Pace, A., Lee, S., Schlain, B. *et al.* (2013) Anti-JCV antibody index further defines PML risk in natalizumab-treated

MS patients. *27th Annual Meeting of the Consortium of Multiple Sclerosis Centers*, Orlando, FL.

Polman, C., O'Connor, P., Havrdova, E., Hutchinson, M., Kappos, L., Miller, D. *et al.* (2006) A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 354: 899–910.

Rice, G., Hartung, H. and Calabresi, P. (2005) Anti-alpha4 integrin therapy for multiple sclerosis: mechanisms and rationale. *Neurology* 64: 1336–1342.

Rudick, R., Stuart, W., Calabresi, P., Confavreux, C., Galetta, S., Radue, E. *et al.* (2006) Natalizumab plus interferon β -1a for relapsing multiple sclerosis. *N Engl J Med* 354: 911–923.

Sargento-Freitas, J., Batista, S., Macario, C., Matias, F. and Sousa, L. (2013) Clinical predictors of an

optimal response to natalizumab in multiple sclerosis. *J Clin Neurosci* 20: 659–662.

Sheremata W.A., Minager A., Alexander J.S., Vollmer T. (2005) The role of alpha-4 integrin in the aetiology of multiple sclerosis: Current knowledge and therapeutic implications. *CNS Drugs* 19(11): 909–22.

Steinman, L. (2005) Blocking Adhesion molecules as therapy for multiple sclerosis: natalizumab. *Nat Rev Drug Discov* 4: 510–518.

Stuve, O., Marra, C., Jerome, K., Cook, L., Cravens, P., Cepok, S. *et al.* (2006) Immune surveillance in multiple sclerosis patients treated with natalizumab. *Ann Neurol* 59: 743–747.

Van Assche, G., Van Ranst, M., Sciot, R., Dubois, B., Vermeire, S., Noman, M. *et al.* (2005) Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 353: 362–368.