

MILESTONE 3

The risk of natalizumab-associated PML is revealed

FDA approval of natalizumab for treatment of multiple sclerosis (MS) in November 2004 was accelerated on the basis of 1-year results from two randomized, placebo-controlled, phase III clinical trials — the AFFIRM and SENTINEL trials (MILESTONE 2). However, in February 2005, natalizumab was withdrawn from the market and ongoing trials were terminated following reports of progressive multifocal leukoencephalopathy (PML) in two patients who had received natalizumab in the SENTINEL trial.

PML is a rare but potentially fatal demyelinating brain disorder caused by the polyomavirus JC virus. The disorder most commonly occurs in people with HIV infection, but has also been reported in patients receiving long-term immunosuppression. JC virus is ubiquitous in the human population and usually infects children and adolescents asymptotically before becoming latent. It almost never causes disease in immunocompetent individuals. Natalizumab is thought to increase the risk of PML infection by preventing lymphocytes from adhering to the endothelium of the blood–brain barrier, thereby reducing their migration from the blood into the CNS and suppressing T cell-mediated immune responses in the brain.

In June 2006, the FDA approved the reintroduction of natalizumab as monotherapy for relapsing–remitting MS. This reintroduction required revised labelling and improved safety warnings to highlight the potential risk of PML and, in

the USA, adherence to a special programme that restricted availability of natalizumab to authorized centres and required ongoing evaluation of patients during treatment to minimize the risks. Subsequently, much research has been carried out to examine the risk of PML with natalizumab treatment, leading to stringent management strategies.

“ clinical vigilance is crucial for early detection of PML ”

Patient monitoring has shown that the global incidence of PML in individuals with MS who have received natalizumab in the post-marketing setting is ~4.2 per 1,000 patients, and the survival rate is ~70–75%. The median time from treatment initiation to onset of PML symptoms has been estimated at 25 months (range 6–80 months). However, PML can also occur up to 6 months after cessation of natalizumab.

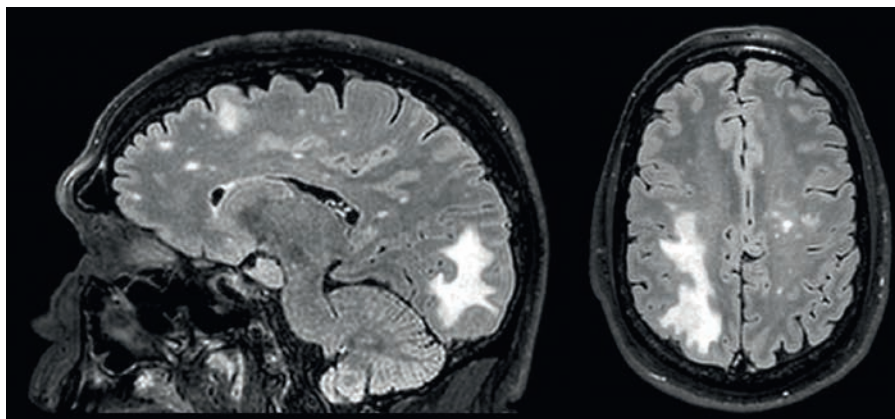
The main identified risk factors for natalizumab-associated PML are positivity for anti-JC virus antibodies in the serum, previous exposure to immunosuppressants and longer natalizumab therapy. Conversely, several factors have been associated with improved survival and outcomes from natalizumab-associated PML, including younger age, lower JC virus viral load

and more localized brain involvement detected with MRI at diagnosis. In addition, extending the time between doses of natalizumab has been suggested as a way to reduce the risk of PML, but further studies are needed to confirm this hypothesis.

No direct antiviral treatment against JC virus is available, so clinical vigilance is crucial for early detection of PML in patients who are receiving natalizumab. Research since the introduction of natalizumab has led to several recommendations for patient monitoring to improve the safety of the antibody. Before treatment, patients can be stratified for risk of PML by use of the JC virus antibody index in anti-JC virus antibody-positive patients with no prior immunosuppression, although there is currently no evidence as to whether this measure reduces the incidence of PML. Once treatment has started, patients should be closely monitored for new neurological symptoms, such as cognitive and behavioural changes, retrochiasmatic visual disturbance, hemiparesis and seizures. Consequently, regular clinical and MRI monitoring are essential. Assessment of JC virus antibody serology status every 6 months, or more frequently in patients who have previously been exposed to immunosuppressants, has been recommended. Similarly, MRI screening every 3–4 months has been recommended for patients at high risk of PML (those who are seropositive for anti-JC virus antibodies and those whose duration of natalizumab treatment is >18 months) and annually for anti-JC virus seronegative patients.

Despite the safety concerns, natalizumab is an effective treatment for relapsing–remitting MS and remains an important option. Insight into the causes and risk factors has enabled management of the risks, but refinement of stratification protocols and research into new biomarkers continue. Furthermore, subsequent development of new MS treatments, including further antibody therapies, has provided alternative options when the risks of PML are high.

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Nature Reviews



MRI scans from a patient with progressive multifocal leukoencephalopathy. Courtesy of Avindra Nath, National Institute of Neurological Disorders and Stroke, USA.

ORIGINAL ARTICLES Kleinschmidt-DeMasters, B. K. & Tyler, K. L. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N. Engl. J. Med.* **353**, 369–374 (2005) | Langer-Gould, A. et al. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N. Engl. J. Med.* **353**, 375–381 (2005) | Pitarokoiili, K. & Gold, R. Progressive multifocal leukoencephalopathy risk stratification. *Nat. Rev. Neurol.* **13**, 710–712 (2017)

FURTHER READING Winkelmann, A. et al. Disease-modifying therapies and infectious risks in multiple sclerosis. *Nat. Rev. Neurol.* **12**, 217–233 (2016)