

## **My fourth medication: the famous Tysabri!**

*Natalizumab is a humanized monoclonal antibody against the cellular adhesion molecule  $\alpha$ 4-integrin. Natalizumab is used in the treatment of multiple sclerosis and Crohn's disease. It is co-marketed by Biogen Idec and Élan as **Tysabri**, and was previously named *Antegren*.*

*Tysabri is administered by intravenous infusion every 28 days. The infusion lasts only an hour, but it is necessary to wait an extra hour for observation each and every time.*

*The drug is believed to work by reducing the ability of inflammatory immune cells to attach to and pass through the cell layers lining the intestines and blood-brain barrier. Natalizumab has proven effective in treating the symptoms of both diseases, preventing relapse, vision loss, cognitive decline and significantly improving quality of life in people with multiple sclerosis, as well as increasing rates of remission and preventing relapse in Crohn's disease.*

*Natalizumab was approved in 2004 by the United States Food and Drug Administration.*

*It was subsequently withdrawn from the market by its manufacturer after it was linked with three cases of the rare neurological condition progressive multifocal leukoencephalopathy when administered in combination with interferon beta-1a, another immunosuppressive drug often used in the treatment of multiple sclerosis.*

*After a review of safety information and no further deaths, the drug was returned to the US market in 2006 under a special prescription program.*

*In August 2008, further incidents of PML were reported<sup>[1]</sup>, and another in October 2008<sup>[2]</sup>. In the European Union, it has been approved only for the treatment of multiple sclerosis.*

*Biogen Idec announced the initiation of the first clinical trial of Tysabri as a potential cancer treatment as of September 5, 2008.*

### **TY SABRI AND MULTIPLE SCLEROSIS**

*Natalizumab was evaluated in two randomized, double-blind, placebo-controlled trials in people with multiple sclerosis. Both studies enrolled individuals with MS who experienced at least one clinical relapse during the prior year and had a Kurtzke EDSS score between 0 and 5. In these trials natalizumab was shown to reduce relapses in individuals with MS by 68% vs. placebo, a margin far greater than had been seen for other approved MS therapies. Natalizumab also slowed the progression of disability in*

patients with relapsing MS. In combination with interferon beta-1a (IB1A), relapsing and disability progression were reduced more than IB1A alone. Other benefits of natalizumab use by patients with relapsing MS included reduced visual loss, a significant increase in the proportion of disease-free individuals, significantly improved assessments of health-related quality of life in relapsing individuals, reduced cognitive decline of a portion of individuals with MS, reduced hospitalizations and steroid use, and prevention of the formation of new lesions. Approximately 6% of individuals receiving natalizumab have been found to develop persistent antibodies to the drug, which reduces its efficacy and produce reactions during the infusion of the drug, as well as hypersensitivity. Natalizumab is approved in the United States and the European Union. It is indicated as monotherapy (not combined with other drugs) for the treatment of highly active relapsing remitting MS in spite of prior treatments. Natalizumab offers a limited improvement in efficacy compared to other treatments for MS, but due to the lack of information about long-term use, as well as potentially fatal adverse events, reservations have been expressed over the use of the drug outside of comparative research with existing medications.

### **MECHANISM OF ACTION:**

Natalizumab is a humanized monoclonal antibody against alpha-4 ( $\alpha 4$ ) integrin, the first drug developed in the class of selective adhesion molecule inhibitors.  $\alpha 4$ -integrin is required for white blood cells to move into organs; natalizumab's mechanism of action is believed to be the inhibition these immune cells from crossing blood vessel walls to reach affected organs.

The symptom-causing lesions of MS are believed to be caused when inflammatory cells such as T-lymphocytes pass through the blood-brain barrier through interaction with receptors on the endothelial cells. Natalizumab appears to reduce the transmission of immune cells into the central nervous system by interfering with the  $\alpha 4\beta 1$ -integrin receptor molecules on the surfaces of cells. The effect appears to occur on endothelial cells expressing the VCAM-1 gene, and in parenchymal cells expressing the osteopontin gene. In animals used to model MS and test therapies, repeated administration of natalizumab reduced migration of leukocytes into the brain's parenchyma, and also reduced lesioning, though it is uncertain if this is clinically significant for humans.

Individuals with MS dosed with natalizumab demonstrated increased CD34-expressing cells, with research suggesting a peak in expression after 72 hours.

## ***SIDE EFFECTS:***

*Common adverse effects include fatigue and allergic reactions with a low risk of anaphylaxis, headache, nausea, colds and exacerbation of Crohn's disease in a minority of patients with the condition.*

*Natalizumab is contraindicated for people with known hypersensitivity to the drug or its components and in patients with a history of PML.*

*Postmarketing surveillance in early 2008 revealed that 0.1% of people taking natalizumab experience clinically significant liver injury, leading to the FDA, EMA and manufacturers recommending that the medication be discontinued in patients with jaundice or other evidence of significant liver damage. This rate is comparable to other immune-suppressing drugs. Evidence of hepatotoxicity in the form of elevated blood levels of bilirubin and liver enzymes can appear as soon as six days after an initial dose; reactions are unpredictable and may appear even if the patient does not react to previous treatment. Such signs reoccur upon rechallenge in some patients, indicating that damage is not coincidental. In the absence of any blockage these liver function tests are predictors of severe liver injury with possible sequelae of liver transplantation or death.*

*Natalizumab has also been linked to melanoma, though the association is unclear. The long-term effects of the drug are unknown and concern has been expressed over the risks of infection and cancer.*

*Natalizumab appears to interact with other immune-modulating drugs to increase the risk of progressive multifocal leukoencephalopathy (PML), an often-fatal opportunistic infection caused by JC virus.*

*In 2005, two people taking natalizumab in combination with interferon beta-1a developed PML. One died, and the other recovered with disabling sequelae. A third fatal case initially attributed to an astrocytoma was reported in a patient being treated for Crohn's disease. Though the patient was being treated with natalizumab in combination with azathioprine, corticosteroids and infliximab, indications of PML infection appeared only after natalizumab monotherapy was re-introduced. No deaths have been linked to natalizumab when it was not combined with other immune-modulating drugs and other rates of opportunistic infections are not increased in patients taking natalizumab possibly due to the drug's mechanism of action. Other than a prior history of PML, there is no known method to identify patients at risk of developing PML. Natalizumab's label indicates that it is contraindicated for immunosuppressed individuals or those with a history of PML. Due to the uncertain risk of PML, natalizumab is only available through a restricted distribution program called the TOUCH program in the United States.*

*As of 2008, four other cases of PML associated with natalizumab have been reported. One of them had not previously taken any other immunomodulator therapy.*

*Though the small number of cases precludes conclusion on the ability of natalizumab alone to induce PML, its black box warning states that the drug has only been linked to PML when combined with other immune-modulating drugs and natalizumab is contraindicated for use with other immunomodulators. Corticosteroids may produce immunosuppression, and the Tysabri prescribing information recommends that people taking corticosteroids for the treatment of Crohn's disease have their doses reduced before starting natalizumab treatment.*

*The risk of developing PML was later estimated to be 1 in 1,000 (0.1%) over 18 months though the longer term risks of PML are unknown.*

*If you would like more information about Tysabri, please, go to the website:  
[www.tysabri.com](http://www.tysabri.com)*