Natalizumab (Tysabri) for Relapsing Multiple Sclerosis
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INTRODUCTION

Multiple sclerosis (MS) affects about 2.5 million individuals worldwide. Approximately 400,000 people in the U.S. have MS, and 200 new cases are diagnosed every week.1 The exact cause of MS is unknown, but researchers believe it is an autoimmune disease in which the body attacks myelin tissue, the fatty sheath that surrounds and insulates nerve fibers in the central nervous system (CNS). Genetics and female sex are thought to make an individual more susceptible to a triggering factor in the environment, such as a virus, trauma, or heavy metal poisoning. Symptoms of the disease include fatigue, difficulty walking, numbness, and vision problems. There is no known cure for MS; these symptoms frequently progress to severe disability and sometimes death.1

Natalizumab (Tysabri) is a recombinant humanized immunoglobulin (IgG-κ) monoclonal antibody produced in murine myeloma cells. After the drug was on the market for only three months, commercial distribution and clinical trials were halted on February 28, 2005, because of safety concerns. Elan Corporation and Biogen Idec, the agent’s sponsors, voluntarily suspended marketing and ongoing trials when progressive multifocal leukoencephalopathy (PML) was diagnosed in three participants in clinical trials.1 Two of these patients had been taking natalizumab in combination with interferon beta-1a (Avonex, Biogen Idec). The third patient had been taking natalizumab alone, but had previously taken azathioprine, an immunosuppressant drug that has also been linked to PML.2

The development of PML in patients receiving natalizumab in combination with interferon beta-1a is thought to be associated with dual suppression of the immune system, leading to reactivation of the JC virus (JCV), a pathogen that many people carry in a latent form. The fact that this CNS disorder has led to the death of two patients with MS has caused researchers to question the use of immune-suppressing agents to treat autoimmune disorders.2,4

After months of evaluating previously natalizumab-treated patients for PML, no additional cases were identified. The FDA lifted the clinical hold on trials for patients with MS. Researchers believed that the drug should be made available as soon as possible, given its clear benefit over existing treatment options. Patients who had benefited from the medication before its removal from the market were anxiously awaiting its return.

On June 5, 2006, the Food and Drug Administration (FDA) approved a supplemental Biologics License Application (sBLA) for the re-introduction of natalizumab to the market as a monotherapy for relapsing MS to slow the progression of disability and to reduce the frequency of clinical relapses. The drug is to be used as monotherapy and is generally recommended for patients who have not responded adequately to, or who cannot tolerate, other MS drugs.5

MECHANISM OF ACTION6

Natalizumab, an alpha4-integrin antagonist, is the first drug in the class of selective adhesion molecule inhibitors. Although the mechanism of action is not fully understood, natalizumab is thought to block the molecular interaction of alpha4, beta1-integrin expressed by inflammatory cells with vascular cell adhesion molecule (VCAM-1) on vascular endothelial cells, and with CS-1 and/or osteopontin expressed by parenchymal cells in the brain. By blocking the adhesion of activated T cells to endothelial cells, this recombinant monoclonal antibody reduces the inflammatory feature of the MS plaque.7

PHARMACOKINETICS AND PHARMACODYNAMICS6

The mean maximum observed serum concentration, after an intravenous (IV) administration of natalizumab to MS patients, was 98 ± 34 mcg/ml. The mean average steady-state natalizumab concentrations over the dosing period are approximately 30 mcg/ml. The mean half-life is 11 ± 4 days, with a clearance of 16 ± 5 ml/hour. The distribution volume of 5.7 ± 1.9 L is consistent with plasma volume.

The agent’s pharmacokinetic properties in children with MS or in MS patients with renal or hepatic insufficiency have not been studied. Natalizumab administration increases the number of circulating leukocytes (including lymphocytes, monocytes, basophils, and eosinophils) as a result of inhibition of transmigration out of the vascular space. Natalizumab does not affect the number of circulating neutrophils.8

INDICATIONS AND USAGE5,6

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. It is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternative MS therapies. Relapsing MS is the most common form of MS at the time of the initial diagnosis. Patients with this clinical course of MS experience exacerbations that are defined by acute worsening of neurological functioning. It is unknown whether or not natalizumab is safe or efficacious beyond two years of use or whether the drug can be used in patients with other forms of the disease, such as chronic progressive MS. The drug is also being investigated for the treatment of Crohn’s disease.

**CLINICAL EFFICACY**

Natalizumab received accelerated approval by the FDA in November 2004. This approval was based on promising results from two randomized, double-blind, placebo-controlled trials in patients with MS. The FDA grants accelerated approval to new drug products that have shown advancement over current drug therapy in serious or life-threatening diseases.

The **AFFIRM Study**

The first study, Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM), enrolled patients who had not received interferon-beta or glatiramer acetate (Copaxane, Teva) for at least the previous six months; approximately 94% had never been treated with these agents. The median age of the patients was 37, with a median disease duration of five years.

Patients were randomly assigned to receive a 300-mg IV infusion of natalizumab (n = 627) or placebo (n = 315) every four weeks for up to 28 months. All patients continued to receive interferon beta-1a 30 mcg IM once weekly. The cumulative probabilities of sustained disability progression at two years were 23% with combination therapy and 29% with interferon beta-1a alone. Patients receiving combination therapy experienced a 24% decrease in the risk of sustained disability progression (P = .02) (Figure 2).

**WARNINGS AND ADVERSE EFFECTS**

The most frequently reported adverse reactions with natalizumab were infections, acute hypersensitivity reactions, depression, and cholelithiasis. The rate of occurrence for these events ranged from 0.8% to 2.1%. The most common events resulting in clinical intervention were urticaria and other allergic reactions.

A black-box warning states that natalizumab increases the risk of PML. Although the cases of PML were limited to patients with recent or concomitant exposure to immunomodulators or immunosuppressants, there were too few cases to rule out the possibility that PML may occur with natalizumab monotherapy. MRI should be performed before therapy is initiated. This may be helpful in differentiating subsequent MS symptoms from PML.

Dosing should be withheld immediately at the first sign or symptom that may be suggestive of the infection. Signs and symptoms include mental deterioration, vision loss, speech disturbances, ataxia, paralysis, and coma. In rare cases, seizures may occur.

Because of the risk of PML, natalizumab is available only through a special restricted distribution program called the TOUCH Prescribing Program. Only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, natalizumab must be

**Figure 1** Kaplan–Meier plots of the time to sustained progression of disability among patients receiving natalizumab, as compared with placebo. (Adapted from Polman C, O’Connor P, Havrdova E, et al. *N Engl J Med* 2006;354:899–910. Copyright © 2006, Massachusetts Medical Society. All rights reserved.)
administered only to patients who are enrolled in and who meet all the conditions of the TOUCH Prescribing Program.

The immune system effects of natalizumab may increase the risk of other infections. In clinical studies, certain types of infections, including pneumonia and urinary tract infections, gastroenteritis, vaginal infections, tooth infections, tonsillitis, and herpes infections, occurred more often in natalizumab-treated patients than in placebo-treated patients.

**DOSAGE AND ADMINISTRATION**

Natalizumab is available as a 300-mg concentrate in a sterile, preservative-free vial. Each package contains a single-use vial. The recommended dose is an infusion of 300 mg IV every four weeks. Patients should be observed during the first infusion and for one hour after the infusion is complete.

**ALTERNATIVE THERAPIES**

Five FDA-approved medications are available for use in patients with MS. These drugs include Avonex, Betaseron, and Rebif, which are forms of beta interferon. Interferon is naturally produced in the body and enhances the body’s ability to regulate the immune system and fight infection. The exact mechanism by which these drugs benefit patients with MS is unknown.

Another medication that has proved beneficial in the treatment of MS is glatiramer acetate (Copaxone). This synthetic protein mirrors the myelin protein that insulates nerve fibers in the brain and spinal cord. By mimicking myelin, it draws white blood cells away from the myelin that is affected by MS.

Mitoxantrone (Novantrone, Immunex), an antineoplastic agent used to treat acute myeloid leukemia and prostate cancer, works in the treatment of MS by suppressing the activity of T cells, B cells, and macrophages that are thought to lead the attack on the myelin sheath.

**CONCLUSION**

Approximately 3,000 patients with MS have been treated with natalizumab in clinical trials, and 5,000 patients have received natalizumab through their primary physician. The risk of developing PML is small with relatively brief use. To date, there have been only three reported cases of PML that developed in patients after natalizumab use.

The FDA’s recommendation to return natalizumab to the market was based on the clear therapeutic benefit for patients with relapsing forms of MS. In addition, natalizumab offers the convenience of a monthly infusion, whereas current therapies are injected daily (Copaxone), every other day (Betaseron), three times per week (Rebif), or weekly (Avonex). The authors believe that there may be some debate about which patients should receive natalizumab. Although it is approved for use as monotherapy and is generally recommended for patients who have not responded adequately to, or who cannot tolerate, other MS drugs, its use may not be restricted to those parameters.

In order to detect future patients who might develop PML as a result of natalizumab use, Elan and Biogen Idec have devised a risk-management program known as the Tysabri Outreach Unified Commitment to Health (TOUCH). This mandatory program is designed to facilitate the appropriate use of natalizumab. More details about the program are expected to be available when the product is launched commercially.

**REFERENCES**