

Natalizumab (Tysabri®)

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Multiple sclerosis (MS) is an autoimmune disease characterized by chronic inflammation of the central nervous system (CNS), ultimately resulting in symptoms such as sensory disturbances, unilateral optic neuritis, diplopia, limb weakness, clumsiness and gait ataxia.³ Approximately 80% to 90% of MS patients develop the relapsing-remitting form of the disease characterized by episodic periods of decreasing neurological function, with periods of stability between the relapses. Patients with relapsing-remitting disease can vary from being relatively asymptomatic to experiencing frequent relapses. Within 25 years of onset, three-quarters of the patients with frequent relapses enter a phase of progressive neurological decline known as secondary progressive MS, with or without superimposed relapses.³

Inflammation in the CNS leads to the destruction of the myelin sheath and axonal injury, causing the lesions characteristic of MS. This process is thought to occur when activated T-lymphocytes cross the blood-brain barrier initiating a series of events resulting in the activation of endothelial cells, recruitment of additional lymphocytes and monocytes and the release of pro-inflammatory cytokines. Although the initiating event of the inflammatory cascade is unknown, the adhesion and trans-endothelial migration of inflammatory cells from the bloodstream across the blood-brain barrier is a critical step in the progression of the disease.³

Disease progression in MS is measured by several scales, with the Kurtzke Expanded Disability Status Scale (EDSS) being the most common.⁴ The scale ranges from zero to ten and progresses in increments of 0.5 degree, with higher scores indicating more severe disease. The scale allows for quantification of disability and allows neurologists to assign a functional score to affected systems, including pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other. The scale is summarized in Table 1.

The treatment approach to MS is a combination of physical, psychological and pharmacologic therapies. Pharmacological treatment for MS includes disease-modifying agents that act to prevent or slow the primary events of MS. Disease-modifying agents include beta interferons, glatiramer acetate and the chemotherapeutic agent, mitoxantrone. Agents for treatment are chosen on the basis of perceived efficacy, frequency, dose, route of administration, immunogenicity, safety, tolerability, and convenience. Other medi-

Summary

Indications. Natalizumab is a recombinant humanized (IgG4κ) murine monoclonal antibody indicated for the treatment of patients with relapsing forms of multiple sclerosis with the goal of reducing the frequency of exacerbations. The safety and efficacy of natalizumab has not been established for chronic progressive multiple sclerosis.¹ Natalizumab is currently being studied for the treatment of other immune-related inflammatory diseases including Crohn's disease and ulcerative colitis.²

Monitoring Parameters. Common adverse events associated with natalizumab therapy include headache, fatigue, depression, urinary tract infection, lower respiratory tract infections and arthralgias. In clinical trials, approximately 10% of patients treated with natalizumab developed anti-natalizumab antibodies. The presence of anti-natalizumab antibodies predisposes patients to hypersensitivity reactions, rigors, nausea and other signs of allergic reactions. Progressive multifocal leukoencephalopathy (PML), a rare opportunistic infection that is often fatal, occurred in clinical trials. Baseline MRI scan should be obtained prior to therapy initiation and for any signs or symptoms suggestive of PML, therapy should be withheld. For diagnosis of PML, a gadolinium-enhanced (Gd-enhanced) MRI brain scan and when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.¹

Dose. The recommended dose of natalizumab for treatment of relapsing forms of multiple sclerosis is 300 mg intravenously every four weeks. The safety and efficacy of natalizumab beyond two years of treatment have not been established.

Pediatrics. The safety and efficacy of natalizumab have not been established in patients less than 18 years of age.

Geriatrics. Clinical trials did not include a sufficient number of patients age 65 years and over to determine if they would respond differently than younger patients.

Pregnancy. Category C. Natalizumab should be used cautiously, if at all, in pregnant patients.

Breast Feeding. It is unknown whether natalizumab is excreted in human milk. Because of the potential for adverse effects in breastfeeding infants, a decision must be made weighing the risks to an infant versus the benefits to continuing therapy in the nursing mother.

Renal Insufficiency. The safety and efficacy of natalizumab have not been established in patients with renal insufficiency.

Hepatic Insufficiency. The safety and efficacy of natalizumab have not been established in patients with hepatic insufficiency.

Stability and Reconstitution. Natalizumab 300 mg should be diluted in 100 mL 0.9% sodium chloride Injection, USP. Following dilution, the product should be used immediately or kept refrigerated at 2-8°C (36-46°F) and used within 8 hours of preparation.¹

Administration. Infuse each natalizumab dose over one hour. If the solution has been refrigerated, it should be allowed to warm to room temperature prior to infusion. Patients should be monitored closely for one hour post-infusion due to the increased incidence of infusion-related reactions.¹

Special Considerations. Patients, prescribers, infusion sites and dispensing pharmacies must be enrolled in the TOUCH™ Program. Hospitals may want to prohibit inpatient use of natalizumab due to educational restrictions imposed by the TOUCH program.

Cost. A 300 mg dose of natalizumab costs approximately \$2,731, based on AWP and excluding the cost of infusion.



TABLE 1. EXPANDED DISABILITY STATUS SCALE

0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self care functions
9.0	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

cations not FDA-approved for treatment of MS that have been used for this indication include methotrexate, cyclophosphamide, intravenous immune globulin, azathioprine and cladribine.

Natalizumab is an alternative disease-modifying agent that has been shown to slow disease progression, reduce disability and limit lesion development.^{5,6} Initial studies indicate natalizumab as a treatment option for patients with relapsing forms of MS with the potential to reduce the frequency of exacerbations.¹ Binding to alpha-4 integrins on the surface of activated T-cells,

natalizumab may have anti-inflammatory effects, potentially suppressing the inflammatory activity at the site of the lesions.⁷

Natalizumab was approved by the FDA in November 2004 and removed from the market February 2005 when the one-year interim safety analyses reported the findings of PML. Progressive multifocal leukoencephalopathy is a demyelinating disease of the central nervous system, caused by JC polyomavirus and occurs almost exclusively in immunocompromised persons. Patients in clinical trials for Crohn's disease⁸ and in clinical trials for MS in combination with interferon beta-1a⁹ were found to have died from PML. All natalizumab trials were halted at that time and all patients were evaluated to determine if PML was found in any other patients.¹⁰ An independent adjudication committee reviewed data from 3417 patients who had received natalizumab. The panel determined that the criteria to defined confirmed PML included progressive clinical disease, MRI findings consistent with PML and detectable JC virus in the cerebrospinal fluid. The three patients with PML had received 8, 29 and 37 infusions and were included in clinical trials, not open-label access. The panel found no additional cases of PML and one indeterminant case in a patient with MS (patient declined further follow-up). The panel estimated the risk of PML to be 1:1,000 patients in the study population who received an average of 17.9 months of therapy with natalizumab. The FDA approved the resumption of natalizumab marketing on June 5, 2006 under a special distribution program.¹¹

PHARMACOLOGY AND PHARMACOKINETICS

Natalizumab is a recombinant humanized (IgG4κ) murine monoclonal antibody directed against alpha-4 integrins. Natalizumab binds to the integrins on the surface of all leukocytes, except neutrophils, inhibiting alpha-4-mediated adhesion of leukocytes to their counter-receptors. By disrupting the molecular interactions, natalizumab prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. This inhibits further recruitment and inflammation of activated immune cells.¹ Although the specific mechanism by which natalizumab effects MS is unknown, it can cross the blood-brain barrier and decrease the formation of plaques that are associated with lesions.

Following the infusion of the recommended natalizumab dose, peak plasma levels occur within 45 minutes. Natalizumab displays linear pharmacokinetics in adult patients. Data regarding the metabolism of natalizumab are currently unavailable, and the safety and efficacy of patients with hepatic and/or renal insufficiency are unknown. The mean elimination half-life of natalizumab is 11 ± four days with an observed clearance of 16 ± 5 mL/hour. The distribution volume of 5.7 ± 1.9 L is consistent with plasma volume.¹ Natalizumab increases the number of circulating leukocytes (including lymphocytes, monocytes, basophils, and eosinophils) due to inhibition of movement out of the vascular space; natalizumab does not affect the number of circulating neutrophils.

CLINICAL TRIALS

Multiple Sclerosis

Miller et al assessed the effect of natalizumab on the formation of brain lesions in subjects with relapsing-remitting or relapsing secondary progressive MS over the six-month trial period.⁷

This randomized, double-blind phase II trial was conducted at 26 clinical centers in Canada, the United Kingdom and the United States. Subjects included men and women between the ages of 18 and 65 with a diagnosis of either relapsing-remitting or secondary progressive MS. To be eligible, the subjects had to have a minimum of two relapses within the previous two years, a baseline score on the EDSS between 2 and 6.5, and a minimum of three lesions on T₂-weighted magnetic resonance image (MRI) of the brain. Subjects were excluded if they received immunosuppressive or immunomodulating treatments three months prior to study enrollment or had had a relapse or received systemic corticosteroids within the previous thirty days.

In the trial, 213 subjects were randomly assigned to receive 3 mg/kg of natalizumab (n=68), 6 mg/kg of natalizumab (n=74) or placebo (n=71) by infusion every 28 days for six months. The primary endpoint of the trial was the number of new gadolinium-enhancing lesions identified during the six-month treatment period. The MRI scans were obtained during the screening phase, immediately before each treatment, and one month, three months and six months after treatment. Other clinical endpoints included the frequency of relapse, changes in EDSS scores and patient self-assessment of well-being.

Results from the trial demonstrated that both natalizumab treated-groups showed a statistically significant decrease in the formation of new gadolinium-enhancing (Gd-enhancing) lesions when compared to the placebo group. Patients in the 3 mg/kg and 6 mg/kg natalizumab groups had a 0.7 and 1.1 (p<0.001) increase in the mean number of lesions per patient respectively, compared to a mean of 9.6 new lesions per patient in the placebo group. There was no significant difference between the two natalizumab groups. In the placebo group, 27 patients had relapses, as compared to 13 patients in the 3 mg/kg group (p=0.02) and 14 in the 6 mg/kg group (p=0.02). Patient self-assessment of well-being was reported in the placebo group as "slight worsening," whereas patients in both natalizumab groups reported an "improvement." There was a statistically significant reduction in the number of persistent enhancing lesions, the number of enhancing lesions and the percentage of scans showing activity in both natalizumab groups as compared with the placebo group. Although subjects treated with natalizumab had fewer relapses compared to placebo, the results did not correlate to improvement or decline in the EDSS score of the subjects.

Dalton et al assessed the effect of natalizumab on the evolution of new Gd-enhancing lesions to T₁-hypointense lesions.¹² In this subanalysis of the trial performed by Miller et al, investigators included a subset of 78 patients who had one or more new Gd-enhancing lesions in months 1-6 of the study. The demographics of the subgroup of 78 patients were similar to those of the whole study cohort. All new Gd-enhancing lesions identified on MRI during the treatment period were assessed for conversion to a new hypointense lesion at month 12.

At month 12, the natalizumab group demonstrated a significant increase in the number of new T₁-hypointense lesions formed from new Gd-enhancing lesions during the treatment period as compared to patients treated with placebo. The mean proportion per patient of new Gd-enhancing lesions that converted to T₁-hypointense lesions at month 12 was 0.28 in the

placebo group and 0.15 in the two combined natalizumab groups (p=0.0005). The subanalysis provides evidence that treatment with natalizumab is associated with a significant reduction in the frequency with which new Gd-enhancing lesions form and in the frequency with which these lesions convert to T₁-hypointense lesions.

Two randomized, double-blind, placebo-controlled phase III trials were conducted to evaluate the safety and efficacy of natalizumab for the treatment of MS.¹ Both were designed as two year trials and excluded patients with primary progressive, secondary progressive or progressive relapsing remitting MS. Both studies enrolled patients who experienced at least one relapse during the prior year and had an EDSS score between 0 and 5. Neurologic evaluations of patients were conducted every 12 weeks and at any time that a patient was experiencing a suspected relapse. The MRI evaluations were performed annually.

The first trial evaluated the safety and efficacy of natalizumab as monotherapy.⁵ The trial, known as the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) trial, included patients with relapsing-remitting MS who had not been treated with beta interferons or glatiramer acetate for at least the previous six months. Patients were randomized to receive 300 mg of natalizumab or placebo every four weeks for up to 28 months.

Nine hundred and forty-two patients were enrolled, 315 of whom received placebo and 627 who received natalizumab. At one year, the primary endpoint was the rate of clinical relapse; the secondary endpoints were the number of new or enlarging hyperintense lesions as detected by T₂-weighted MRI, the number of lesions as detected by Gd-enhanced MRI and the proportion of disease-free patients. At two years, the primary endpoint was the cumulative probability of sustained progression of disease as defined as an increase in EDSS from baseline of 1.0 or more or an increase of 1.5 or more from baseline that is sustained for more than 12 weeks. Secondary outcome measures included new or enlarging T₂-hyperintense lesions on MRI, the number of new Gd-enhancing lesions and the rates of clinical relapse.

At two years, the cumulative probability of disease progression was 17% in the natalizumab-treated group compared to 29% in the placebo group (hazard ratio, 0.58; 95 percent confidence interval 0.43 to 0.77; p<0.001). After one year of therapy, natalizumab reduced the annualized rate of relapse to 0.26 relapse per year, as compared with 0.81 relapse per year in the placebo group (p<0.001), corresponding to a 68% relative reduction in the annualized relapse rate which was maintained at two years. For comparison, currently available therapy with interferon beta-1a or glatiramer achieve around 30% relative reduction in the annualized relapse rates.¹³ The proportion of natalizumab-treated patients who remained relapse-free was significantly higher than in the placebo-treated patients, 77% vs 56%, p<0.001, respectively at one year and 67% vs. 41%, p<0.001 at two years. There was an 83% reduction in the mean number of new or enlarging hyperintense lesion detected by T₂-weighted MRI as compared to placebo (p<0.001). Over two years, no new or enlarging lesions were detected in 57% of natalizumab-treated patients compared to 15% in the placebo group. The Gd-enhancing lesions were absent in 97% of natalizumab-treated patients compared with 72% of placebo-treated patients at two years.

Every 12 weeks during the trial, subjects were screened for natalizumab antibodies. A presence of antibody-positivity to natalizumab was associated with a substantial decrease in the effectiveness of the medication. Fifty-seven patients treated with natalizumab had detectable antibodies during the study. Persistent antibodies developed in 6% of the 57 patients (37) and in whom loss of efficacy and infusion-related adverse events were increased. The most common serious adverse events were MS relapses (6% natalizumab, 13% placebo, $p < 0.001$), cholelithiasis ($< 1\%$ in both groups), and the need for rehabilitation therapy ($< 1\%$ in both groups). Two deaths occurred in the natalizumab treatment group; neither was attributed to treatment. Infections were common in both treatment groups. Infusion reactions were reported by 24% of natalizumab-treated patients compared to 18% of placebo-treated patients ($p = 0.04$); with headache being the most common infusion-related reaction. Six percent of natalizumab-treated patients discontinued therapy due to adverse effects compared to 4% of those receiving placebo.

In the second phase III trial, the efficacy of natalizumab in combination with interferon beta-1a (Avonex[®]) was evaluated in patients with relapsing-remitting MS who had experienced one or more relapses while on interferon beta-1a therapy during the year prior to study entry.⁶ In this trial, known as the Safety and Efficacy of Natalizumab in Combination with Avonex[®] (SENTINEL) trial, patients were randomized to receive 300 mg of natalizumab or placebo every four weeks for up to 28 months or placebo; all patients continued to receive interferon beta-1a at a dose of 30 mcg weekly by intramuscular injection.

Investigators enrolled 1,171 patients, 582 of whom received placebo and 589 who received natalizumab. Primary and secondary outcome measures were identical to the AFFIRM trial.

The study was stopped one month early on February 28, 2005 due to PML concerns. Of the 1,171 patients, 86% completed the 120-week study and 14% of patients withdrew from the study (12% in natalizumab plus interferon beta-1a and 16% interferon beta-1a alone). Baseline demographics of enrollees were similar with only the duration of disease differing between groups. Estimates of the cumulative probability of sustained disability progression at two years were 23% with combination therapy and 29% with interferon beta-1a alone ($p = 0.02$). The annualized rate of relapse between groups at one year was 0.82 with interferon beta-1a alone compared to 0.38 with combination therapy ($p < 0.001$), which corresponds to a 54% reduction. This reduction was maintained at the two-year endpoint (55% reduction with combination therapy, $p < 0.001$). Fifty-four percent of patients were relapse-free at two years in the combination therapy group compared to 32% with interferon beta-1a alone. Significantly more patients had T₂-hyperintense lesions reduced with natalizumab treatment vs. interferon beta-1a alone (0.9 lesions vs. 5.4 lesions, respectively, $p < 0.001$). There was an 89% reduction in the mean number of Gd-enhancing lesions in natalizumab-treated patients compared to interferon beta-1a alone ($p < 0.001$).

Serious adverse events were reported in 18% of combination therapy and 21% of interferon beta-1a alone ($p = 0.23$), with the most serious adverse event noted as a MS relapse reported by 5% in natalizumab group compared to 9% in interferon beta-1a alone ($p = 0.002$). Two cases of PML were reported as serious

adverse events. The incidence of infection was similar; 83% in combination group and 81% in interferon beta-1a alone. Infusion reactions were also similar between groups, 24% in combination group, 20% in interferon beta-1a alone, ($p = 0.11$) with headache the most common. Study withdrawal due to adverse events was low, with 8% in natalizumab-treated patients and 7% in interferon beta-1a alone groups.

Crohn's Disease

Ghosh et al conducted a double-blind, placebo-controlled trial of natalizumab in 248 patients with moderate to severe Crohn's disease.¹⁴ Patients were enrolled at 35 study centers in Belgium, the Czech Republic, Denmark, Germany, Israel, the Netherlands, Sweden and the United Kingdom. Eligible patients included males or females at least eighteen years old who had clinical evidence of moderate-to-severe Crohn's disease, defined by a score on the Crohn's Disease Activity Index (CDAI) between 220 and 450 (scores range from 0-600, with higher scores indicating more severe disease). Subjects receiving azathioprine or mercaptopurine were required to have been on a stable dose for at least four months in order to be enrolled; however, subjects were excluded if they received methotrexate, cyclosporine or any investigational agent within three months of randomization. Additional exclusion criteria included prior treatment with any antibody agent, current daily dose of > 25 mg oral prednisolone (or equivalent dose of another corticosteroids), current use of an elemental diet or parenteral nutrition, infectious or neoplastic diseases of the bowel, bowel surgery within three months of randomization, the presence of an ostomy, symptoms due to fibrotic strictures and the clinical impression that the patient was likely to require abdominal surgery soon.

Patients were randomized to one of four treatment options. Each group received two intravenous infusions four weeks apart. The regimens included two infusions of placebo; one infusion of 3 mg/kg natalizumab, followed by one infusion of placebo; two infusions of 3 mg/kg natalizumab; or two infusions of 6 mg/kg natalizumab. The primary efficacy measure was the change in CDAI score at week six. A clinical response was defined by a decrease of at least 70 points from baseline, while a clinical remission was defined as a CDAI score of < 150 . Other outcome measures included health-related quality of life and C-reactive protein levels. All treatment groups were similar in demographic characteristics, CDAI scores, sites of disease and medication use at baseline.

Only the group of patients receiving 3 mg/kg of natalizumab for two infusions achieved significance vs. placebo for the primary outcome measure of remission at week six (44% vs. 27%, $p = 0.03$). At weeks eight and 12, significantly more patients in both groups receiving two doses of natalizumab achieved remission vs. the placebo group. Clinical response at weeks 4, 6 and 8 was achieved by significantly more patients receiving natalizumab vs. placebo; however, the response was sustained at week 12 only in the patients who had received two doses of natalizumab.

There was a significant increase in health-related quality of life scores as measured by the inflammatory bowel disease questionnaire (IBDQ) at week six in all patients receiving natalizumab. By week 12, only patients who had received two doses of natalizumab continued to have scores that were significantly higher than those

measured in the placebo group. A decrease in C-reactive protein levels was seen at week six in patients treated with two doses of natalizumab; the decrease was significant when compared to placebo ($p < 0.05$). The investigators concluded that patients treated with natalizumab at a dose of 3 mg/kg x 2 had a significantly better rate of remission vs. placebo at all evaluation points and that the 6 mg/kg doses did not produce an improved response.

Two phase III trials, the International Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-1) and Evaluation of Natalizumab as Continuous Therapy (ENACT-2) have been conducted to evaluate the safety and efficacy of natalizumab as induction and maintenance therapy in Crohn's disease.¹⁵ In the ENACT-1 trial, 905 patients with Crohn's disease were randomized to receive 300 mg of natalizumab or placebo, dosed at weeks 0, four and eight. The primary clinical endpoint of the trial was the same as that of the trial conducted by Ghosh et al.¹⁴ No patients met the clinical endpoints of response or remission by week 10. Forty-nine percent of patients in placebo group compared to 56% in the natalizumab group had a response at ten weeks ($p = 0.05$) and 30% of placebo group and 37% of natalizumab group were in remission at 10 weeks, ($p = 0.12$). A subgroup of patients with high C-reactive protein levels, those with active disease despite immunosuppressant therapy, and patients who had previously received anti-TNF alfa therapy were more likely to achieve a response or remission than other patients enrolled in the study.

The second phase III trial, ENACT-2, enrolled patients who had responded in ENACT-1.¹⁵ The 428 patients were re-randomized after 3 months to one of two treatment groups, natalizumab 300 mg or placebo, administered monthly for 12 months. The primary endpoint of the trial was maintenance of response through month 6. Of the patients re-randomized to placebo, 28% had a sustained response through month six compared to 61% randomized to natalizumab ($p < 0.001$). A sustained remission was reported by 26% of placebo-treated patients compared to 44% of natalizumab-treated patients ($p = 0.003$). Discontinuation of corticosteroids was achieved by 28% of placebo-treated patients who reported use of corticosteroids at baseline compared

to 58% of natalizumab-treated patients ($p < 0.001$)

One patient, who had been on azathioprine during the course of the study and had received five doses of natalizumab, died due to PML in this study. Acute infusion reactions occurred in 8% of placebo-treated patients and 11% of natalizumab-treated patients. Of those who tested positive for natalizumab antibodies, 45% reported infusion reactions, as compared to the 9% of patient without antibodies ($p < 0.001$).

A recent Cochrane review summarized the use of natalizumab for induction of remission in Crohn's disease.² Their conclusion was that natalizumab may be effective for induction of clinical response and remission in patients with moderate to severely active Crohn's disease. The benefit appears to be greater in a subset of patients with characteristics of active inflammation and chronically active disease, despite optimal therapy. The suggestion was to weigh the risk and benefit, given the risk of PML in this population. Identification of patients at risk for PML would help to mitigate the risk in patients with Crohn's disease. A supplemental biologics license application has been submitted to the FDA seeking marketing approval for natalizumab in the treatment of moderately to severely active Crohn's disease.¹⁶ The application includes the risk management program similar to the TOUCH program used in MS.

ADVERSE EFFECTS

The most frequently reported serious adverse reactions associated with natalizumab treatment include infections (3.2%), hypersensitivity reactions (1.1%), depression (1%) and cholelithiasis (0.8%).¹ Other reported adverse reactions include headache, fatigue and arthralgias.

Twenty-four percent of patients receiving natalizumab developed infusion-related reactions compared to 18% of placebo-treated patients.¹ Frequently reported adverse reactions that resulted in discontinuation of therapy were urticaria and associated hypersensitivity reactions. The majority of the patients that showed infusion-related reactions did so within two hours of the start of the infusion.

TABLE 2. MULTIPLE SCLEROSIS MEDICATIONS

Generic Name	Brand Name	FDA-Approved Indication	Usual Dose, Route, and Frequency	Estimated AWP Cost per Year
Interferon beta-1b	Betaseron®	Treatment of relapsing forms of MS	250 mcg subcutaneously every other day	\$23,719
Interferon beta-1a	Avonex®	Treatment of relapsing forms of MS and for a single clinical episode if MRI features consistent with MS are also present	30 mcg intramuscularly once a week	\$20,903
Glatiramer acetate	Copaxone®	Treatment of relapsing-remitting forms of MS	20 mg subcutaneously every day	\$23,513
Interferon beta-1a	Rebif®	Treatment of relapsing forms of MS	44 mcg subcutaneously three times a week	\$24,072
Natalizumab	Tysabri®	Treatment of relapsing forms of MS	300 mg intravenously every four weeks	\$32,772*

*Does not include infusion costs

Anaphylaxis, or severe hypersensitivity associated with antibodies, was seen in less than 1% of patients. In the phase III clinical trials, antibodies to natalizumab were detected in approximately 9% of patients at least once during treatment, with persistent antibody-positivity in 6%.¹ Patients who become persistently positive for the presence of natalizumab antibodies are more likely to develop infusion-related reactions. Infusion-related reactions most often associated with persistent antibody-positivity include urticaria, rigors, nausea, vomiting, headache, flushing, dizziness, pruritus, tremor, feeling cold and pyrexia. In addition, the presence of antibodies and the subsequent reduction in serum natalizumab levels is associated with a substantial decrease in efficacy with natalizumab.¹

DRUG INTERACTIONS

Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may increase the risk of infections, including PML and other opportunistic infections. The safety and efficacy of natalizumab in combination with antineoplastic, immunosuppressant, or immunomodulating agents have not been established. Concurrent use of short courses of corticosteroids was associated with an increase in infections in clinical trials; however, the increase in infections in natalizumab-treated patients who received corticosteroids was similar to the increase in placebo-treated patients who received corticosteroids. In addition, no data are available on the effects of vaccination with either attenuated or live virus vaccines.¹

COST, DOSE AND HOW SUPPLIED

Natalizumab is supplied in 300 mg/15 mL sterile, single-use vials. The AWP cost for one vial of natalizumab is \$2,731, excluding the costs of infusion. The estimated annual cost of natalizumab is \$32,772, excluding infusion costs. Table 2 provides comparative cost information for the available immunomodulating treatments for MS. The cost scenarios do not consider insurance benefits and their implications as the self-injectable medications are typically covered under the pharmacy benefit; whereas, natalizumab is clinic administered and typically covered under a medical benefit.

Because of risks associated with PML, the special distribution program known as TOUCH™ is required for all patients, prescribers, infusion staff and distribution pharmacies. The program requires patients to have a baseline brain MRI to differentiate potential future MS symptoms from PML. The risk minimization program, known as TOUCH™, is a distribution program to evaluate the risk of PML and promote informed risk-benefit decision making with patient and provider.¹¹ Those involved with natalizumab are educated about the risks of PML, including prescribers, pharmacists, infusion center staff and patients. Prescribers, infusion centers, pharmacies and patients must be registered in the TOUCH™ program in order to prescribe, administer, dispense and receive natalizumab. Once enrolled in the program and prior to infusing the medication, infusion staff must provide the patient with a Medication Guide and complete a Pre-Infusion Patient Checklist, which upon completion of the infusion, must be faxed to the manufacturer. Pharmacies that dispense na-

talizumab must dispense the medication only to authorized infusion sites and maintain an inventory tracking log for every dose of natalizumab. The log must be kept for at least five years from the final date of entry. Prescribers must evaluate the patient three and six months after the initial infusion and every six months thereafter as long as natalizumab therapy continues. The data collected will be reported to the FDA to evaluate the effectiveness of the risk management program.

CONCLUSION

Natalizumab was approved by the FDA in November 2004 under the Accelerated Priority Review process on the basis of the preliminary results of two on-going phase III clinical trials. When the requested preliminary results were presented, the cases of PML were found. Because of the therapeutic niche that natalizumab therapy offers, and after the development of a risk management program, the medication was re-released onto the market. Natalizumab decreases the annualized relapse rate by 68% as compared to other currently available therapy using interferon beta-1 or glatiramer, which achieve around 30%. The relapses lead to significant morbidity and mortality. Natalizumab has shown efficacy for the treatment of Crohn's disease and is currently under FDA review for expanded indications. Hospitals may want to prohibit the use of natalizumab for inpatients because of the educational restrictions imposed by the TOUCH™ program. In addition, guidelines for use may be helpful to provide criteria for use for practitioners and define the place in therapy. ●

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