

# Natalizumab in the treatment of multiple sclerosis

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**Abstract:** Natalizumab is a monoclonal antibody, representing a new class of medication for treating relapsing multiple sclerosis (MS). Conventional treatments include interferons, glatiramer acetate and chemotherapies such as mitoxantrone and cyclophosphamide. These therapies offer only modest clinical benefits and are commonly not tolerated due to side effects. Natalizumab has been proven in large-scale, blinded, randomized, controlled trials to have an exceptional effect on preventing relapses, decreasing the risk of sustained progression of disability, and increasing the rate of disease-free patients over a 24-month period compared to placebo. These trials led to the speedy approval of natalizumab for treating relapsing MS, but its use was halted a few months after its induction after several cases of progressive multifocal leukoencephalopathy (PML), a fatal demyelinating disease affecting the central nervous system. After a long deliberation by an FDA advisory panel and strong support from the MS community, natalizumab was reapproved with stringent restrictions including patient, provider and site registration. Natalizumab is now considered second-line therapy for patients who have failed first-line agents such as interferon or glatiramer acetate. As little is known about additional risk factors for PML and other potential infections, patients and providers must work together to carefully decide if potential benefits outweigh these rare but potentially devastating complications.

**Keywords:** natalizumab, multiple sclerosis, progressive multifocal leukoencephalopathy

## Introduction

Multiple sclerosis (MS) is a chronic, progressive, irreversible, inflammatory disease involving the central nervous system, typically affecting white matter in the brain as well as the spinal cord. It is believed that MS is an autoimmune disease in which auto-reactive T-cells migrate across the blood-brain barrier and mediate an immune response against the central neurons. Specifically, the myelin sheath that covers the nerve's axon and acts as an insulator is directly affected leading to demyelination of the nerve cell. Recent data suggest that direct axonal damage also occurs. This destruction of myelin and central neurons leads to conduction abnormalities, which can affect many different areas of the body. Patients suffering from MS may experience a variety of symptoms including fatigue, changes in sensation, locomotion, and cognition, loss of bladder or bowel control and many other troublesome effects. The diagnosis and monitoring of patients relies on excluding other causes and is largely based on clinical examination.<sup>1</sup> However, cranial and spinal magnetic resonance imaging (MRI) scans provide practitioners with objective evidence, as lesions are often observed. Several subtypes of MS have been defined; however, most patients are initially diagnosed with

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relapsing-remitting MS. This type is characterized by varying lengths of symptom-free periods interrupted by relapses, or attacks, marking new disease activity. A relapse is defined as a worsening of symptoms, peaking within 24 to 48 hours that usually lasts several weeks and may or may not resolve completely. Objectively, during an acute episode, lesions may be observed on T<sub>1</sub>-weighted MRI images after gadolinium dye administration, which represent inflammation and acutely active demyelination. Performing a T<sub>1</sub>-weighted MRI with contrast is the standard when searching for new or newly active lesions in MS. Detecting and monitoring chronic damage is also performed using MRI scans. Lesions observed when performing T<sub>2</sub>-weighted MRI scans usually represent chronic and generally irreversible demyelination.

The therapeutic goals of treating MS are to reduce the frequency, severity and duration of relapses, to slow the progression of disability and to prevent sub-clinical activity and progression on MRI. It is thought that decreasing the number of acute, inflammatory relapses may lead to less long-term neurodegeneration and disability. Conventional treatments include interferons, glatiramer acetate and chemotherapies such as mitoxantrone and cyclophosphamide, among others. These therapies offer only modest benefits and are commonly not tolerated due to side effects such as flu-like symptoms, injection site reactions, depression, thyroid abnormalities, hepatic enzyme abnormalities, infections or even left ventricular dysfunction and hemorrhagic cystitis in the cases of mitoxantrone and cyclophosphamide, respectively.<sup>2</sup> The search for safer and more effective options continues, with investigations examining alternate targets and developing medications with unique mechanisms of action.

Natalizumab (Tysabri®; Biogen Idec, Cambridge, MA, USA) is a monoclonal antibody, representing a new class of medication for treating MS. Natalizumab also has an Food and Drug Administration (FDA)-approved indication for treating moderately to severely active Crohn's disease in patients who are nonresponsive or are unable to tolerate conventional therapies, but this paper will review the available efficacy and safety data on natalizumab for treating MS.

## What is natalizumab?

Natalizumab is a recombinant humanized IgG4κ monoclonal antibody produced in murine myeloma cells. Specific proteins, called integrins, exist on the surface of all leukocytes, except neutrophils. Integrin binding to a counter-receptor located on endothelium is required for the passage of leukocytes across the endothelium, into inflamed parenchymal tissue. Natalizumab binds to the α<sub>4</sub>-subunit of α<sub>4</sub>β<sub>1</sub> and α<sub>4</sub>β<sub>7</sub>

integrins on the surface of leukocytes and inhibits their adhesion to endothelial receptors, specifically vascular cell adhesion molecule-1 on activated vascular endothelium and mucosal addressin cell adhesion molecule-1 present on vascular endothelial cells of the gastrointestinal tract. Without this binding, leukocytes are unable to transmigrate across endothelium into inflamed parenchymal tissue. It is believed that in MS, by inhibiting this transmigration of specifically, T-lymphocytes into the brain, the autoimmune attack and subsequent inflammatory response to the central neurons is greatly reduced.<sup>3</sup>

Natalizumab is available as a 20 mg/mL solution that must be diluted before administration. The standard dose is 300 mg (one 15 mL vial), diluted in 100 mL of 0.9% sodium chloride and infused intravenously over one hour every 4 weeks.<sup>3</sup>

## Efficacy data

Natalizumab has been studied in two large, randomized controlled trials. Polman et al randomized 942 patients with relapsing remitting MS to natalizumab 300 mg or placebo iv every 4 weeks in a 2:1 ratio for up to 116 weeks in the AFFIRM trial.<sup>4</sup> The AFFIRM trial took place in 99 clinical centers throughout Europe, North America, Australia, and New Zealand beginning on November 6, 2001. The primary outcomes were rate of clinical relapse at 1 year and the cumulative probability of sustained progression of disability at 2 years. The cumulative probability of sustained progression of disability was measured using the Expanded Disability Status Scale (EDSS). The EDSS is a rating system that is frequently used for classifying and monitoring the extent of disability in patients with MS.<sup>5</sup> The scale ranges from 0, which is a normal neurological examination, to 10, which is death from MS. The investigators defined sustained progression of disability as an increase of 1 or more on the EDSS from a baseline score of 1 or more or an increase of 1.5 or more from a baseline score of 0 that was sustained for 12 weeks. Secondary outcomes were the presence of sub-clinical MRI data indicative of active disease or disease progression at the end of the 1- and 2-year time periods. Baseline characteristics were similar between the two groups with 70% of the patients being female. The mean age of the whole group was 36 years with mean disease duration of 5 years. The patients had relatively active disease; averaging 1.52 relapses within the previous year, but had minimal disability with a mean EDSS score of 2.3.

The results of the AFFIRM trial demonstrated a large benefit for patients taking natalizumab. At 2 years,

the cumulative probability of progression was 17% for natalizumab and 29% for placebo ( $P < 0.001$ ). This represents a 42% relative decrease in the risk of sustained progression of disability for patients taking natalizumab for 2 years. The effect on relapse rate at 1 year was also significant. The mean annualized relapse rate was reduced from 1.53 to 0.26 relapses per year in the natalizumab group compared to a reduction from 1.5 to 0.81 relapses per year in the placebo group. This represents a 68% relative reduction in annualized relapse rate for natalizumab, which was maintained throughout the second year of follow-up ( $P < 0.001$ ).

For the secondary, sub-clinical outcomes, natalizumab also showed good effects. The mean number of new or enlarging hyperintense lesions detected on  $T_2$ -weighted MRI, was reduced by 83% in natalizumab treated patients compared to placebo ( $P < 0.001$ ). Furthermore, evidence of acutely active disease, represented by the appearance of gadolinium-enhancing lesions on  $T_1$ -weighted MRI, was reduced by 92% for natalizumab patients compared to placebo ( $P < 0.001$ ).

The SENTINEL trial was the second study examining natalizumab, but did so as combination therapy.<sup>6</sup> This trial randomized 1171 patients with relapsing remitting MS to natalizumab 300 mg or placebo iv every 4 weeks in a 1:1 ratio in addition to interferon  $\beta$ -1a (Avonex, Biogen Idec) 30  $\mu$ g intramuscularly once weekly for up to 116 weeks. The SENTINEL trial took place in 124 clinical centers throughout Europe and the United States beginning on January 14, 2002. The primary outcomes were the same as those used in the AFFIRM trial; the rate of clinical relapse at 1 year and the cumulative probability of sustained progression of disability at 2 years. Secondary outcomes were also similar, including various sub-clinical MRI outcomes.

The combination of natalizumab with interferon  $\beta$ -1a proved to be considerably more effective than interferon  $\beta$ -1a alone. The risk of disability progression over a 2-year period was reduced by 24% with combination therapy compared to interferon  $\beta$ -1a alone ( $P = 0.02$ ). This effect was not as large as that reported in the AFFIRM trial, which is expected since all patients in the SENTINEL trial were receiving some therapy, but this benefit is substantial nonetheless. The annualized relapse rate was reduced by 54% with natalizumab plus interferon  $\beta$ -1a compared to interferon  $\beta$ -1a alone for the first year, which was maintained throughout the second year of follow-up ( $P < 0.001$ ).

The addition of natalizumab to interferon  $\beta$ -1a also had dramatic effects on the predefined MRI outcomes, which

were comparable to the AFFIRM trial. The effect on new or enlarging hyperintense lesions was exactly the same as was seen in the AFFIRM study with an 83% reduction observed with combination therapy compared to interferon  $\beta$ -1a alone ( $P < 0.001$ ). The appearance of gadolinium-enhancing lesions on  $T_1$ -weighted MRI was reduced by 89% for combination therapy compared to interferon  $\beta$ -1a alone ( $P < 0.001$ ).

A closer look at data from the AFFIRM trial presented at the World Congress on Treatment and Research in Multiple Sclerosis in Montreal in 2008 continued to show positive results of treatment with natalizumab.<sup>7</sup> Investigators were interested in determining how many of the patients who received natalizumab were disease free over the 24 month period compared to placebo. After 2 years of therapy, the proportion of patients who were free of MRI lesion activity, defined as no gadolinium-enhancing lesions and no new or enlarging  $T_2$ -hyperintense lesions, was 57.7% for natalizumab versus 14.2% for placebo ( $P < 0.0001$ ). Furthermore, the proportion of patients who were free of MRI lesion activity *and* free of clinical activity, defined as no new lesions on MRI as defined above *and* no relapse or progression of disability was 36.7% for natalizumab versus 7.2% for placebo ( $P < 0.0001$ ). These data are encouraging since the baseline level of disease activity was relatively high with 90% of the patients having experienced one to two relapses during the year prior to randomization.

Though the clinical efficacy of natalizumab was clearly demonstrated in the AFFIRM and SENTINEL trials, unfortunately, the SENTINEL trial was stopped approximately one month early on February 28, 2005, because of two reports of progressive multifocal leukoencephalopathy and natalizumab was voluntarily, but temporarily, withdrawn from the market by the manufacturer.

## Progressive multifocal leukoencephalopathy (PML)

PML is a fatal demyelinating disease affecting the central nervous system of individuals who are immunosuppressed.<sup>8</sup> It is caused by the reactivation of the JC virus, a polyomavirus against which approximately 80% of the adult population has antibodies.<sup>9</sup> As an opportunistic infection, it is commonly observed in patients with acquired immunodeficiency syndrome at a rate of about 4%.<sup>10</sup> Other risk factors include lympho- and myeloproliferative disorders, solid tumors, congenital immunodeficiency disorders, and the use of chronic corticosteroids and chemotherapy.<sup>11</sup> Though corticosteroids and chemotherapy are commonly used to treat MS, PML had

not been observed among the MS population prior to the use of natalizumab.

Presenting symptoms vary widely, but the most commonly observed are limb weakness, cognitive deficits, speech and visual deficits, incoordination, seizures, and paralysis.<sup>12</sup> Unfortunately, other than reconstitution of the immune system, there is currently no effective treatment for PML, and the mortality rate remains as high as 50%.<sup>8</sup>

The first patient to develop PML in the SENTINEL trial was a 46-year-old female who had received 37 doses of natalizumab beginning in April 2002 through January 2005 as add on therapy to interferon  $\beta$ -1a.<sup>13</sup> In November 2004 she reported new problems with hand-eye coordination and problems with her speech. She was treated with corticosteroids but her condition worsened, as she developed right-sided hemiparesis and worsening nonfluent aphasia. She eventually became nonresponsive and further work-up for various viral, bacterial and fungal etiologies was negative. At this time, the treating neurologist suspected PML and a cerebrospinal fluid (CSF) sample was sent out for JC virus PCR testing, which returned positive. The patient subsequently died on February 24, 2005.

The second patient was a 45-year-old male who had received 28 doses of natalizumab from October 2002 through December 2004 as add on therapy to interferon  $\beta$ -1a.<sup>14</sup> During a routine study visit in November 2004, the patient's physician observed uncharacteristic, inappropriate behavior. The patient subsequently reported to family members that he was having difficulty with attention and concentration. Over the following weeks, cognitive impairment developed along with mild left-sided hemiparesis and dysarthria. In February 2005, serum samples sent for JC virus PCR testing returned positive, as did *in situ* hybridization testing from brain biopsy samples. Despite receiving a course of intravenous cidofovir and a course of intravenous immune globulin, his condition continued to worsen, now with left-sided hemiplegia, anesthesia and neglect accompanied by right-sided hemiparesis and apraxia, nonfluent aphasia, severe cognitive impairment, and delirium. Intravenous cytarabine was initiated in early April, which caused pancytopenia that was treated successfully. Two weeks later, the patient started to improve. A second course of cytarabine was administered 4 weeks after the first course and by the end of May, the patient was starting to be able to walk and talk, but was left with disabling ataxia, cognitive impairment, mild neglect, and mild left hemiparesis.

Though the administration of cytarabine to this particular patient was followed by dramatic improvement, this is an area

that requires further research as one randomized, controlled trial failed to prove that this agent was effective in treating HIV-infected patients with PML.<sup>15</sup> As the authors of this case report point out, if the beneficial outcome seen in their patient was attributable to the administration of cytarabine, this may be due to the significant break-down of this patient's blood-brain barrier, as was seen on MRI, allowing the drug to better penetrate into the CNS. This permeability of the blood-brain barrier was a characteristic not shared by the patients treated in the HIV-infected study.

One must also note that reconstitution of the immune system is considered the only truly effective treatment for PML, which in HIV-infected individuals consists of administering highly active antiretroviral therapy.<sup>8</sup> In cases involving natalizumab induced PML, this may require allowing significant time for the biological effects of the drug to wear off, which has been shown to be approximately 3 months.<sup>16</sup> In the previously discussed case, the patient did experience a central nervous system inflammatory reaction 3 months after his last dose of natalizumab, which represents a reconstitution of the immune system and offers another reason for his overall improvement.

Around the same time that these cases were being reported, a third case of PML was diagnosed in a 60-year-old male receiving natalizumab in a clinical trial for treating Crohn's disease.<sup>17</sup> Shortly before beginning treatment with natalizumab, he received treatment with infliximab. After starting natalizumab treatment, he was concurrently receiving azathioprine for a short period of time. He died in December 2003 after receiving a total of eight doses of natalizumab.

These case reports resulted in the withdrawal of natalizumab from the market in February 2005, which marked the beginning of a lengthy investigation by an FDA advisory panel constructed to weigh the risks against the benefits of using natalizumab. After 16 months and dozens of testimonies from patients<sup>18</sup> requesting that natalizumab be allowed back on the market, in June 2006 the FDA approved the return of the drug, but not without restrictions.<sup>3</sup> The first restriction is that natalizumab is only to be used as monotherapy, since the original cases of PML were only seen in those patients who were receiving combination therapy. Secondly, natalizumab is only to be used as second-line therapy when patients have failed first-line agents. And lastly, all patients receiving natalizumab have to be enrolled in a registry. The manufacturer developed the Tysabri® Outreach: Unified Commitment to Health (TOUCH™) Prescribing Program. The TOUCH™ Prescribing Program is a registry in which patients, prescribers, pharmacies and infusion sites are registered.



It was designed to promote informed benefit-risk decision making, identify patients who may not be candidates for natalizumab therapy (ie immunosuppressed patients), and to monitor for and track the incidence of PML with natalizumab therapy. Outside of North America, a similar registry exists called the Tysabri® Global Observational Program in Safety (TYGRIS).

Unfortunately, the story on PML with natalizumab therapy doesn't end there. Since its return to the market in June of 2006, about 52,000 patients have received natalizumab world-wide. Since that time, there have been an additional 10 cases of PML reported in patients receiving natalizumab.<sup>19</sup> According to an emailed letter from the manufacturer, (July 9, 2009) the six females and four males ranging from 27 to 59 years old, received natalizumab as monotherapy for 12 to 33 months. Nine of the patients had received prior treatment with other disease-modifying agents, including interferons, glatiramer acetate, mitoxantrone, intravenous immune globulin G, and azathioprine. One of the patients did not survive, while the others are left with varying degrees of neurological deficit ranging from being bedridden and requiring ventilatory support to slight hemiparesis and requiring ambulatory aids. These postmarketing cases have brought to light a couple of important concerns. Firstly, none of these patients were being treated with combination therapy. Therefore, practitioners must now assume that PML is possible when treating patients with natalizumab as monotherapy. Secondly, and perhaps more importantly, one of the patients was treatment naïve. These factors now make it clear that anyone receiving natalizumab therapy may be at risk for developing PML, regardless of past or current therapies.

Although it is difficult to pinpoint the incidence of PML in natalizumab treated patients, it does appear that it is far less than the originally stated 1 per 1000 patients;<sup>20</sup> current estimations are closer to 3 per 10,000 patients treated for 2 years or more.<sup>19</sup> Nonetheless, it is important to remember that this potentially fatal infection has not been observed in the MS population prior to the introduction of natalizumab. Cyclophosphamide drew great attention in the MS community with the publication of a study reporting the stabilization of progressive MS patients after receiving high-dose cyclophosphamide infusions in 1983.<sup>21</sup> Similarly, mitoxantrone was shown to stabilize rapidly progressing MS patients in a study published in 1992.<sup>22</sup> With over 25 years of experience with potent immunosuppressants, PML has never been observed in this population. Further research is imperative to establish a mechanism for natalizumab in causing PML

and more importantly, to establish risk factors for identifying those at higher risk.

Optimistic data have emerged regarding possible treatments for patients receiving natalizumab who develop PML. As previously mentioned, reconstitution of the immune system appears to be the most promising approach to treating PML.<sup>8</sup> Plasma exchange or immunoadsorption may offer some benefit for accelerating the clearance of natalizumab and thus restoring the function of leukocytes, which may prove vital for improving survival in natalizumab-induced PML cases. One such study enrolled 12 MS patients receiving natalizumab who underwent three plasma exchange sessions over 5 or 8 days after stopping natalizumab infusions. The investigators were able to reduce serum natalizumab concentrations in these patients by a mean of 92% after 1 week.<sup>23</sup> With few other options for treating these patients, these methods are often employed. All ten of the post-marketing patients who developed PML underwent either plasma exchange or immunoadsorption.

In addition, 5 of the patients were started on mefloquine. This antimalarial medication has been shown to inhibit JC virus replication in vitro.<sup>24</sup> Furthermore, 2 of the patients were treated with mirtazapine. The serotonergic receptor, 5-HT<sub>2a</sub> has been shown to be a cellular receptor for the JC virus on human glial cells. In vitro, 5-HT<sub>2a</sub> receptor antagonists inhibited JC virus infection.<sup>25</sup> Mirtazapine is a 5-HT<sub>2a</sub> receptor antagonist that has been used to treat HIV-infected patients with PML.<sup>26</sup> Data supporting the use of these agents are limited, but these therapies may be considered for treating natalizumab-induced PML.

## Other infections

In clinical trials, natalizumab did not appear to increase the overall risk of infection when compared to placebo. Common infections, which were deemed mild to moderate, included nasopharyngitis, influenza, upper respiratory tract infections, urinary tract infections, and pharyngitis.<sup>4</sup> Results were similar when natalizumab was added to interferon  $\beta$ -1a with the exception of pharyngitis. Seven percent of the patients treated with this combination developed pharyngitis compared to only 4% of the patients who received interferon  $\beta$ -1a alone ( $P \leq 0.05$ ).<sup>6</sup> Of interest, one case of cryptosporidial gastroenteritis, an opportunistic infection, was reported in a patient receiving natalizumab.<sup>4</sup> No other opportunistic infections were seen in clinical trials. However, at the FDA hearing for reapproval in 2006, several cases of opportunistic infections occurring in patients being treated for Crohn's disease with natalizumab were presented, including

a fatal case of *Pneumocystis carinii* pneumonia, one fatal case of pulmonary aspergillosis, a case of mycobacterium avium intracellulare complex pneumonia, and a case of *Burkholderia cepacia* pneumonia.<sup>27</sup> Reactivation of herpes virus is also now a concern as one fatal case of herpes virus encephalitis and one nonfatal case of herpes virus meningitis have now been reported in patients receiving natalizumab.<sup>28</sup> In addition, data now exist showing that a larger percentage of patients receiving natalizumab have detectable varicella zoster virus DNA in their blood and saliva compared to subjects not receiving natalizumab. Furthermore, patients receiving natalizumab were three times more likely to have a herpes labialis eruption than untreated subjects.<sup>29</sup> At this stage, these case reports are noteworthy but there is insufficient evidence to suggest a definitive relationship to treatment with natalizumab. However, patients should continue to be closely monitored for any evidence of opportunistic infections and herpes reactivation. One question that may warrant further investigation is the use of the varicella zoster vaccine in patients scheduled to receive natalizumab. At this time, the vaccine is only indicated for individuals who are greater than 60 years old.<sup>30</sup>

## Abnormal laboratory values

In clinical trials, the incidence of elevated hepatic enzymes was no different between natalizumab and placebo or control.<sup>4,6</sup> However, in February 2008, the company updated the package insert to include hepatotoxicity as a warning for using natalizumab. After receiving several reports of clinically significant liver injury in patients having received natalizumab and evidence in some patients upon rechallenge, the company now recommends monitoring patients for elevations in hepatic transaminases and total bilirubin as well as advising patients to watch for signs and symptoms of liver injury.<sup>3</sup>

The only other notable abnormal lab values from clinical trials were increased plasma concentrations of lymphocytes, monocytes, eosinophils, and basophils.<sup>4,6</sup> This is an expected observation, since the mechanism of action of the medication is the prevention of cellular transmigration across endothelial tissue, in essence sequestering these cells within the vasculature. Notably, these effects are reversible, typically returning to baseline within 16 weeks after the last dose.

## Immunogenicity

The development of neutralizing antibodies has long been a concern with MS therapies, ever since the first approved medication for treating MS, interferon  $\beta$ -1b, was

approved in 1993.<sup>31</sup> Though it is generally thought that the development of these antibodies renders interferons useless, 15 years later there is still controversy surrounding how to interpret these findings. There is also debate on how to monitor for and manage patients who develop antibodies.<sup>32</sup> This situation is not unlike that of natalizumab induced neutralizing antibodies. In the monotherapy treated patients, 9% of the patients receiving natalizumab developed neutralizing antibodies at some time during the study. However, some patients only develop transient antibody production, which is thought not to affect the effectiveness of the medication. Overall, 6% of the patients developed persistent antibodies, which was defined as detectable titers at least twice, separated by at least 42 days. Interestingly, these patients not only had loss of efficacy, but were more likely to experience infusion-related adverse events.<sup>4</sup> Similar findings were observed when natalizumab was combined with interferon  $\beta$ -1a. Twelve percent of the patients receiving natalizumab and interferon  $\beta$ -1a developed antibodies at some time during the trial, whereas 6% displayed persistent antibody production to natalizumab with similar clinical outcomes.<sup>6</sup>

In clinical practice, the utility of checking for neutralizing antibodies remains uncertain. If antibodies are present, this does not necessarily mean that the patient will remain producing antibodies and, therefore, they must be rechecked several weeks later. This could potentially delay a change in therapy that may be warranted if the second test reveals antibodies as well. Overall, it remains the case that it is best to treat patients clinically. However, one scenario in which antibodies should be measured is if a patient develops a reaction after receiving natalizumab, and the practitioner decides that treating through the reaction is an option. Treating through a reaction should not be done if a patient is producing neutralizing antibodies as this represents a true allergic type response to the medication.

## Allergic reactions

Infusion reactions were defined as any event that occurred within two hours of the beginning of the infusion. In trials, 24% of natalizumab infused patients experienced infusion reactions compared to 18% of the placebo patients ( $P = 0.04$ ). The most common reaction was headache, but also included dizziness, fatigue, urticaria, pruritus, and rigors. Most reactions were treated symptomatically and did not lead to discontinuation of the drug. Four percent of patients receiving natalizumab experienced hypersensitivity reactions, whereas no patients receiving placebo did. A hypersensitivity reaction was deemed as such by

the investigator based on clinical judgment and severity. Hypersensitivity reactions were reported as urticaria, allergic dermatitis, and anaphylactic or anaphylactoid reactions. Overall, eight of the reactions (1.3%) were considered serious reactions and five of them (0.8%) were considered anaphylactic or anaphylactoid reactions. All of the patients recovered without sequelae.<sup>3,4</sup> Interestingly, there is no official recommendation by the company for premedicating patients before receiving natalizumab. As is recommended with other monoclonal antibodies,<sup>33,34</sup> it makes sense that premedication may be considered for some patients at the prescriber's discretion. The manufacturer does require patients to remain at the infusion site for 1 hour after the completion of their infusion for observation.<sup>3</sup>

Although most allergic reactions have been known to occur within two hours after the initiation of natalizumab infusions, it is now clear that delayed allergic reactions may occur as well. One such case involved a 23-year-old male patient with MS who presented to his physician 6 days after receiving his second dose of natalizumab, claiming eight hours after the infusion he collapsed and developed a fever of 39.4 °C, which he initially dismissed as a possible viral infection. Three days later he developed an itchy rash on his thighs and chest followed by a swollen lower lip 3 days after that. After ruling out other causes, the authors attributed this delayed reaction to natalizumab. The patient also tested positive for neutralizing antibodies to natalizumab that persisted for 8 weeks following discontinuation of the drug.<sup>35</sup>

It is clear that regardless of when the reaction occurs, the proper action to take if neutralizing antibodies are present is to discontinue natalizumab therapy. The decision becomes less clear when a patient has a reaction that could potentially be prevented or treated but without producing antibodies. One such paper describes two patients, in whom delayed systemic reactions occurred, consisting of arthralgias, headache, fever, neck stiffness, general malaise, tremor, and vertigo, beginning several hours to days after the first infusion. Neither of the patients tested positive for neutralizing antibodies so they were continued on natalizumab therapy with subsequent infusions preceded by intravenous corticosteroids, histamine antagonists, and a reduced natalizumab infusion rate. In both cases the reactions diminished over time to a tolerable level and in one patient the reaction completely disappeared.<sup>36</sup>

A third case exists describing a very late allergic reaction that developed after 12 natalizumab infusions. This 46-year-old male developed a mild arthralgia and headache 2 days after his twelfth infusion that worsened over the course of the following week. A painful, erythematous, total body

rash developed 8 days after the infusion, for which he was admitted to the hospital. Further work-up ruled out other causes, and although neutralizing antibodies to natalizumab were negative, he was deemed to have had a delayed allergic reaction to natalizumab. The patient went on to receive three more doses without premedication and without incident.<sup>37</sup> These cases may offer some guidance for treating patients who develop mild to moderate reactions to natalizumab without neutralizing antibody production.

## Malignancy

In clinical trials, malignancy was rare with natalizumab therapy, occurring less than 1% of the time, which was not significant compared with placebo. Malignancies that were reported included breast cancer, cervical cancer, basal cell carcinoma and one fatal case of malignant melanoma.<sup>4,6</sup> Since its reapproval, there have been additional case reports of melanoma in patients receiving natalizumab. The first patient was a 46-year-old woman who only received one dose of natalizumab before she noticed a mole located on her shoulder that began to rapidly change. It was diagnosed as melanoma that had metastasized to regional lymph nodes. The second patient was a 45-year-old woman with a long-standing history of an ocular nevus that developed into ocular melanoma after "several" (actual number of doses not reported) doses of natalizumab.<sup>38</sup> Though these are only case reports, patients must be aware of this possibility and should be instructed to seek dermatologic evaluation should they have concerns about changes in skin lesions. It may also be prudent for patients to be examined by dermatology prior to initiating natalizumab therapy.

A third case report exists of a patient who developed primary central nervous system lymphoma (PCNSL).<sup>39</sup> PCNSL is a rare variant of extranodal non-Hodgkin lymphoma, primarily affecting patients in the seventh and eighth decades of life, for which immunosuppression is considered the major risk factor.<sup>40</sup> This 40-year-old male patient received 21 doses of natalizumab as monotherapy for relapsing-remitting MS. Prior therapies included about 8 months of high-dose interferon therapy, followed by about 6 months of azathioprine therapy; neither of which were associated with significant benefit. Following a four week wash out period, he was started on natalizumab. His response was less than optimal; however natalizumab was continued until an MRI scan revealed a new large gadolinium-enhancing lesion associated with mass effect and a midline shift. A brain biopsy, along with extensive diagnostic work-up to rule out extracerebral sources established the diagnoses of PCNSL.

The natalizumab therapy was discontinued and the patient underwent plasmapheresis, to accelerate the natalizumab clearance, followed by high-dose methotrexate therapy to treat the PCNSL.

MS is not known to be a risk factor for developing PCNSL. Since this patient was not significantly immunosuppressed, the association of natalizumab causing PCNSL can not be ruled. However, the authors also note that the potential role of azathioprine cannot be excluded either, as historically, there is a clear association between azathioprine and PCNSL.

## Other adverse events

As monotherapy, other than allergic reactions, the only other adverse event that was reported more frequently and with statistical significance with natalizumab in comparison to placebo was fatigue. Twenty-seven percent of patients on natalizumab reported fatigue compared to 21% receiving placebo ( $P = 0.048$ ).<sup>4</sup> The actual clinical significance of this finding is unknown; however, it is feasible that this may inhibit some patients from tolerating the treatment. This finding was not seen when natalizumab was combined with interferon  $\beta$ -1a. However, anxiety, sinus congestion, and peripheral edema were seen more commonly in the combination group than in those who received interferon  $\beta$ -1a alone.<sup>6</sup> Again, the clinical significance of these events is unclear, and in some respects, less relevant as combination is to be avoided regardless.

## Is there a rebound phenomenon?

In the AFFIRM trial, a subgroup analysis of 51 patients did not show an excessive rebound effect when patients stopped medication. Although their disease activity returned to baseline after discontinuation of natalizumab, their disease was no worse than patients receiving placebo.<sup>4</sup> These data are challenged, however, by a smaller analysis of 21 patients from a single trial site, enrolled in either the AFFIRM or the SENTINEL trial.<sup>41</sup> The suspension of natalizumab provided the opportunity for these investigators to assess rebound effects demonstrated by both clinical and MRI parameters. As a clinical outcome, no rebound effect was observed with the pretreatment annualized relapse rate being 1.15 and the post withdrawal annualized relapse rate being 0.73. However, on MRI, they found a significant increase in the development of new and enlarging  $T_2$ -lesions in patients during the 15 months following natalizumab treatment compared to their lesion load during the 7 to 54 month pretreatment period; median annualized number of new and enlarging  $T_2$ -lesions equals 10.32 and 3.43, respectively ( $P = 0.014$ ). Interestingly, this

disparity was primarily driven by patients who had a short exposure to natalizumab, ranging from one to eight infusions with a median of two infusions. Though these effects are marked, until these data are replicated in larger samples of patients, it is difficult to draw definitive conclusions. It is probable, however, that patients who receive at least 6 months of therapy are at less risk of excessive rebound effects should they have to discontinue therapy.

Another study found different results. The investigators enrolled 21 patients originally being treated in the AFFIRM or the SENTINEL trial, and followed them for 14 months after stopping natalizumab.<sup>42</sup> To assess for the presence of any rebound effects, they monitored annual relapse rate, neurologic disease progression assessed by the EDSS, disease surrogate markers on MRI, and cellular and humoral immune markers in peripheral blood and CSF. Decreased lymphocyte cell numbers returned to normal after 14 weeks post-natalizumab, but they did not observe any clinical, radiographic, or immunologic rebound phenomenon. These patients received a median of 30 doses (range, 1 to 41).<sup>43</sup> These data support the hypothesis that patients who are treated for extended periods of time with natalizumab are unlikely to be at risk for a rebound phenomenon should they need to discontinue therapy.

## Summary

Conventional therapies for treating MS offer modest efficacy and are not without considerable adverse effects. In this disabling disease, researchers struggle with developing novel agents aimed at halting its progressive nature, while maintaining an acceptable adverse event profile. Natalizumab has been proven in large-scale, blinded, randomized, controlled trials to have good effect on preventing relapses and decreasing the risk of sustained progression of disability in patients with relapsing MS. Furthermore, it has been shown to increase the rate of disease-free patients over a 24-month period compared to placebo. The rare occurrence of PML with natalizumab initially appeared to have devastating effects on the future of this medication. However, overwhelming support by the MS community along with a careful risk-benefit analysis won over the concerns of the FDA, allowing natalizumab to become reapproved for use as monotherapy in treating relapsing MS. Along with enrollment in the TOUCH Prescribing Program, natalizumab should only be considered for those patients with definite relapsing MS, patients who have not responded to or tolerated first line therapies, and patients who are not immunosuppressed nor have received immunosuppressive



therapies within the last 3 months. These requirements aim to reduce the risk of developing PML and to catch potential cases of PML as early as possible. Nonetheless, until more is known about additional risk factors, patients must be informed that individual susceptibility is not known and, therefore, clear risk assessment is difficult at this time. Likewise, with postmarketing case reports of serious herpes reactivation, early identification of such events is imperative. Continued analysis will clarify the true safety profile of natalizumab and better define its role in the treatment of multiple sclerosis.

## Disclosures

The author declares no conflicts of interest.

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