

**REGIONAL DRUG AND THERAPEUTICS CENTRE  
(NEWCASTLE)**

**THE USE OF NATALIZUMAB IN THE  
MANAGEMENT OF MULTIPLE SCLEROSIS**

**Wolfson Unit  
Claremont Place  
Newcastle upon Tyne  
NE2 4HH**

**March 2007**





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## ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre (Newcastle). The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rest solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

<b>Subject</b>	<b>Date issued</b>
The use of Entecavir in the management of chronic hepatitis B infection	March 2007
Palonosetron for the prevention of nausea and vomiting associated with cancer chemotherapy	March 2007
Alemtuzumab in the management of chronic lymphocytic leukaemia	March 2007
Omalizumab in the management of severe, persistent, allergic asthma	June 2006
Bortezomib second-line in the management of multiple myeloma	March 2006
Adjuvant docetaxel or paclitaxel in the management of early stage breast cancer	March 2006
Erlotinib in the management of non-small cell lung cancer	March 2006
Ibritumomab in the management of B-cell follicular non-Hodgkin's lymphoma	March 2006
Rituximab in combination with CVP chemotherapy for the management of follicular non-hodgkins lymphoma.	March 2006
Pemetrexed in the management of malignant pleural mesothelioma	February 2006
Pegvisomant in the management of acromegaly	January 2006
Ibandronic acid in the management of hypercalcaemia of malignancy, bone pain and the prevention of skeletal events associated with skeletal metastases	August 2005
Teriparatide in the management of osteoporosis	July 2004
Adefovir dipivoxil for the treatment of chronic hepatitis B infection <b>(N)</b>	May 2004
An update on newer agents for the treatment of pulmonary hypertension	February 2004
Drotrecogin alfa (activated) in the management of severe sepsis <b>(N)</b>	December 2002
Agalsidase alfa and beta in the management of Fabry disease	July 2002
Carbamyl glutamate in the management of N-acetylglutamate synthetase deficiency	July 2002
Erythropoietin in the management of cancer related anaemia	July 2002
Interferon alfa in the management of malignant melanoma	November 2001
Imatinib (Glivec®, STI-571), in the management of chronic myeloid leukaemia <b>(N)</b>	November 2001
Atypical antipsychotics in the management of dementia	June 2001
Iloprost and epoprostenol in the management of pulmonary hypertension	February 2001
Verteporfin for age related macular degeneration	November 2000
Temozolomide for high grade gliomas <b>(N)</b>	May 2000
New drugs for rheumatoid arthritis <b>(N)</b>	May 2000

Ribavirin and interferon alfa for chronic hepatitis C (N)	March 2000
Low molecular weight heparins in venous thrombo-embolic disease	November 1999
Low molecular weight heparins in unstable coronary artery disease	November 1999
Octreotide	July 1999
Drug treatment of obesity (N)	July 1999
Interferon alfa in Hepatitis C (N)	May 1999
Interferon beta in MS (N)	May 1999 (update)
Topotecan for ovarian cancer (N)	December 1998 (update)
Somatotrophin for GHD in adults	December 1998 (update)
Paclitaxel in ovarian cancer (N)	December 1998 (update)
Interferon alfa for haematological malignancy	July 1998
Irinotecan for colorectal cancer (N)	July 1998
Antiretroviral therapy	July 1998
Topotecan for ovarian cancer (N)	July 1998
Dornase alfa for cystic fibrosis	July 1998 (update)
New drugs for Alzheimer's disease (N)	February 1998
Atypical antipsychotics in the management of schizophrenia (N)	February 1998
Somatropin for GHD in adults (N)	January 1998
Taxanes in breast cancer (N)	July 1997
Alglucerase for Gaucher's disease	July 1997 (update)

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Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by the presence of a (N) after the report name. Please refer to the NICE website to access the guidance for these agents/conditions.

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## SUMMARY

- **Multiple sclerosis is a chronic condition characterised by prolonged periods of little or no disease, punctuated by acute disabling relapses. Most patients will progress to a form of the condition characterised by progressively increasing disability. There are an estimated 52,000 to 62,000 multiple sclerosis patients in England and Wales (approximately 100 to 120 per 100,000).**
- **Natalizumab is a novel monoclonal antibody that inhibits the migration of leukocytes into the central nervous system. It is licensed for monotherapy of highly active relapsing-remitting multiple sclerosis for patients who have received little or no benefit from interferon beta therapy or for patients with severe relapsing-remitting multiple sclerosis.**
- **Natalizumab has been investigated in two phase III trials. Compared to placebo it reduced the probability of progression of disability at two years by 12% and in combination with interferon, compared to interferon alone, reduced the same measure by 6%.**
- **Natalizumab is associated with an increased frequency of infection and fatigue. Persistent anti-natalizumab antibodies occur in about 6% of patients and are associated with decreased efficacy and increased hypersensitivity. The incidence of leukoencephalopathy, a serious and potentially fatal infection, has been estimated at 1 in 1000.**
- **Current evidence indicates that natalizumab should be reserved only for those patients who have active disease and have failed to respond to other therapies. Natalizumab should be considered as a second-line or subsequent disease-modifying therapy behind established treatments which have longer follow-up data, established safety profiles, and lower acquisition costs.**
- **Natalizumab should only be prescribed by clinicians with suitable experience to identify those patients likely to derive the most benefit. This constraint, and the requirement for monthly intravenous infusions, will restrict its use to secondary care.**
- **The annual drug cost per patient is £14,690. The incremental cost to prevent one patient progressing with disability over two years is between £102,000 and £156,000.**
- **Numerous on-going studies are evaluating other novel monoclonal antibodies, as well as several other treatments including 'statins', 'glitazones', immunosuppressants, and cytotoxic drugs, in modifying the course of the disease.**

## BACKGROUND

### **DISEASE CHARACTERISTICS**

Multiple sclerosis is the most common cause of neurological disability in young adults, especially in Europe and North America.<sup>1</sup> It is a progressive demyelinating disease of the central nervous system with attendant inflammation and neuronal damage. The exact mechanism of demyelination has not been determined although an autoimmune-mediated attack on some or all of either the myelin itself, myelin producing cells called oligodendrocytes, and nerve axons and neurons is believed to be present. Neither is the cause of multiple sclerosis known, however some evidence points to an environmental agent, possibly a transmissible virus, coupled with genetically determined susceptibility.<sup>2,3</sup>

Myelin is a material predominantly consisting of lipid and some protein that is wrapped around nerve fibres in segments. The effect of this is that nerve impulses are transmitted between the segments of myelin at a faster rate than if they were propagated contiguously along a nerve axon. In the absence of myelin, nerve fibres may still function and impulses can still be propagated but they progress slowly resulting in an apparent loss of function.<sup>4</sup> It is the loss of nerve function that produces the neurological symptoms of multiple sclerosis.<sup>5</sup>

The autoimmune attack on oligodendrocytes and myelin is believed to be mediated by leukocytes which proliferate due to an unknown stimulus, probably myelin antigens produced by macrophages.<sup>6</sup> Leukocytes, specifically lymphocytes and monocytes, are able to cross the blood-brain barrier through interaction between alpha-4 integrin located on their cell surfaces and specific receptors called adhesion molecules on the surfaces of endothelial cells.<sup>7</sup> Once inside the central nervous system they release cytokines that further damage myelin and propagate the immune response.<sup>6,7</sup>

A process of remyelination tends to occur only in the early stages of multiple sclerosis when the oligodendrocytes are healthy enough to repair myelin damage. However the new myelin is thinner and may result in slower conduction of nerve impulses.<sup>2</sup> Infiltration of the central nervous system by leukocytes not only damages myelin but also oligodendrocytes.<sup>6</sup> Early on in the condition, where neuronal damage has occurred, the brain is able to reorganise the traffic of impulses through unaffected pathways and remyelination occurs. Consequently symptoms may improve or disappear.<sup>2</sup>

Multiple sclerosis is an incurable condition characterized by variable and diverse symptoms.<sup>3</sup> Primary symptoms appear as a result of demyelination, inflammation or neuronal damage within the brain and spinal cord. They include weakness, fatigue, numbness, tingling, depression, bladder, bowel and sexual dysfunction, visual problems, pain, cognitive deficits and ataxia. Secondary symptoms arise later in the course of the illness and, in common with other neurologically disabling diseases, include contractures, urinary tract infections, osteoporosis, muscle atrophy, and skin breakdown. Tertiary symptoms arise from a loss of mobility, income, status and social life with increasing disability. These include social isolation and depression.<sup>2</sup>

When primary symptoms arise they develop abruptly within hours or days and this is known as an attack or relapse.<sup>3</sup> A relapse is defined as the appearance of new neurological symptoms or the recurrence of old symptoms persisting for more than 24 hours in the absence of fever or infection.<sup>2</sup> A relapse will typically reach a peak within a few days and slowly resolve over the following weeks such that during a typical relapse a patient will be symptomatic for about eight weeks from onset to recovery. Initially, resolution of a relapse is often complete however symptoms can progress with little or no discernible resolution. Attacks occur about every 12 to 18 months when patients first develop multiple sclerosis and in the early years of the disease. In many patients, over a period of 5 to 15 years, the attacks begin more indolently, persist more chronically and remit less completely such that they gradually transform into a pattern of steady deterioration rather than episodic flares.<sup>3</sup>

The Expanded Disability Status Scale (EDSS) was proposed by Kurtzke in 1983<sup>8</sup> and is a commonly used index of clinical disability associated with multiple sclerosis measuring such factors as ambulation, bowel and bladder control, and sensory and mental functions.<sup>8,9</sup> The EDSS has become well accepted as the standard method for categorizing patients by disease severity.<sup>10</sup> The scale consists of discrete increases of 0.5 with an initial single transition from 0 to 1. An EDSS score of 0 is normal, 1.0 to 2.5 refers to minimal objective abnormality, 3.0 to 4.5 refer to mild disorder, 5.0 to 6.5 refer to impairment of usual daily activities with progressive loss of motor function, 7.0 to 9.0 refer to severe multiple sclerosis, 9.5 refers to incapacitated non-communicative patients and 10 represents death due to multiple sclerosis.<sup>8</sup> There is an emphasis on ambulation capabilities with scores higher than 4.<sup>9</sup> Patients progress up the EDSS in a reasonably ordered and consistent way although the EDSS steps are non-linear and so the rate at which patients' progress varies at different points.<sup>10</sup> For example, a transition from 3 to 4 is not of equivalent magnitude to a transition from 4 to 5. Most multiple sclerosis populations display a bimodal distribution of EDSS scores with peaks at values of 1 and 6 (the latter representing ambulation with unilateral assistance). The time that a patient spends at a particular level also shows non-linear variation with the median time spent at level 4 or 5 being 1.2 years, level 1 being four years and level 6 being three years.<sup>9</sup> Due to the subjective nature of some of the EDSS parameters, intra- and inter-rater reliability are poor even with formal training of assessors.<sup>10</sup>

## **DIAGNOSIS**

Multiple sclerosis is difficult to diagnose due to highly inter-patient variable and non-specific symptoms that are easily confused with other conditions. There is no single specific diagnostic test available so diagnosis is made on the basis of a history indicating the probability of disease, neurological examination with findings consistent with multiple sclerosis, positive paraclinical evidence from MRI (magnetic resonance imaging/image) scans and other tests, and cerebrospinal fluid (CSF) analysis.<sup>2,11</sup> The signs looked for on a MRI scan are the presence of lesions of demyelinated or scarred white matter and, by inference, areas of axon and neuron degeneration.<sup>2</sup> MRI scan results can be a good indicator of multiple sclerosis although they are not used in isolation for diagnosis. Other techniques are sometimes employed to aid diagnosis, for example CSF analysis and measuring the evoked potentials of nerve fibres.<sup>3</sup>

The principal diagnostic criteria established for multiple sclerosis are the McDonald criteria.<sup>12,13</sup> These vary from earlier criteria by establishing a role for MRI in assessing the condition. Essentially, individuals are classified as either having multiple sclerosis, not having multiple sclerosis, or possibly having multiple sclerosis. MRI scans enable the observation of lesions in time and space, although a recent review concluded that the use of MRI to confirm multiple sclerosis on the basis of a single attack of neurological dysfunction, as permitted within the McDonald criteria, may lead to over-diagnosis and consequently over-treatment.<sup>14</sup> It further concludes that multiple sclerosis remains predominantly a clinical diagnosis and this is supported by a recent revision of the McDonald criteria.<sup>13</sup>

## **PROGNOSIS**

The course of the disease is relatively indolent, with life expectancy typically decreased by about 6 to 11 years.<sup>2</sup>

Standard terms exist to determine the pattern and course of the illness:<sup>9</sup>

- Relapsing-remitting multiple sclerosis: clearly defined relapses with full recovery or with sequelae and residual deficit on recovery. The periods between the disease relapses are characterised by a lack of disease progression.
- Primary progressive multiple sclerosis: disease progression from onset with occasional plateaus and temporary minor improvements allowed.
- Secondary progressive multiple sclerosis: initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions or plateaus.

Two severity outcomes are also described:<sup>9</sup>

- Benign multiple sclerosis is a disease in which the patient remains fully functional in all neurological systems 15 years after the disease onset.
- Malignant multiple sclerosis is a disease with a rapid progressive course, leading to significant disability in multiple neurological systems or death in a relatively short time after disease onset.

Relapsing-remitting multiple sclerosis affects the majority of patients at onset (80%) and is characterized by well spaced and short-lived exacerbations or relapses.<sup>11</sup> A relapse is believed to be due to inflammation and demyelination.<sup>1,3</sup> Initially relapses may be 12 to 18 months apart and persist for about eight weeks. Eventually the relapses become more and more frequent and persist for longer periods of time such that it becomes difficult to distinguish any period of remission.<sup>3</sup> This is known as secondary progressive multiple sclerosis and affects about 50% of patients with relapsing-remitting multiple sclerosis during the first 10 years of the illness. A smaller proportion of patients may have primary progressive multiple sclerosis in which the condition slowly progresses from onset with no obvious periods of remission.<sup>11</sup> Progression of multiple sclerosis is believed to be due to an increasing burden of neuronal damage as neurons, once damaged, cannot be replaced.<sup>2</sup>

Factors associated with an unfavourable prognosis include male sex, older age at onset, motor or cerebellar signs at onset, short interval between initial and second attack, incomplete remission after first relapses, early disability, and a high CNS lesion load.<sup>15</sup>

## **INCIDENCE**

The disease can strike at any age although it typically presents between the ages of 20 and 40 years.<sup>2</sup> Multiple sclerosis is female dominant at a ratio of about 2:1<sup>5,9</sup> and occurs with a much greater incidence in Caucasian populations.<sup>3,9</sup> In England and Wales between three and seven people per 100,000 population are diagnosed with multiple sclerosis each year and about 100 to 120 people per 100,000 population have multiple sclerosis. From these rates it is estimated that about 1,800 to 3,400 people are newly diagnosed with multiple sclerosis each year and that 52,000 to 62,000 people have multiple sclerosis.<sup>11</sup>

## **CURRENT TREATMENT OPTIONS**

There are three dimensions to treating multiple sclerosis: managing the day to day symptoms, treating acute relapses, and modifying disease progression.<sup>2</sup>

Symptoms can be managed using a range of pharmacological and non-pharmacological measures, some of which are specifically licensed for multiple sclerosis. Some examples of drug treatment include oxybutynin and desmopressin for commonly encountered symptoms of urinary frequency and nocturia, baclofen and tizanidine for muscle spasticity, oral laxatives for constipation, and various analgesics.<sup>2</sup>

Relapses are managed with high-dose corticosteroids, typically a three- to five-day course of intravenous or oral methylprednisolone. Frequent use of this therapy is associated with adverse effects of its own and should be limited to no more than three occasions per year and for no longer than three weeks per episode.<sup>11</sup>

Disease-modifying drugs can affect the course of multiple sclerosis. Although not curative, disease-modifying drugs reduce the number and severity of relapses. They also reduce the number of new lesions. It is not yet known whether these drugs slow the rate of disability in the long term.<sup>16</sup> There are currently four disease modifying agents licensed for the treatment of multiple sclerosis: interferon beta 1a and 1b, glatiramer, and natalizumab.<sup>17-22</sup>

Interferon beta has a multitude of distinct immunomodulatory effects. The benefits from its use in multiple sclerosis are believed to relate to its anti-inflammatory effect and direct effects preserving the integrity of the blood-brain barrier.<sup>10</sup>

Glatiramer is a quadri-peptide that is believed to modify the immune response by closely mimicking the structure of myelin basic protein.<sup>10</sup> Glatiramer is proven to have a positive effect on the relapse rate in relapsing-remitting multiple sclerosis and has demonstrated positive effects on MRI parameters but has not proven beneficial in any other aspect of multiple sclerosis.<sup>21</sup>

Interferon and glatiramer have demonstrated significant benefits in clinical trials but on the balance of their clinical and cost effectiveness<sup>23</sup> the therapies were introduced to the NHS under a unique risk sharing scheme negotiated between the Department of Health and the various manufacturers.<sup>24</sup> The scheme was established so that a cohort of over 5,000 patients will be followed for 10 years, with the NHS price being determined according to certain clinical endpoints from the group.<sup>24</sup> Specific clinical criteria were established for recruiting patients into the follow-up cohort.<sup>24,25</sup> Currently there are no restrictions on the prescribing of these therapies.

Natalizumab, the most recently developed of the licensed disease-modifying agents, is a murine monoclonal antibody with affinity for the leukocyte cell surface adhesion molecule. Specifically, natalizumab binds to the alpha-4 subunit of cell surface integrin molecules inhibiting interaction between them and several endothelial adhesion molecules. Ultimately leukocytes are prevented from migrating across the endothelium into inflamed parenchymal tissue. In the case of multiple sclerosis, basophils, eosinophils, lymphocytes, and monocytes, are prevented from crossing the blood-brain barrier. Natalizumab is marketed by Biogen Idec in a joint venture with Elan Pharma under the brand name Tysabri<sup>®</sup>. It is licensed for monotherapy of highly active relapsing-remitting multiple sclerosis for patients with high disease activity despite interferon beta therapy or for patients with rapidly evolving severe relapsing-remitting multiple sclerosis.<sup>22</sup>

The purpose of this report is to evaluate the efficacy and safety of natalizumab in the management of relapsing-remitting multiple sclerosis.

## **EFFICACY**

Natalizumab has been studied in two phase III trials.<sup>26,27</sup> Only one of these studies, known as AFFIRM<sup>26</sup> (natalizumab safety and efficacy in relapsing-remitting multiple sclerosis) was evaluated in a scenario similar to the current UK licensed indication, i.e. as monotherapy. The other phase III trial, known as SENTINEL<sup>27</sup> (safety and efficacy of natalizumab in combination with interferon beta-1a in patients with relapsing-remitting multiple sclerosis) evaluated natalizumab in combination with interferon.

The AFFIRM<sup>26</sup> study was a randomised, placebo-controlled, double-blind, multicentre, international trial that recruited 942 patients aged between 18 and 50 years with diagnosis of relapsing-remitting multiple sclerosis. Additionally patients were required to have an EDSS score of between 0.0 and 5.0 and have had at least one documented relapse within the previous 12 months. Randomization was performed on a 2:1 basis with 627 patients randomized to natalizumab 300 mg and 315 patients to placebo infusions once every four weeks for up to 116 weeks. The primary endpoints were the rate of clinical relapse at one year, defined as new or recurrent neurological symptoms not associated with fever or infection that lasted for at least 24 hours and accompanied by new neurological signs, and the cumulative probability of sustained progression of disability at two years, defined as an increase of  $\geq 1.0$  on the EDSS from a baseline score of  $\geq 1.0$  or an increase of  $\geq 1.5$  from a baseline score of  $\geq 0.0$  that was sustained for at least 12 weeks. Secondary endpoints at two years included the relapse rate and the number of new lesions detected by MRI scan.

Randomised patients were predominantly female (70%), white (95%), and young (mean age 36 years). The median duration of multiple sclerosis was five years with the majority (58%) having experienced only one relapse in the previous year (mean 1.52). The mean EDSS score was 2.3. The results for the primary endpoints are, at one year, natalizumab-treated patients' annualised relapse rate 0.27 (95% confidence interval {CI} 0.21 to 0.33) compared to 0.78 (95% CI 0.64 to 0.94) in the placebo group ( $p < 0.001$ ). At two years the corresponding rates were 0.23 (95% CI 0.19 to 0.28) and 0.73 (95% CI 0.62 to 0.87) respectively ( $p < 0.001$ ). The primary endpoint at two years, the probability of sustained progression of disability, was 0.17 in the natalizumab group and 0.29 with placebo ( $p < 0.001$ ). The hazard ratio of this outcome was 0.58 (95% CI 0.43 to 0.77). The number of new or enlarging lesions detected by MRI scan was also in favour of the natalizumab group with a median of 0 (range 0 to 196) compared to a median in the placebo group of 5 (range 0 to 91). Fifty-seven per cent of patients in the natalizumab group recorded no new or enlarging lesions compared to 15% in the placebo group; conversely 68% of placebo patients recorded  $\geq 3$  new or enlarging lesions compared to 18% in the natalizumab group. In an unpublished sub-group analysis of patients with rapidly evolving relapsing-remitting multiple sclerosis, defined as patients with  $\geq 2$  relapses and  $\geq 1$  gadolinium enhancing lesion, the annualised relapse rate was 0.282 in natalizumab-treated patients ( $n = 148$ ) and 1.455 in placebo-treated patients ( $n = 61$ ,  $p < 0.001$ ).<sup>22</sup> The hazard ratio for disability progression in the same patient group was 0.36 (95% CI 0.17 to 0.76,  $p = 0.008$ ).<sup>22</sup> It should be noted that this was not a pre-planned analysis and the AFFIRM study was not sufficiently powered to investigate this patient sub-group therefore until this data is fully published it is not possible to determine the significance of these results.

Additional unpublished results from the AFFIRM study, including analysis of quality of life data, have been supplied by Biogen Idec.<sup>28</sup> In summary, the proportions of patients progressing to a sustained EDSS score  $\geq 4.0$  at two years were 5% with natalizumab and 13% with placebo ( $p < 0.001$ ). The proportions of patients progressing to a sustained EDSS score  $\geq 6.0$  at two years were 2% with natalizumab and 6% with placebo ( $p = 0.002$ ). The proportions of patients disease free at two years, defined as an absence of relapse, sustained disability progression, and MRI-detected lesions, were 28% with natalizumab and 6% with placebo ( $p < 0.001$ ). The proportions of patients relapse free at two years were 67% with natalizumab and 41% with placebo ( $p < 0.001$ ), and the proportions free of sustained progression of disability at two years were 83% with natalizumab and 73% with placebo ( $p < 0.001$ ). Quality of life was assessed within a sub-population of the initial trial population (536 and 264 respectively) using the multiple sclerosis quality of life index. This index has at its core the Short-Form 36-item quality of life index (SF-36), supplemented by other scales measuring symptoms relevant to multiple sclerosis patients. At two years natalizumab-treated patients showed small improvements in the mental and physical component scales of the SF-36, compared to small decreases in the placebo group ( $p = 0.011$  and  $0.003$  respectively). There were no statistically significant differences with respect to the additional quality of life measures evaluating factors such as fatigue, pain, sexual satisfaction, bladder and bowel control, vision, and mental health ( $p > 0.05$  for all measures). Overall scores were not provided.

In the SENTINEL<sup>27</sup> study, a randomised, placebo-controlled, double-blind, multicentre, international trial, the investigational group (n = 589) received natalizumab 300 mg once every four weeks plus interferon beta-1a 30 micrograms once weekly, with the control group (n = 582) receiving interferon plus a placebo infusion in place of natalizumab, for up to 116 weeks. Patient selection criteria were similar to those used in the AFFIRM study with notable exceptions being an age range of 18 to 55 years, and treatment with interferon beta-1a for  $\geq 12$  months before randomisation. The primary endpoints at one and two years and the secondary endpoints at two years were the same as those used in the AFFIRM study. Randomised patients were predominantly female (74%), white (93%), and young (mean age 39 years). The median duration of multiple sclerosis was seven years with the majority (64%) having experienced only one relapse in the previous year (mean 1.47). The mean EDSS score was 2.4. The results at one year yielded an annualised relapse rate of 0.38 (95% CI 0.32 to 0.45) for the natalizumab plus interferon group and a rate of 0.81 (95% CI 0.72 to 0.92) for the interferon plus placebo group ( $p < 0.001$ ). At two years the relapse rates were 0.34 (95% CI 0.29 to 0.39) and 0.74 (95% CI 0.67 to 0.84) respectively ( $p = 0.001$ ). The primary endpoint at two years was the cumulative probability of sustained disability progression, which was 0.23 for the natalizumab plus interferon group and 0.29 for the interferon plus placebo group ( $p = 0.02$ ). The hazard ratio for this effect was 0.76 (95% CI 0.61 to 0.96). The number of new or enlarging lesions detected by MRI scan was also in favour of the natalizumab plus interferon group with a median of 0 (range 0 to 27) compared to a median in the control group of 3 (range 0 to 64). Sixty-seven per cent of patients in the natalizumab plus interferon group recorded no new or enlarging lesions compared to 30% in the control group; conversely 50% of control patients recorded three or more new or enlarging lesions compared to 14% in the natalizumab plus interferon group.

Natalizumab has been studied in three relevant phase II trials.<sup>29-31</sup>

Miller et al recruited 213 patients aged between 18 and 65 years with relapsing-remitting or secondary progressive multiple sclerosis, with at least two relapses in the previous two years and an EDSS score of between 2.0 and 6.5.<sup>29</sup> Patients were randomized to treatment with natalizumab 3 mg/kg (n = 68), 6 mg/kg (n = 74) or placebo (n = 71) once every four weeks for six months. The primary outcome measure was the number of new lesions over the six-month treatment period defined as the period following the first infusion until one month after the last infusion (i.e. the end of month six). Patients were predominantly female (71%) and young (mean age < 45 years). Thirty-two per cent (69 patients) had secondary progressive multiple sclerosis, with the remainder (68%, 144 patients) having relapsing-remitting multiple sclerosis. The mean duration of multiple sclerosis ranged from 10.2 to 13.1 years (range 0 to 40 years) and the mean number of relapses in the previous two years was 2.9 to 3.1 (range 2 to 12). The mean EDSS score ranged from 4.2 to 4.4 (range 0.0 to 6.5). The results yielded a mean of 9.6 new lesions in the placebo group, 0.7 in the natalizumab 3 mg/kg group, and 1.1 in the 6 mg/kg group. The differences between each of the active treatment groups and placebo were significant ( $p < 0.001$ ), with no significant difference observed between the two natalizumab treated groups.

Natalizumab has also been investigated as potential treatment for an acute multiple sclerosis relapse.<sup>30</sup> O'Connor et al recruited 180 patients with relapsing-remitting or secondary progressive multiple sclerosis, aged between 18 and 65 years, and with EDSS scores of  $\leq 5.5$ . The qualifying relapse for the treatment provided was required to be of between 24 and 96 hours duration prior to receiving treatment. Patients were randomised to treatment with a single dose of natalizumab at 1 mg/kg ( $n = 57$ ), 3 mg/kg ( $n = 60$ ) or placebo ( $n = 63$ ) and followed up for 14 weeks. The primary outcome measure was the mean change in the EDSS score between treatment groups at one week after treatment. Patients were predominantly female (82%) and young (mean age  $\leq 40$  years). Nine per cent (16 patients) had secondary progressive multiple sclerosis, with the remainder (91%, 164 patients) having relapsing-remitting multiple sclerosis. The mean duration of multiple sclerosis ranged from 7.6 to 9.2 years and the mean number of relapses in the previous two years was 1.9 to 2.5. The mean EDSS score ranged from 4.3 to 4.5. The results did not show any significant advantage for the use of natalizumab in this scenario with mean changes (reductions) in EDSS scores at one week from baseline of 1.0 with placebo, 0.6 with natalizumab 1 mg/kg, and 0.9 with natalizumab 3 mg/kg.

Tubridy et al randomised 72 patients to natalizumab 3 mg/kg or placebo, for two doses four weeks apart.<sup>31</sup> Patient selection criteria included age between 18 and 55 years, diagnosis of relapsing-remitting or secondary progressive multiple sclerosis, two or more relapses in the previous 18 months and  $>$  four weeks since the onset of the last MS exacerbation, and an EDSS score between 2.0 and 7.0. The primary outcome measure was the number of new active and new enhancing lesions seen on MRI during weeks 1 to 12. Patients were predominantly female (64%) and young (mean age  $\leq 41$  years). Twenty-six per cent (19 patients) had secondary progressive multiple sclerosis, with the remainder (74%, 53 patients) having relapsing-remitting multiple sclerosis. The mean duration of multiple sclerosis ranged from 117 to 119 months (approximately 10 years) with the majority (65%) experiencing one or two relapses per year in the previous 18 months. The mean EDSS score ranged from 4.7 to 4.9. The results yielded an adjusted mean number of new active lesions of 1.8 in the natalizumab group ( $n = 37$ ) compared to 3.6 in the placebo group ( $p = 0.042$ ). The adjusted mean number of new enhancing lesions per patient was 1.6 and 3.3 respectively ( $p = 0.017$ ).

## ADVERSE EFFECTS

### GENERAL ADVERSE EFFECTS

Table 1. General adverse effects with an incidence  $\geq 15\%$ , or where a significant difference was observed between treatment groups, in the AFFIRM<sup>26</sup> and SENTINEL<sup>27</sup> studies.

	AFFIRM <sup>26</sup>		SENTINEL <sup>27</sup>	
	Natalizumab 300mg (%)	Placebo (%)	Natalizumab 300mg plus interferon (%)	Placebo plus interferon (%)
Headache	38	33	46	44
Fatigue	27	21*		
Limb pain			22	21
Depression	19	16	21	18
'Flu-like illness			20	19
Urinary tract infection	20	17		
Diarrhoea			19	16
Arthralgia	19	14		
Insomnia			18	17
Lower respiratory tract infection	17	16		
Influenza			17	15
Nausea			17	15
MS Relapse	6	13*	5	9*
Anxiety			12	8*
Allergic reaction	9	4*		
Nasopharyngitis			39	35
Pharyngitis			7	4*
Sinusitis			18	15
Sinus congestion			6	3*
Peripheral oedema			5	1*

\*  $p < 0.05$

The SENTINEL study was terminated one month earlier than planned due to two incidences of progressive multifocal leukoencephalopathy (PML), one of which was fatal.<sup>27,32,33</sup> PML is a demyelinating disease due to papovavirus seen in immunosuppressed hosts.<sup>34</sup>

Reports of adverse events in the phase II trials of natalizumab in multiple sclerosis<sup>29-31</sup> are consistent with the data from the phase III trials, with only one trial<sup>31</sup> reporting any adverse events, fatigue and insomnia, at a significantly greater frequency ( $p \leq 0.05$ ) in the natalizumab treated group compared to placebo.

The manufacturers of natalizumab are conducting a post-marketing study called TYGRIS (Tysabri® global observation programme in safety) which will follow 5,000 patients for five years to evaluate long-term safety of the drug.<sup>35</sup>

### **PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY**

The two cases of PML in the SENTINEL study<sup>32,33</sup> and a fatal case of PML in a Crohn's disease trial<sup>36</sup> led to the license holder temporarily suspending treatment in all active trials, and suspending marketing of natalizumab in the USA where it was already licensed, in 2005.<sup>37</sup> A thorough structured review of patients who had participated in phase III trials of natalizumab for multiple sclerosis and Crohn's disease, and all patients in a phase II trial of natalizumab in rheumatoid arthritis, was undertaken.<sup>38</sup> Over 3,000 trial patients were specifically included in the review and a further 1,700 trial patients were included by means of a review of adverse effect databases. About 7,000 other patients were also included but only via physician referral. The investigators did not identify any additional cases of PML other than the three that they were already aware of and concluded that the risk of PML is 1 per 1,000 patients (95% CI 0.2 to 2.8 per 1,000) at a mean of 17.9 monthly doses of natalizumab (range 1 to 41). It is worth noting the relatively small number of doses administered to patients within this review considering that the drug is intended for use over a much longer term. It is also worth noting that natalizumab is licensed only as monotherapy and in each case of PML the patient was receiving, or had a recent history of, additional immunotherapy. The natalizumab summary of product characteristics specifically recommends that before initiation of treatment a recent (usually within three months) MRI should be available and patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If new neurological symptoms occur further dosing must be suspended until PML has been excluded. If PML is suspected, further evaluation including MRI scan (compared with the pre-treatment MRI), CSF testing, and repeat neurological assessments, should be considered. Administration of natalizumab can only resume when PML has been excluded. Natalizumab is contra-indicated in immunocompromised patients and should be used cautiously in patients with a history of immunosuppression (excluding the use of short courses of corticosteroids).<sup>22</sup>

### **IMMUNOLOGICAL**

Only three studies report the incidence of anti-natalizumab antibodies, ranging from 9% to 12%.<sup>26,27,31</sup> In the two phase III trials, each of two years duration, 6% of patients displayed persistent antibodies, associated with a greater incidence of infusion related adverse events and a loss of efficacy of natalizumab.<sup>26,27</sup> Additional unpublished results from the AFFIRM study relating to anti-natalizumab antibodies have been supplied by Biogen Idec.<sup>28</sup> These data indicate that patients who were persistently positive for anti-natalizumab antibodies were associated with a greater probability of sustained disability progression compared to other natalizumab-treated patients, both of which were greater than placebo treated patients (0.34, 0.17, and 0.29 respectively).

## HYPERSENSITIVITY

Hypersensitivity reactions were observed in a small proportion of patients in phase III trials (4.0 and 1.9%),<sup>26,27</sup> including an incidence of serious hypersensitivity reactions of 1.3% in the AFFIRM study.<sup>26</sup> Consequently patients should be closely observed during and for at least one hour after completion of the infusion in an environment where appropriate resources for dealing with hypersensitivity reactions are present. Patients who experience a hypersensitivity reaction to natalizumab must discontinue treatment permanently.<sup>22</sup>

## DOSAGE, ADMINISTRATION AND COST

Natalizumab is supplied in glass vials containing 15 ml natalizumab concentrate 20 mg/ml, i.e. 300 mg per vial. The concentrate must be diluted with 100 ml sodium chloride 0.9% solution for injection and infused intravenously over one hour at a rate of approximately 2 ml per minute. No other diluent is recommended and it must not be mixed with other medicinal products. The infusion is intended for single use and should be used as soon as possible after preparation. Vials of concentrate should be stored in a refrigerator at 2 to 8°C, and protected from light.<sup>22</sup>

The licensed dose is 300 mg once every four weeks with no adjustments recommended for patients with decreased renal or hepatic function. Treatment is intended to be long term although published trial data does not exceed two years therefore therapy beyond this time should be considered only following a reassessment of the potential for benefit and risk.<sup>22</sup>

Excluding VAT, the cost of a 300 mg vial of natalizumab is £1,130<sup>39</sup> resulting in an annual drug cost of £14,690 per patient.

Alternative treatments for multiple sclerosis include interferon or glatiramer. These are displayed in table 2.

Table 2. Annual drug cost of treating a multiple sclerosis patient with disease-modifying therapies.

<i>Drug</i>	<i>Proprietary name</i>	<i>Licensed maintenance dose</i> <sup>17-22</sup>	<i>Dose frequency</i> <sup>17-22</sup>	<i>Annual cost (52 weeks)</i> <sup>39,40</sup>
Interferon beta-1a	Avonex <sup>® 17</sup>	30 mg	Weekly	£8,502
Interferon beta-1a	Rebif <sup>® 18, 19</sup>	22 micrograms	Three times weekly	£7,513
		44 micrograms		£8,942
Interferon beta-1b	Betaferon <sup>® 20</sup>	250 micrograms	Alternate days	£7,279
Glatiramer acetate	Copaxone <sup>® 21</sup>	20 mg	Daily	£5,839
Natalizumab	Tysabri <sup>® 22</sup>	300 mg	Once every four weeks	£14,690

Additional costs associated with natalizumab will be the requirement for a MRI scan prior to commencement of therapy. This has been estimated at £165.<sup>41</sup> Any subsequent MRI scans will incur a similar cost on each occasion. Additionally natalizumab requires intravenous administration once every four weeks within a secondary care setting which will have attendant costs in terms of hardware, accommodation, and staff time. The cost of each visit is estimated at £100.<sup>42</sup> Therefore the total annual cost of natalizumab is estimated at about £16,000. There are likely to be costs on top of this figure due to the occasional requirement for subsequent MRI scans, CSF analysis, other haematological screening (e.g. for anti-natalizumab antibodies), and treatment of infective and hypersensitivity complications. It has not been possible to reliably quantify these costs.

The licensed indication for natalizumab is specific about the patient group to be treated. An estimate of the proportion of multiple sclerosis patients that may fit the criteria (i.e. relapsing-remitting multiple sclerosis, with high disease activity or rapidly evolving) can be derived from an estimate of the proportion of multiple sclerosis patients eligible for interferon or glatiramer as per the Association of British Neurologists guidelines.<sup>24,25</sup> The estimate in this case is 12.5% to 15.0% of patients meeting the criteria of being able to walk independently (EDSS  $\leq$  5.5), having at least two relapses in the previous two years, and aged  $\geq$  18 years. Using this estimate and combining with a prevalence of between 100 and 120 per 100,000, as stated previously,<sup>11</sup> results in a cost of between £192,000 and £288,000 per 100,000 population per annum (i.e. between 12 and 18 patients). Because this estimate has been derived from the eligibility criteria for existing disease modifying therapies it is fair to assume that if these patients were not receiving natalizumab they would be receiving one of these therapies instead. Therefore costs of between £6,000 and £9,000 per patient per annum may be offset against each patient treated, or between £72,000 and £162,000 per 100,000 population per annum. This results in an estimated increase cost for natalizumab of between £84,000 and £180,000 per 100,000 population per annum.

Using the absolute difference of 12% in the probability of sustained progression of disability at two years observed between the natalizumab and placebo group in the pivotal phase III AFFIRM study yields a number needed to treat (NNT) of nine, i.e. nine patients need to be treated with natalizumab for two years to prevent one of them sustaining a progression of disability.<sup>26</sup> The drug cost associated with this NNT is £264,420, and the net cost is between £102,420 and £156,420.

Pivotal studies of multiple sclerosis disease-modifying therapies have recruited patients with similar disease characteristics (mean baseline EDSS 2.3 to 2.9) and used common measures (annualised relapse rate, proportion of relapse free patients, and disease progression, usually over two years).<sup>26,43</sup> Comparing these common outcomes relative to the cost of therapy can provide a crude comparison of efficacy, as represented in appendix 1.

## PLACE IN TREATMENT

Natalizumab is the first alpha-4 integrin antagonist launched which specifically inhibits non-neutrophil leukocyte migration into the central nervous system. It offers a new treatment option with proven efficacy relating to delaying disability progression superior to interferon alone, although only at an absolute benefit of 12%.<sup>26</sup>

The primary outcome in both phase III studies is an appropriate measure when assessing an intervention for multiple sclerosis.<sup>26,27</sup> However, the condition follows a slowly progressive course for the majority of patients, and certainly for most of those recruited into the studies which required an EDSS score  $\leq 5.5$ . The principal flaw in the design of the studies is their duration – two years is a short amount of time for the majority of patients with relapsing multiple sclerosis. Even in the placebo group of the AFFIRM study after two years 46% of patients reported no relapses. With natalizumab therapy likely to be required for as long as periodic relapses are the dominant feature of the condition the long-term efficacy and safety of the therapy are important and, so far, undetermined.

Another important point is the development of anti-natalizumab antibodies, which in 6% of patients results in a greater risk of hypersensitivity reactions and reduced efficacy of natalizumab.<sup>26-28</sup> Long-term data are required to determine whether the development of antibodies is inevitable in all patients or whether it occurs at a fixed rate. It will also be useful to identify any contributory factors for developing anti-natalizumab antibodies and to determine the time parameters for their development. This will aid the targeting of treatment to those patients who are likely to benefit most and may reduce the occurrence of hypersensitivity reactions. A test for anti-natalizumab antibodies is available and persistently positive patients should permanently discontinue therapy,<sup>22</sup> thus reducing expenditure on a drug that is no longer optimally effective.

Longer term follow up will be required to determine if the apparent benefits of natalizumab are maintained. The result is highly statistically significant but the clinical significance is not known. For example, all the patients recruited to the AFFIRM study, from which this result is derived, had EDSS scores at the lower end of the scale. A proportion of the observed difference, and hence the treatment effect, may be attributable to transitions that mean little in practical or clinical terms for the patient. Furthermore, progression is defined by a minimum transition on the EDSS from one point to the next therefore the primary outcome measure is obscuring the degree, or severity, of the observed changes.

Alternative disease-modifying treatments for multiple sclerosis are available in subcutaneous or intramuscular injections which can often be administered within the patient's home environment. The requirement to attend a specific centre for an intravenous infusion of natalizumab could have a substantial impact on patient quality of life.

When the National Institute for Health and Clinical Excellence assessed four disease-modifying treatments for multiple sclerosis in 2002 they concluded that they were not cost-effective at their list price.<sup>23</sup> This resulted in the implementation of a novel risk sharing pricing policy with the price paid by the NHS dependent upon patient outcomes.<sup>24</sup> On the basis of the AFFIRM and SENTINEL study results natalizumab may be more effective than existing disease-modifying therapies for multiple sclerosis,<sup>43</sup> it is also more expensive but may still be as cost effective as some existing treatments (see appendix 1). When the Scottish Medicines Consortium reviewed natalizumab in December 2006 they concluded that the economic case had not been demonstrated and therefore did not recommend its use.<sup>44</sup>

Current evidence indicates that natalizumab should be reserved only for those patients who have active disease and have failed to respond to other therapies. The AFFIRM and SENTINEL trials recruited many patients who were at a low risk of progressive disability over the duration of the studies, and in these patients the short-term data do not provide sufficient evidence that the risk and expense of treatment are balanced by the benefits. Longer-term follow-up data is required particularly as evidence is emerging that early treatment of inflammatory processes can result in a smaller burden of neurological deficit in later years.<sup>45</sup>

Natalizumab should be considered as a second-line or subsequent disease-modifying therapy behind established treatments which have longer follow-up data, established safety profiles, and lower acquisition costs.

## **ARRANGEMENTS FOR PRESCRIBING**

Natalizumab should only be prescribed by clinicians with suitable experience to identify those patients likely to derive the most benefit. Natalizumab requires specialist handling and administration and should therefore remain within secondary care. It is an expensive treatment for a long-term condition therefore access will need to be agreed locally by medicines management groups.

## **FUTURE DEVELOPMENTS**

There are a multitude of on-going clinical trials investigating many aspects of multiple sclerosis. Specifically regarding disease modification there are studies investigating several novel immunomodulatory monoclonal antibodies, immunosuppressants such as mycophenolate, vaccine therapy, cytotoxic drugs such as mitoxantrone, cyclophosphamide, and methotrexate, nucleoside analogues such as cladribine, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors such as simvastatin, atorvastatin and pravastatin, and thiazolidinediones such as pioglitazone.<sup>46</sup>

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## APPENDICES

### APPENDIX 1: COMPARISON OF KEY OUTCOME MEASURES AND ASSOCIATED COST-EFFICACY OF DISEASE-MODIFYING THERAPIES IN MULTIPLE SCLEROSIS

Drug	Dose	Relative reduction in relapse rate after two years (%)	Relative reduction in disease progression after two years (%)	Proportion patients relapse-free after two years (%)	Cost efficacy of relapse absence
Interferon beta-1a (Avonex)	30 micrograms once weekly	32	37*	38	£44,747
Interferon beta-1a (Rebif)	22 micrograms three times weekly	29	23	27	£55,652
Interferon beta-1a (Rebif)	44 micrograms three times weekly	32	31	32	£55,888
Interferon beta-1b	250 micrograms alternate days	34	29 <sup>§</sup>	31	£46,961
Glatiramer	20 mg daily	29	12	34	£34,347
Natalizumab	300 mg once every four weeks	68	41	57	£56,140

Data taken from review by Galetta et al<sup>43</sup> except data for natalizumab which was taken from the AFFIRM study.<sup>26</sup>

The costs used are taken from table 2 except for the cost of natalizumab (£16,000 per annum) which includes an estimated service/administration cost. Period of progression of disability was minimum of three months except (♦) which was for six months.

(§): Disease progression data for interferon beta-1b is measured after three years.<sup>47</sup>

All of the studies from which the data is derived were randomised, double-blind, placebo-controlled, multicentre, two-year trials. The primary outcome measures varied from study to study, therefore some studies may not have been sufficiently powered to demonstrate the differences in the outcomes shown in the table above.<sup>26,43</sup>

## APPENDIX 2: SUMMARY OF TRIALS

Key: CI – confidence interval; DB – double blind; EDSS – expanded disability status scale; IM – intramuscular; MAb – monoclonal antibodies; MC – multicentre; MRI – magnetic resonance image/imaging; MS – multiple sclerosis; NatAb – anti-natalizumab antibodies; Pbo – placebo-controlled; PML – progressive multifocal leukoencephalopathy; PPMS – primary progressive multiple sclerosis; PRMS – progressive relapsing multiple sclerosis; R – randomised; RRMS – relapsing-remitting multiple sclerosis; SPMS – secondary progressive multiple sclerosis.

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion criteria	Primary outcome	Results	Adverse effects
Polman et al 2006 <sup>26</sup>	DB, MC, Pbo, R, Phase III	Natalizumab 300 mg or placebo infusion once every 4 weeks for up to 116 weeks.	n = 627  n = 315	RRMS according to McDonald criteria Age 18–50 years. EDSS score 0.0–5.0. MRI scan results consistent with MS. At least one medically documented relapse within the preceding 12 months.	PPMS, SPMS, PRMS according to McDonald criteria. Relapse within 50 days preceding study. Treatment with mitoxantrone or cyclophosphamide in the previous year Treatment with interferon, glatiramer, cyclosporine, azathioprine, methotrexate or immunoglobulin in the previous 6 months. Treatment with interferon and/or glatiramer for more than six months.	At one year, the rate of clinical relapse defined as new or recurrent neurological symptoms not associated with fever or infection, persisting for > 24 hours, and accompanied by new neurological signs. At two years: the cumulative probability of sustained progression of disability defined as an increase $\geq 1.0$ on the EDSS from a baseline $\geq 1.0$ , or an increase $\geq 1.5$ from a baseline score of 0.0, sustained for 12 weeks.	One year (95% CI): Natalizumab group relapse rate 0.27 (0.21 to 0.33); placebo relapse rate 0.78 (0.64 to 0.94, $p < 0.001$ ).  Two years: probability of sustained disability progression, natalizumab group 17%, placebo 29% ( $p < 0.001$ )	Natalizumab vs. placebo respectively ( $p > 0.05$ unless stated): headache (38% vs. 33%), fatigue (27% vs. 21%, $p = 0.048$ ), depression (19% vs. 16%), arthralgia (19% vs. 14%), urinary tract infection (20% vs. 17%), lower respiratory tract infection (17% vs. 16%), urinary urgency or frequency (9% vs. 7%), abdominal discomfort (11% vs. 10%), rash (11% vs. 9%), allergic reaction (9% vs. 4%, $p = 0.012$ ).  NatAb were detected in 9% of all natalizumab-treated patients and persisted in 6%.

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion criteria	Primary outcome	Results	Adverse effects
Rudick et al 2006 <sup>27</sup>	DB, MC, Pbo, R, Phase III	Natalizumab 300 mg infusion once every 4 weeks plus interferon beta-1a 30 micrograms IM weekly or interferon beta-1a 30 micrograms IM weekly plus placebo infusion once every 4 weeks for up to 116 weeks.	n = 589  n = 582	RRMS according to McDonald criteria. Age 18–55 years. EDSS score 0.0–5.0. MRI scan results consistent with MS. At least one medically documented relapse within the preceding 12 months. Treatment with interferon beta-1a for at least 12 months prior to randomisation.	PPMS, SPMS, PRMS according to McDonald criteria. Relapse within 50 days preceding study. Treatment with an approved disease-modifying drug other than IM interferon beta-1a once weekly within the preceding 12 months.	At one year: the rate of clinical relapse defined as new or recurrent neurological symptoms not associated with fever or infection, persisting for > 24 hours, and accompanied by new neurological signs. At two years: the cumulative probability of sustained progression of disability defined as an increase $\geq 1.0$ on the EDSS from a baseline $\geq 1.0$ , or an increase $\geq 1.5$ from a baseline score of 0.0, sustained for 12 weeks.	One year (95% CI): Natalizumab plus interferon group relapse rate 0.38 (0.32 to 0.45); interferon plus placebo relapse rate 0.81 (0.72 to 0.92), ( $p < 0.001$ ).  Two years: probability of sustained disability progression, natalizumab plus interferon group 23%, interferon plus placebo 29% ( $p = 0.02$ )	Natalizumab plus interferon vs. interferon plus placebo respectively ( $p > 0.05$ unless stated): headache (46% vs. 44%), nasopharyngitis (39% vs. 35%), pain in arms or legs (22% vs. 21%), depression (21% vs. 18%), flu-like illness (20% vs. 19%), diarrhoea (19% vs. 16%), insomnia (18% vs. 17%), anxiety (12% vs. 8%, $p < 0.01$ ), pharyngitis (7% vs. 4%, $p < 0.05$ ), sinus congestion (6% vs. 3%, $p < 0.01$ ), peripheral oedema (5% vs. 1%, $p < 0.001$ ).  Two cases of PML in natalizumab plus interferon-treated patients (1 fatal).  NatAb were detected in 12% of all natalizumab-treated patients and persisted in 6%.

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion criteria	Primary outcome	Results	Adverse effects
Miller et al 2003 <sup>29</sup>	DB, MC, Pbo, R, Phase II	Natalizumab 3 mg/kg or natalizumab 6 mg/kg or placebo infusion once every 4 weeks for 6 months (6 doses).	n = 68  n = 74  n = 71	RRMS or SPMS. Age 18–65 years. ≥ 2 relapses within preceding two years. EDSS score between 2.0 and 6.5. ≥ 3 T2-weighted lesions on MRI brain scan.	Immuno-suppressive or -modulating treatments within the preceding 3 months. Relapse within preceding 30 days. Systemic corticosteroids within preceding 30 days.	Number of new lesions over the 6-month treatment period.	Mean number of new lesions per patient during the treatment period was 0.7 in the natalizumab 3 mg/kg group, 1.1 in the 6 mg/kg group and 9.6 in the placebo group (p < 0.001 for each treatment group compared to placebo).	Recorded during treatment phase, natalizumab 3 mg/kg vs 6 mg/kg vs placebo respectively: headache (40% vs. 27% vs. 38%), infection (22% vs. 19% vs. 15%), urinary tract infection (22% vs. 18% vs. 15%), pharyngitis (15% vs. 22% vs. 11%), myasthenia (18% vs. 9% vs. 15%), rash (10% vs. 11% vs. 8%), paraesthesia (13% vs. 16% vs. 13%), pruritis (12% vs. 5% vs. 10%), back pain (4% vs. 12% vs. 8%), diarrhoea (10% vs. 3% vs. 6%), sinusitis (10% vs. 4% vs. 4%).
O'Connor et al 2004 <sup>30</sup>	DB, MC, Pbo, R, Phase II	Natalizumab 1 mg/kg or natalizumab 3 mg/kg or placebo stat infusion, with 14 week follow-up.	n = 57  n = 60  n = 63	RRMS or SPMS Age 18–65 years. EDSS score ≤ 5.5 prior to relapse (EDSS score at time of relapse > 3.0). Symptoms of an acute MS relapse for between 24 and 96 hours prior to receiving treatment. No changes to pyramidal, cerebellar, brainstem and visual function ≥ 30 days prior to relapse.	Relapse improvement prior to treatment Relapse relating only to sensory, bladder/bowel or cognitive function. Prior exposure to MAb or murine proteins. Immuno-modulating or investigational therapy in the preceding 3 months. Systemic steroids within the preceding 30 days. Intolerant of MRI or gadolinium contrast agent.	Mean change in EDSS score one week after treatment.	At one week post-treatment the mean change (reduction) in EDSS score per patient was 0.6 in the natalizumab 1 mg/kg, 0.9 in the 3 mg/kg group and 1.0 the placebo group (p > 0.05).	Natalizumab 1 mg/kg vs 3 mg/kg vs placebo respectively: any adverse event (91% vs. 90% vs. 89%), headache (33% vs. 47% vs. 40%), pharyngitis (32% vs. 23% vs. 30%), dizziness (18% vs. 12% vs. 13%), nausea (14% vs. 13% vs. 17%), pain (12% vs. 10% vs. 13%), insomnia (14% vs. 13% vs. 11%), asthenia (7% vs. 17% vs. 10%), back pain (4% vs. 18% vs. 11%), paraesthesia (12% vs. 7% vs. 11%), depression (12% vs. 2% vs. 6%), diarrhoea (11% vs. 7% vs. 10%).

Reference	Design	Intervention	Patient Numbers	Inclusion criteria	Exclusion criteria	Primary outcome	Results	Adverse effects
Tubridy et al 1999 <sup>31</sup>	DB, MC Pbo, R, Phase II	Natalizumab 3 mg/kg or placebo infusion, 2 doses, 4 weeks apart.	n = 37  n = 35	RRMS or SPMS. Age 18–55 years. Weight < 90 kg. EDSS score 2.0–7.0. ≥ 2 relapses in the previous 18 months. ≥ 4 weeks since last relapse.	PPMS. Women of child-bearing age unless using contraception. Pregnant or breast-feeding. Normal MRI brain study at enrolment. Immunosuppressive drugs, including beta-interferon, in the preceding 6 months. Alcohol consumption > 315 mg (21 units) per week or abuse of other drugs. Previous exposure to any other murine protein, or other MAbs, or CD4 antibodies. History of total lymphoid irradiation. Methylprednisolone or oral prednisolone in the preceding 4 weeks.	The cumulative number of new active and new enhancing lesions seen on MRI during weeks 1 to 12 from the start of treatment after baseline correction.	Mean cumulative number of new active lesions per patient from weeks 1 to 12: 1.8 in natalizumab-treated patients and 3.6 in placebo-treated patients (p = 0.042).  Mean cumulative number of new enhancing lesions per patient from weeks 1 to 12: 1.6 in natalizumab-treated patients and 3.3 in placebo-treated patients (p = 0.017).	Natalizumab (n = 37) vs placebo (n = 33) respectively. Assessed from weeks 0 to 12: any adverse effect (86% vs 97%), fatigue (27% vs. 9%, p = 0.065), ≥ 1 acute MS exacerbation (24% vs. 30% p = 0.57). Assessed from weeks 0 to 24: fatigue (32% vs 11%, p = 0.047), insomnia (0% vs 11%, p = 0.05), ≥ 1 acute MS exacerbation (49% vs. 36% p = 0.30). Assessed from weeks 12 to 24: any adverse effect (51% vs 69%), ≥ 1 acute MS exacerbation (38% vs. 9%, p = 0.005). Development of NatAb (11% vs. 0%).