Natalizumab (Tysabri®)—Re-defining Efficacy in Multiple Sclerosis—Data from Clinical Trials to Post-marketing Experience

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Abstract

Multiple sclerosis (MS) is a chronic, disabling condition with severe clinical and social consequences. Current first-line disease-modifying treatments have limited efficacy and do not halt long-term disease progression in the majority of patients. Natalizumab (Tysabri®) is the only monoclonal antibody licensed for use in relapsing–remitting MS (RRMS). It is regarded by many neurologists as the most effective MS drug on the market today, and has the potential to re-define successful MS therapy. Its efficacy has been demonstrated both in large-scale clinical trials and in post-marketing settings. Beneficial effects include reduction of relapse rates and disease progression, as well as magnetic resonance imaging (MRI) measures of disease activity. Natalizumab treatment has a substantial impact on patient quality of life. Moreover, patients have shown significant improvement following natalizumab treatment, making continuing clinical remission a realistic goal in MS for the first time. However, the benefits of natalizumab must be balanced against risk. Progressive multifocal leukoencephalopathy (PML) is a rare event associated with natalizumab treatment that may be minimized with a risk management plan to educate physicians on patient selection and management.

Keywords

AFFIRM, natalizumab, progressive multifocal leukoencephalopathy (PML), relapsing–remitting multiple sclerosis (RRMS), Tysabri

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Multiple sclerosis (MS) is a chronic, inflammatory, and neuro-degenerative disease in which T cells cross the blood–brain barrier and attack the myelin sheath, initiating an inflammatory cascade. The consequences of these events are plaques of demyelination, gliosis, and axonal degeneration.[1] MS is the leading cause of non-traumatic disability among young adults, with a total estimated prevalence for the last three decades of 83 cases/100,000 population and an annual European incidence of 4.3 cases/100,000 population. The prevalence ratio of females to males is approximately 2:1[2] and may be increasing. The disease affects men and women in different ways, including age at onset, disease course, and prognosis.[3] Many geographical variations affect prevalence, including increased latitude both north and south of the equator.[4] The onset of MS can span five decades, although it is most common between 20 and 30 years of age. The age at onset appears to affect prognosis, with younger patients generally taking longer to progress to a worse state of disability than older patients (progression to an Expanded Disability Scale Score [EDSS] of 4, at which walking is limited).[5]

MS results in significant disability: many patients are unable to walk unaided after a median of 15 years,[6] and are wheelchair-bound by 25 years after disease onset.[7] A number of variables have been shown to predict the time between onset of disease and onset of irreversible disability: gender, age, symptoms, disease course, degree of recovery from the first relapse, time to second neurological episode, and number of relapses in the first five years of the disease. However, these variables do not influence the subsequent progression of irreversible disability.[5] In addition to physical disability, 43% of MS patients have some degree of cognitive dysfunction.[8] The social cost of MS is high and includes a limited ability to participate in the workforce, perform routine household tasks, and function socially, as well as increased psychopathology.[9] Multiple sclerosis is also a life-shortening disease, causing an average 10–12-year reduction in life expectancy.[10,11] A study of deaths among MS patients found that complications from MS accounted for 47% of deaths, and the suicide rate was 7.5-fold higher than that for the age-matched general population.[12]

The clinical course of MS is heterogeneous, with variability both between and within patients, and has been categorized as relapsing–remitting MS (RRMS), primary progressive MS (PPMS), or secondary progressive MS (SPMS); the former accounts for 85% of MS patients in the initial disease course. This article will focus on RRMS, which is

Table 1: Comparison of Efficacy of Two-year Clinical Trials of Current First-line Disease-modifying Treatments in Multiple Sclerosis

Treatment Type	n	Dosage	Annual Relapse Rate		Disability Progression		Reference
			% Reduction	p-value	% Reduction	p-value	
IFNβ-1a	189 (560 total)	22µg SC 3 times a week	29	<0.005	23	<0.05	Galetta et al., 2002[21]
IFNβ-1a	184 (560 total)	44µg SC 3 times a week	32	<0.005	30	<0.05	Galetta et al., 2002[21]
IFNβ-1b	372	250µg SC every other day	34	0.0001	29	NS	IFNB, 1993[18]
IFNβ-1a	301	30µg IM once a week	32*	0.002	37	0.02	Jacobs et al., 1996[19]
Glatiramer acetate	251	20mg SC daily	29	0.007	12	NS	Johnson et al., 1995[20]

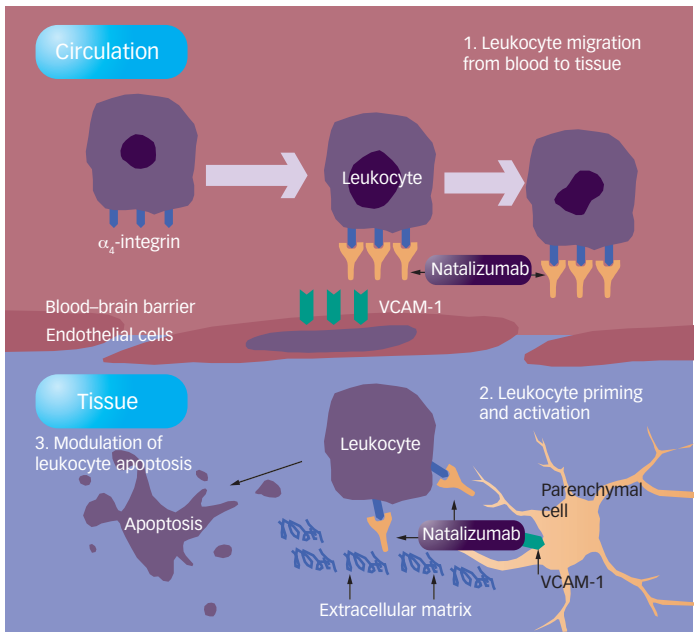
**Calculated for patients who completed at least 104 weeks on study. IFN = interferon; IM = intramuscular; SC = subcutaneous; NS = not significant.*

characterized by relapses during which new symptoms may occur and old ones worsen, and remissions during which the patient fully or partially recovers from the deficits acquired during the relapse.[13]

Efficacy of Current First-line Disease-modifying Treatments

The formation of the inflammatory lesions that characterize MS is thought to be initiated by lymphocyte migration across the blood–brain barrier. This is mediated by adhesion molecules and ligands expressed on endothelial cells and leukocytes. Currently available disease-modifying treatments (DMTs) act via multiple proposed mechanisms of action, including altering the interaction between the adhesion moleule $\alpha_4\beta_1$ integrin and the ligand vascular cell adhesion molecule 1 (VCAM-1). Some DMTs have been observed to increase expression of VCAM-1 in active plaques in the brain and spinal cord, which may bind activated T cells and prevent them from crossing the blood–brain barrier.[14–16] The existing treatments include the interferons beta IFNβ-1a (administered subcutaneously [SC], Rebif®, or intramuscularly [IM], Avonex®) and IFNβ-1b (administered SC, Betaferon®). The precise mode of action of glatiramer acetate, also known as copolymer 1 (Copaxone®), is as a decoy, given its structural similarity to myelin. In clinical trials, all DMTs reduced the annualized relapse rate (ARR), but only IFNβ-1a (IM and SC) significantly reduced disability progression as determined by change in EDSS score compared with placebo[17–21] (see *Table 1*). However, these treatments show only moderate efficacy and most MS patients still show disease progression. The majority (62–75%) of patients relapse within two years, and 20–27% of patients worsen by ≥1 point on the EDSS within two years. Moreover, adherence to DMT treatment regimens is problematic, largely due to side effects such as injection-site reactions and influenza-like symptoms. A chart-based study in Ireland on 394 MS patients determined an overall IFNβ stopping rate of 28% over five years.[22] The study also showed a significant difference between the IFNβ stopping rates for RRMS (14%) and SPMS (23%) after three years (p=0.0003). Patients were shown to stop IFNβ due to side effects after a median of 13 months, and due to treatment failure after a median of 35 months (p=0.0004). Furthermore, many patients with MS have breakthrough disease activity despite therapy with these agents, or are unresponsive to treatment.[23] Therefore, there is a continuing and substantially unmet need for more effective treatments that limit relapses and disease progression within MS.

Figure 1: Points Where Natalizumab Could Inhibit the Inflammatory Process in Multiple Sclerosis



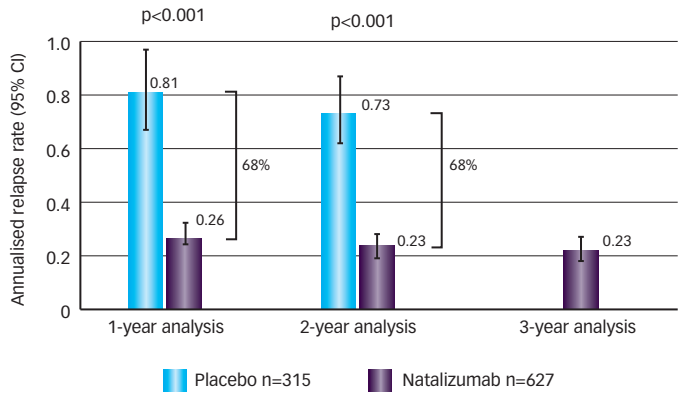
VCAM = vascular cell adhesion molecule.

Natalizumab (Tysabri®) is a recently introduced recombinant humanized anti-α_4-integrin antibody that is generally reserved for second-line use in MS, although it can be used as a first-line agent in cases of rapidly evolving severe RRMS.[24] The aim of this article is to review the broad spectrum of efficacy of natalizumab across traditional and non-traditional outcomes from clinical trials and post-marketing studies.

Mode of Action of Natalizumab

Natalizumab is the first α_4-integrin antagonist in the class of selective adhesion molecule (SAM) inhibitors. It is a humanized monoclonal antibody that binds to α_4-integrin on the surface of activated T cells, which prevents adhesion between the T cell and the endothelial cell and disrupts the resulting inflammatory cascade. Natalizumab has three putative modes of action (see *Figure 1*). It decreases leukocyte

Figure 2: Annual Relapse Rate During AFFIRM and the Safety Extension



CI = confidence interval.
Source: O'Connor et al., 2006.[27]

migration across the blood–brain barrier by blocking adhesion to endothelial cells and interaction with extracellular matrix (ECM) proteins, e.g. fibronectin. It also limits leukocyte priming and activation by blocking interaction with osteopontin and VCAM-1 expressed on microglial cells and monocytes in the brain parenchyma, and modulates leukocyte apoptosis by blocking interaction of α_4-integrin-expressing leukocytes with ECMs. After a 300mg intravenous infusion of natalizumab, the elimination half-life is six to nine day. However, α_4-integrin receptors remain 80% saturated for approximately one month; therefore, administration is by monthly infusion.[16]

Data from Clinical Trials Supporting Natalizumab Use in Multiple Sclerosis

Two key large phase III clinical studies evaluating the clinical use of natalizumab involved a total of 2,113 patients and 3,804 patient-years of exposure. The Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) study assessed natalizumab versus placebo treatment for 120 weeks in 942 patients with RRMS.[25] The Safety and Eficacy of Natalizumab in Combination with Interferon Beta-a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) study compared combined treatment with natalizumab and IFNβ-1a versus IFNβ-1a treatment alone for 120 weeks in 1,171 patients with RRMS.[23] The sample cohorts in both trials were large compared with previous trials of DMTs (see *Table 1*). Since natalizumab is currently only recommended as a monotherapy, this article will focus on the AFFIRM study.

The AFFIRM Study

The AFFIRM study was a large phase III clinical trial. Eligibility requirements were age 18–50 years, a diagnosis of RRMS, one or more documented clinical relapses within the prior 12 months, EDSS between 0 and 5.0, and having magnetic resonance imaging (MRI) lesions consistent with MS.[25] The primary end-points of the study were the rate of clinical relapse at one year and the rate of sustained disability progression at two years, which was defined as an increase of 1.0 or more on the EDSS from a baseline score of 1.0 or more or an increase of 1.5 or more from a baseline score of 0 that was sustained for 12 weeks (progression could not be confirmed during a relapse). Patients were randomized to natalizumab 300mg (n=627) or placebo (n=315) by intravenous infusions every four weeks for up to 30 infusions. Neurological evaluations were carried out every 12 weeks, and proton-density-weighted or T_2-weighted and gadolinium-enhanced T_1-weighted MRI scans of the brain were performed at baseline and weeks 52 and 104. Patients had a mean age of 36.7 and 35.6 years and 67 and 72% were female in the placebo and natalizumab groups, respectively. Demographics and MS disease histories were similar between the two groups.

Natalizumab demonstrated substantial benefit over two years compared with placebo not only in the overall population but also in the subgroup of highly active patients, who were defined as having at least two relapses in the previous year and at least one gadolinium-enhancing lesion at baseline. The rate of clinical relapse was reduced by 68% (p<0.001) in one year in the overall population, which was sustained at two years (see *Figure 2*), and by 81% (p<0.001) in the highly active population.[26] The risk of a sustained progression of disability (defined as EDSS progression sustained at 12 and 24 weeks) was reduced by 42–54% (p<0.001), and by 53–64% (p=0.029 and p=0.008) versus placebo in the highly active population. During an open-label extension study of the AFFIRM trial, the low ARR was maintained and there was minimal progression in EDSS during the third year of natalizumab therapy.[27]

Efficacy of natalizumab on MRI measures of disease activity was also demonstrated. Over two years, the mean number of new or enlarging T_2-hyperintense MRI lesions was reduced by 83% (p<0.001), and new lesions detected by gadolinium-enhanced MRI were reduced by 92% (p<0.001).

Within this trial, natalizumab had an acceptable safety and tolerability profile, and the only adverse events occurring significantly more frequently in the natalizumab group than in the placebo group were fatigue and allergic reactions. Hypersensitivity reactions were seen in 4% of patients receiving natalizumab, and serious hypersensitivity reactions were seen in 1%.[25]

Non-traditional Outcomes

Various *post hoc* analyses of the AFFIRM data have demonstrated risk reduction versus placebo in several non-traditional outcomes following natalizumab treatment. Natalizumab significantly improved health-related quality of life (HRQoL) based on Short Form-36 (SF-36) Physical and Mental Component Summary scores.[28] It also reduced visual loss assessed as low-contrast letter acuity testing by 35–47% (p≤0.008); such testing may act as a useful outcome measure in future clinical trials.[29] Over two years of treatment, natalizumab significantly lessened deterioration in ambulation, arm/hand function, and cognitive function. In addition, natalizumab reduced the ARR requiring steroid use and the annualized rate of MS-related hospitalizations.[30] In AFFIRM subjects, classification of disability progression was also evaluated by the worsening of either Multiple Sclerosis Functional Composite component by 20% (MSFC-20) or by 15% (MSDC-15), and appears to be a sensitive and comprehensive assessment method.[31]

Re-defining Treatment Goals

Freedom from disease activity and improvement are the ultimate goals of treatment in inflammatory conditions, but to date this has not been considered attainable by MS clinicians.[17–19] Despite extensive therapy

with current DMTs, most patients with MS continue to show disease activity and progression.

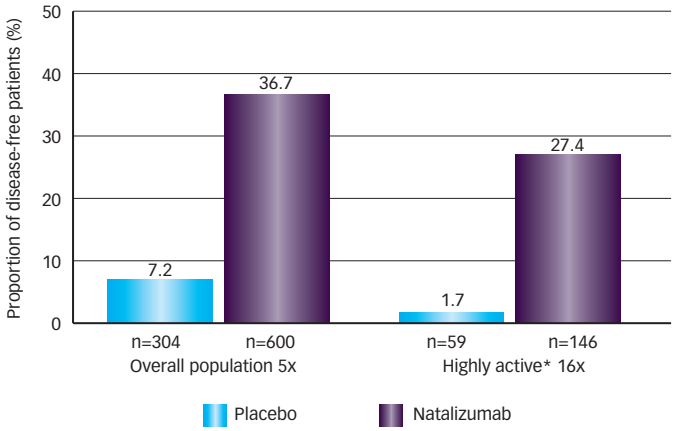
A retrospective analysis of the AFFIRM data showed that in patients with a baseline EDSS ≥2, treatment with natalizumab significantly increased the probability of sustained improvement in disability (defined as a one-point decrease in EDDS score sustained for 12 weeks) by 69% relative to placebo (p=0.006). Furthermore, patients with highly active disease showed a 143% improvement over placebo (p=0.045).[32] The mechanisms underlying these improvements are not yet understood. However, preliminary data from post-marketing studies indicate that natalizumab promotes neuronal remyelination, particularly in RRMS, but further investigations are required to validate this finding.[33]

Other recent analyses showed a 164% increase relative to placebo in freedom from clinical disease activity (p<0.0001, defined as absence of relapses and sustained clinical progression as measured by EDSS) and a four-fold increase over placebo in freedom from radiological disease activity (p<0.0001, defined as absence of gadolinium-enhancing lesions and absence of new or enlarging T_2-hyperintensive lesions) over two years. When the results were expressed as a composite of clinical and radiological measures, the improvement in the treatment group was five-fold higher than that in the placebo group, suggesting that disease remission may become a realistic treatment goal in the future. In the highly active disease subgroup, the proportion of natalizumab-treated patients who were disease-free at two years represented a 16-fold improvement relative to placebo (see *Figure 3*). The effect of natalizumab treatment was greatest in the second year, indicating that efficacy may increase over time.[34]

A long-term study followed up a subgroup of 23 MS patients who had previously been enrolled in two phase III trials evaluating natalizumab.[35] At 14 months after natalizumab treatment cessation, no clinical, radiographic, or immunological rebound phenomena were observed. In addition, decreased lymphocyte numbers and altered cell ratios returned to normal during this period, and no infectious complications were observed. These findings from a limited patient population suggest that recurrence of disease and other complications may not be problematic, at least during the period of observation, after cessation of natalizumab.

The effects of natalizumab treatment cessation were investigated by analysing data from a large-scale safety extension[36] that included patients who had participated in the AFFIRM study,[25] the SENTINEL study,[23] and the GLatiramer Acetate and Natalizumab Combination Evaluation (GLANCE) safety study (a phase II study of natalizumab with glatiramer acetate versus placebo with glatiramer acetate in 110 patients with RRMS over 24 weeks).[37] The safety extension study was terminated early when dosing of natalizumab was voluntarily suspended following the report of two cases of progressive multifocal leukoencephalopathy (PML) in MS patients; the suspension of natalizumab dosing provided an opportunity to evaluate the effects of stopping therapy. The analysis included data from 946 original natalizumab patients who returned for safety evaluations after the voluntary suspension; these patients had received a mean 34±4 doses (range six to 41) before natalizumab was stopped. The data confirmed that, as would be expected from natalizumab's mechanism of action and pharmacodynamics, disease activity had returned to on-study placebo levels by four months following cessation of treatment. This return of disease activity, in terms of ARR, was similar in all clinical subgroups. Patients who had highly active disease before they were enrolled in the original studies showed a greater absolute increase in disease activity compared with those with less active MS. This was believed to be a result of the greater severity of the underlying disease process during the original studies. Disease activity following cessation of natalizumab did not rebound in excess of pre-existing disease activity levels. In addition, the use of other DMTs after stopping natalizumab did not appear to delay the return of disease activity, but this finding requires further confirmation in a larger patient population.[36]

Figure 3: Proportions of Disease-free Patients Receiving Natalizumab or Placebo in the Overall and Highly Active Disease Populations



**Patients with ≥2 relapses in prior year and ≥1 Gd+ lesion at baseline.*
p<0.0001, natalizumab versus placebo for both overall and highly active patients.
5x: Expressing results as a composite of clinical and radiological measures, the improvement in the treatment group was five-fold over placebo.
16x: In the highly active disease subgroup, the proportion of natalizumab-treated patients who were disease-free at two years showed a 16-fold improvement over placebo.
Source: Havrdova, 2009.[34]

Post-marketing Experience

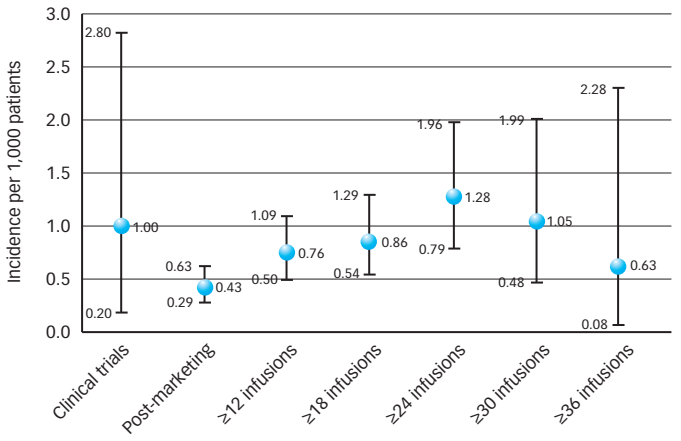
As of June 2009, natalizumab was approved in over 40 countries for the treatment of RRMS in patients who have an inadequate response to or are unable to tolerate another MS medication. It is also approved by the US Food and Drug Administration (FDA) in adult patients with moderately to severely active Crohn's disease. As of November 2009, over 60,000 patients had been treated with natalizumab in the post-marketing setting. An overview of post-marketing data from natalizumab patient registries and treated cohorts around the world, including effects on relapse rates and disability progression, is given in *Table 2*. These 'real-world' data show that, generally, patients being treated in the clinic are slightly older and have longer disease durations, higher EDSS, and higher baseline ARR than patients recruited into clinical trials. Despite these baseline differences, patients treated with natalizumab in clinical practice showed stabilization of disability and attenuation of disease activity, which was comparable to observations in clinical trials. The proportion of patients discontinuing natalizumab treatment were similar across all four studies (8.2–15%), and the safety profile

Table 2: Real-life Findings from Clinical Use of Natalizumab in Patient Registries and Cohorts Around the World

Patient Registry/Cohort Reference	n	Baseline ARR, EDSS	On-study ARR, EDSS	% Relapse-free	% Discontinuation
Danish registry[46]	234[a]	2.53 (2.33–2.75) 4.0 (0–8) (median)	0.68 (0.57–0.81) N/A	63	15
Essen, Cologne, Erlangen, St Gallen cohort[47]	97[b]	2.3±0.6 3.6±0.8 (mean)	0.17±0.1 3.2±0.8 (mean)	80	8.2
Nord-Alsace cohort[48]	384	2.19±1.23 3.53±1.68 (mean)	0.59± 0.84[c] 3.02±1.73[c] (mean)	60[c]	9.1
Tysabri® Observational Program (TOP) cohort[49]	1,011	2.07±1.08[d] 3.8±1.7[e]	0.26 (0.22, 0.32)[d] 3.6±1.8[e] (reduction: 0.2±0.97)	N/A	10.6[f]

a. Proportion of patients with an EDSS 1.0-point progression 0.09, median observation period of 11.3 months (range 3–21.5); b. Mean treatment duration 19.3±6.1 months; c. Based on 127 patients observed for at least 1 year; d. Based on 587 patients observed for at least 6 months; e. Based on 292 patients observed for at least 12 months; f. Includes therapy discontinuation and study withdrawal. ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale.

Figure 4: Natalizumab Progressive Multifocal Leukoencephalopathy Incidence Estimates Based on Patients Exposed and Treatment Duration



Blue circles represent estimated incidence, bars represent confidence intervals.
Data updated November 30, 2009 based on 28 cases.
Source: Hyde et al., 2009.[38]

of natalizumab was similar to that seen in the AFFIRM study.[25] A health economic study on natalizumab in the UK concluded that natalizumab therapy is cost-effective in all patients with highly active RRMS compared with current DMTs.[38]

Long-term Safety

Natalizumab was voluntarily withdrawn from the market one year after its FDA approval in 2004 following three confirmed cases of PML in two patients from the SENTINEL study and in one patient with Crohn's disease.[39,40] The FDA and European Medicines Agency (EMEA) re-approved natalizumab with revised labeling in 2006, and it is now recommended only as monotherapy.[41] In the US, natalizumab is available to prescribers only through a registry called Tysabri Outreach: Unified Commitment to Health (TOUCH). In TOUCH, patients are screened for PML symptoms before each natalizumab infusion.[42]

Since the re-launch of natalizumab in 2006, rare cases of PML have been confirmed in patients exposed to monotherapy.[43] As of November 30, 2009, 28 cases of PML have been confirmed in more than 60,000 natalizumab-treated patients in the post-marketing setting.[43] It should be noted that the absolute number of PML cases must be evaluated in the larger context of the number of patients actually exposed to natalizumab. Therefore, the actual number of PML cases is a less informative measure than the incidence rate. The duration of natalizumab dosing prior to PML diagnosis ranged from approximately one year to more than 3.5 years (12–44 infusions), while the incidence of PML generally increases with duration of exposure, as shown in *Figure 4*. The rate of PML is consistent with that seen in pre-approval clinical trials. There is, however, limited experience in patients who received more than three years of natalizumab treatment.

To date, clinical signs and symptoms that prompted evaluation for PML in natalizumab-treated patients have been new or worsening neurological symptoms evolving over several weeks, focal neurological signs and other symptoms, such as hemiparesis, focal myoclonia, aphasia, retrochiasmal visual deficits, and changes in cognition, behavior, and personality.

MRI assessments of PML cases typically revealed non-enhancing T_2-hyperintense lesions in frontal, temporal, parietal, or occipital regions. Many of these lesions were unifocal, and gadolinium-enhancing lesions were identified. JC virus DNA has been observed in the cerebrospinal fluid of patients with PML when analysed using the polymerase chain reaction. In most patients, however, titers were low (<500 copies/ml). In PML not associated with natalizumab, new or worsening neurological signs or symptoms, changes in mental status, seizure, or fever were usually not associated with gadolinium-enhancing lesions.[43]

Natalizumab was discontinued when the first signs or symptoms and/or MRI findings suggestive of PML were identified. The majority of patients who developed PML in the post-marketing setting received plasma exchange and/or immunoadsorption to accelerate removal of natalizumab from circulation.

During recovery from PML, immune reconstitution recovery syndrome (IRIS) is an expected condition. This appears universal in PML

associated with natalizumab, unlike PML in AIDS, regardless of whether natalizumab is removed rapidly or simply discontinued.[39] IRIS generally occurred four weeks after stopping natalizumab treatment, but in some cases it occurred earlier. Corticosteroids, sometimes multiple courses, given early in the course of IRIS appeared to lead to improvement in most patients. To date, most of the natalizumab-treated patients who developed PML have survived, but exhibit varying levels of disability.[43]

A quantitative risk–benefit analysis demonstrated that the substantial benefits of natalizumab, particularly in patients with highly active disease or those who do not respond to other DMTs, far outweigh the risk of PML.[44] At present, there are multiple long-term evaluation programs in progress that are designed to further characterize the long-term safety and efficacy of natalizumab (see *Table 3*). There are currently insufficient data on the efficacy and safety of natalizumab in patients with progressive forms of MS to recommend its use in primary or secondary progressive MS.[45]

Table 3: The Multiple Long-term Programs for Monitoring the Safety and Efficacy of Natalizumab in Clinical Use

Program	STRATA	TOUCH	TYGRIS	TOP
Regulatory commitment	Yes (EU)	Yes	Yes	Yes (EU)
Interventional study (3b)	Yes	No	No	No
Mandatory prescribing program	No	Yes	No	No
Observational program	No	No	Yes	Yes
Efficacy data collection	Yes	No	No	Yes
Safety data collection	Yes	Yes	Yes	Yes
Number of patients	850	Unlimited	5,000	3,000
Duration (years)	5	Unlimited	5	5

STRATA = Safety of Tysabri Re-dosing And Treatment study; TOUCH = Tysabri Outreach: Unified Commitment to Health Prescribing Program; TYGRIS = Tysabri Global Observation Program in Safety observational cohort study; TOP = Tysabri Observational Program.

Discussion

MS is a serious disease with devastating clinical and social consequences for which there is a great need for more effective therapies. The high levels of efficacy demonstrated by natalizumab in clinical trials and post-marketing studies confirm its importance, and have enhanced the therapeutic outcome goals in MS. Natalizumab reduces measures of disease activity such as clinical relapse rate, gadolinium enhancement, and new and enlarging T_2 lesions in patients with relapsing MS. It also improves measures of disease severity such as EDSS progression rate and T_1 and T_2 lesion burden detected by MRI in patients with RRMS. It has produced substantial improvements in health-related quality of life and physical and cognitive function. Its effect is particularly marked in those patients with highly active disease. Furthermore, natalizumab has been shown to bring about sustained improvement in disability and an absence of disease activity, representing a new goal in MS therapy. However, the increased benefits of natalizumab have to be balanced against the risks. PML and other opportunistic infections are rarely seen. Physician and patient education plays a key role as early diagnosis of PML and early discontinuation of natalizumab in cases of suspicion might improve the outcome. Predictors of the risk of developing PML are currently being investigated. Since natalizumab has improved disease status even in patients with highly active MS, future clinical studies should assess the efficacy of MS treatments not only in slowing progression, but also in improving disability or achieving remission. ■

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