

Natalizumab: A new treatment for relapsing remitting multiple sclerosis

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Abstract: Natalizumab, a new disease-modifying therapy for relapsing remitting multiple sclerosis (RRMS), is a humanized monoclonal antibody which binds to $\alpha_4\beta_1$ -integrin. In a Phase 3 trial, 2 years of natalizumab monotherapy reduced the mean annualized relapse rate (ARR) by 68% compared with placebo ($p < 0.001$) and the risk of sustained disability progression was reduced by 42% in the natalizumab group (hazard ratio [HR] 0.58; 95% confidence interval [CI] 0.43–0.77; $p < 0.001$). Natalizumab decreased the mean number of new or enlarging T2-hyperintense lesions by 83% over 2 years and the mean number of Gd+ lesions by 92% at 2 years (both $p < 0.001$). In another Phase 3 trial, natalizumab with interferon (IFN) β -1a reduced the mean ARR by 55% at 2 years compared with IFN β -1a alone ($p < 0.001$) and risk of sustained disability progression was reduced by 24% (HR 0.76; 95% CI 0.61–0.96; $p = 0.02$). Six percent of patients developed persistent antinatalizumab antibodies with loss of efficacy. The risk of developing progressive multifocal leukoencephalopathy (PML) is been estimated at 1:1000 over 18 months; the longer term risk for PML is uncertain. The benefits and risks of natalizumab support its use as monotherapy for RRMS with high disease activity despite treatment with IFN β , and for patients with rapidly evolving severe RRMS.

Keywords: natalizumab, Tysabri, multiple sclerosis, α_4 -integrin antagonist, selective adhesion molecule (SAM) inhibitor, disease-modifying therapy

Introduction

Multiple sclerosis (MS) is a chronic disabling autoimmune neurological disease affecting approximately 2.5 million people worldwide. The initial presentation in most patients (85%) is relapsing-remitting MS (RRMS) with relapses and remissions due to self-limiting plaques of inflammatory demyelination disseminated in time and place in the central nervous system (CNS). Subsequently, chronic noninflammatory loss of CNS axons gives rise to progressive disability (secondary progressive MS [SPMS]). Approximately 10%–15% of MS patients have progressive disability from the outset (primary progressive MS [PPMS]). (MSIF 2006; NMSS 2006). Clinical relapses in MS are due to acute inflammatory CNS demyelinating lesions causing white matter plaques. After a variable period (usually 10–15 years) of recurrent relapses with accumulating residual disability, the patient enters a course of inexorable slowly progressive disability (SPMS) due to secondary axonal degeneration. The pathogenesis is best understood as a complex interaction between genetic predisposition and environmental stimuli. Autoimmune reaction against different components of the CNS, particularly myelin structures, is thought to play an important role in the initiation of the inflammatory process. The transmigration of cells into the target tissue is regulated by chemotactic cytokines and adhesion molecule expression at the blood-brain barrier. The primary goals of MS therapy are to reduce relapses, reduce accumulating residual disability, and to prevent or delay the onset of progressive disability. Although the cause of

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MS is unknown, effective therapies are aimed at reducing the inflammatory disease process; natalizumab is the first targeted therapy which blocks an essential mechanism for lymphocyte entry to the CNS and thus prevents acute demyelinating relapses.

While some treatments for MS provide only symptom relief, disease-modifying therapies (DMTs) are administered with the goal of altering the course of the disease. Available DMTs include interferon beta-1a (IFN β -1a) (Avonex[®], Biogen Idec, Cambridge, MA, USA; Rebif[®], Serono, Rockland, MA, USA), IFN β -1b (Betaseron[®], Berlex Laboratories, Montville, NJ, USA), glatiramer acetate (GA) (Copaxone[®], TEVA Neuroscience, Kansas City, MO, USA), and mitoxantrone (MITO) (Novantrone[®], Serono, Rockland, MA, USA). First-line DMT for MS is one of the IFNs or GA, which are generally well tolerated but only modestly effective (IFNB 1993; Johnson et al 1995; Jacobs et al 1996; PRISMS 1998; 2001); because of toxicity concerns, mitoxantrone is used more selectively in patients with very active disease characterized by frequent relapses and accumulating disability (Ghalie et al 2002; Avasarala et al 2003; Cohen and Mikol 2004). Since approximately two thirds of patients treated with IFNs or GA relapse and eventually experience disease progression, there is a clear unmet medical need for more effective agents (IFNB 1993; Johnson et al 1995; Jacobs et al 1996; PRISMS 1998; 2001). Detailed analysis of therapeutic studies of current first-line DMT therapy in MS may be found in a number of reviews (Galletta et al 2002; Filippini et al 2003; Munari et al 2003; Rice et al 2006).

Natalizumab (Tysabri[®], Biogen Idec, Cambridge, MA, USA) is a new DMT licensed in 2006 in the EU and in the US for the treatment of RRMS. The main focus of this article is to review evidence from the Phase 1, 2, and 3 clinical trials of natalizumab that led to its approval. Advantages of natalizumab in treating MS include a unique mechanism of action, a new level of clinical efficacy greater than that of other available DMTs, good tolerability, and a convenient monthly dosing regimen.

Methods

A search of articles indexed in the PubMed database (January 1966–February 2006) and the Cochrane Library was conducted using the query terms natalizumab, Tysabri, Antegren, multiple sclerosis, and MS. The results of clinical trials described in the published literature, as well as data provided by Biogen Idec, were used in this review.

Mechanism of action

Natalizumab is the first in a class of DMTs known as selective adhesion molecule (SAM) inhibitors (Léger et al 1997) and acts by preventing the specific inflammatory events leading to the development of MS lesions.

Endothelial cells on the lumen of blood vessels express vascular cell adhesion molecule-1 (VCAM-1) at sites of active MS lesions (Osborn et al 1989; Carlos et al 1990). VCAM-1 is bound by $\alpha_4\beta_1$ -integrin (also known as very late antigen-4), an adhesion molecule found at high levels on the surface of all leukocytes except neutrophils (Elices et al 1990; Lobb and Hemler 1994). The interaction between VCAM-1 and $\alpha_4\beta_1$ -integrin is required for leukocyte adhesion, firm attachment, and transmigration across the blood-brain barrier into the CNS (Damle and Aruffo 1991; Burkly et al 1991; Lobb and Hemler 1994). Natalizumab, a recombinant, humanized antibody, binds to $\alpha_4\beta_1$ -integrin and blocks its interaction with VCAM-1. As a result, leukocyte migration into brain tissue is inhibited, reducing inflammation and preventing the formation of lesions (Tubridy et al 1999; Rudick and Sandrock 2004). Natalizumab may also inhibit ongoing CNS inflammation, mediated by leukocytes already present in the CNS, by interrupting the interactions between α_4 -integrin-expressing leukocytes and extracellular matrix proteins such as fibronectin and osteopontin (Lobb and Hemler 1994; Bayless et al 1998).

Natalizumab binds rapidly and with high affinity to α_4 -integrin. Maximal binding ($\geq 80\%$ saturation), measured in vitro on isolated lymphocyte membranes, occurred 24 hours after intravenous (IV) doses of natalizumab 1 mg/kg to 6 mg/kg; saturation persisted for 1 to 6 weeks, with longer residence times achieved at higher dose levels (Rudick and Sandrock 2004; Biogen Idec Data on File). MS patients treated with natalizumab 3 mg/kg or 6 mg/kg IV achieved approximately 80% and 90% mean saturation of α_4 -integrin, respectively (Miller et al 2003; Biogen Idec Data on File). Weight-based dosing data from Phase 2 trials suggested that a single fixed dose of 300 mg would maintain maximal α_4 -integrin saturation for over 4 weeks (Bennett et al 2002; Rudick and Sandrock 2004). The dosage of 300 mg, administered every 4 weeks in Phase 3 trials of natalizumab, saturated α_4 -integrin to a mean level of $\geq 70\%$ (Biogen Idec Data on File).

Pharmacokinetics

The pharmacokinetics of natalizumab (0.03 mg/kg to 6 mg/kg) was examined in four Phase 1 trials: one in

healthy volunteers and three in patients with MS (Sheremata et al 1999; Rudick and Sandrock 2004; Vollmer et al 2004; Biogen Idec Data on File). Serum natalizumab concentrations quickly dropped below the detection limits with 0.03 mg/kg or 0.1 mg/kg IV doses, but were measurable for 1 week with the 0.3 mg/kg IV dose and for 3 to 8 weeks with the 1 mg/kg and 3 mg/kg IV doses (Sheremata et al 1999). Higher doses of natalizumab resulted in longer mean half-lives and slower mean total body clearance, despite the use of weight-based dosing (Sheremata et al 1999).

Analysis of pharmacokinetic data from Phase 2 trials and population modeling indicated that natalizumab clearance was only weakly correlated with body weight (over the range of 40 kg to 100 kg), but that natalizumab exposure (area under the plasma concentration-time curve and maximum plasma concentration), increased in proportion to weight despite the use of weight-based dosing (Bennett et al 2002; Rudick and Sandrock 2004; Biogen Idec Data on File). However, the effect of patient weight on natalizumab clearance and exposure was within the typical inter-patient range and was not considered clinically relevant. The 300 mg fixed dose selected to achieve maximum α 4-integrin saturation was expected to produce acceptable pharmacokinetics in Phase 3 trials (Table 1). The clearance of natalizumab allows dosing once every 4 weeks, during a clinic visit lasting 2 hours, while most other DMTs must be self-injected daily, on alternate days, or weekly.

Coadministration of other drugs does not appear to significantly affect natalizumab pharmacokinetics. In a Phase 1 trial, 38 patients with RRMS who had been treated with a stable weekly dose of IFN β -1a 30 μ g intramuscularly (IM) for at least 3 months prior to enrollment received a single IV dose of natalizumab 3 mg/kg or 6 mg/kg (Vollmer et al 2004). Natalizumab serum levels were slightly elevated when given in addition to IFN β -1a. Natalizumab treatment

had no significant effect on the pharmacokinetics of IFN β -1a (Vollmer et al 2004). A Phase 2 trial investigated the use of natalizumab in combination with GA and the potential effects of each drug on pharmacokinetics (Table 2; see also below under "Phase 2b trial") (Goodman et al 2005); however, results have not yet been published.

Efficacy data from clinical studies

As described in this section, the efficacy of natalizumab in treating MS has been evaluated in a number of randomized, controlled clinical studies (Tubridy et al 1999; Miller et al 2003; O'Connor et al 2004; Goodman et al 2005; Polman et al 2006; Rudick, Stuart, et al 2006). To date, no study has directly compared monotherapy with natalizumab against monotherapy with a different DMT. Therefore, comparisons of natalizumab and other DMTs must consider differences in patient characteristics, comedication, study design, and choice of endpoints. Clinical trials recruit different types of patients in terms of MS diagnosis (eg, RRMS and secondary progressive MS [SPMS]), previous treatment history (none, recent, IFN β -1a, and GA), and duration of disease.

Phase 2 trials

The Phase 2 trials of natalizumab are summarized in Table 2. To assess the efficacy of natalizumab in the short-term control of brain lesion formation, a randomized, double-blind, placebo-controlled, multicenter trial was conducted in patients with RRMS or SPMS (Tubridy et al 1999). Patients received two IV infusions of natalizumab 3 mg/kg (n = 37) or placebo (n = 35), administered at weeks 0 and 4, and were followed through week 24. Between weeks 1 and 12, natalizumab reduced the mean number of new active lesions per patient by half compared with placebo (1.8 vs 3.6, respectively; p = 0.042). Patients treated with natalizumab also developed fewer new gadolinium-enhancing (Gd+) lesions, which are associated with breakdown of the blood-brain barrier, than patients receiving placebo (1.6 vs 3.3 mean lesions per patient, respectively; p = 0.017) during weeks 1 to 12. During weeks 12 to 24, there were no statistically significant differences between treatment groups in the mean cumulative number of new Gd+ lesions or in the proportion of scans without new Gd+ lesions. It also was noted that, during weeks 12 to 24, patients who had been treated with natalizumab had a higher relapse rate than those who had received placebo. This difference was attributed to an unusual decrease in relapses in the placebo group, rather than to an increase in the natalizumab group. No other studies have

Table 1 Pharmacokinetic parameters after repeated doses of natalizumab 300 mg in patients with multiple sclerosis (Tysabri PI 2006)

Parameter	Mean \pm SD
C _{max} , μ g/mL	110 \pm 52
C _{ss} , μ g/mL	23 to 29
CL, mL/h	16 \pm 5
V _d , L	5.7 \pm 1.9
t _{1/2} , d	11 \pm 4

Abbreviations: CL, clearance; C_{max}, maximum plasma concentration; C_{ss}, mean steady-state concentration; SD, standard deviation; t_{1/2}, elimination half-life; V_d, volume of distribution.

Table 2 Phase 2 studies of natalizumab

	Objectives	Inclusion criteria	N	Treatment	Results for primary endpoint
Tubridy et al 1999	Effect of natalizumab on MRI lesions in patients with RRMS or SPMS	18–55 years, EDSS of 2.0–7.0, ≥ 2 relapses within past 18 months, relapse-free in past 4 weeks	72	Natalizumab 3 mg/kg or placebo (1:1), at 0 and 4 weeks for a total of 2 infusions	Mean number of new active lesions ^a through week 12: 1.8 natalizumab vs 3.6 placebo (p = 0.042) Mean number of new Gd+ lesions through week 12: 1.6 natalizumab vs 3.3 placebo (p = 0.017)
Miller et al 2003	Safety and efficacy of natalizumab in patients with RRMS or SPMS	18–65 years, EDSS 2.0–6.5, ≥ 2 relapses in past 2 years, ≥ 3 T2 lesions	213	Natalizumab (3 or 6 mg/kg) or placebo (1:1) every 4 weeks for 6 months	Mean number of new Gd+ lesions through month 6: 0.7 natalizumab 3 mg/kg, 1.1 natalizumab 6 mg/kg, 9.6 placebo (p < 0.001 for comparison of each active group vs placebo)
O'Connor et al 2004	Effect of a single dose of natalizumab in patients with RRMS or SPMS during an acute relapse	18–65 years, EDSS ≤ 5.5 , stable FSS scores for ≥ 30 days prior to qualifying acute relapse ^b	180	Natalizumab (1 mg/kg or 3 mg/kg) or placebo (1:1), single dose	Mean change in EDSS between treatment groups at 1 week after treatment: no treatment differences were observed
Goodman et al 2005	Safety and efficacy of natalizumab when added to the standard regimen of GA in patients with RRMS	18–55 years, MRI lesions, EDSS 0.0–5.0, GA treatment for past 12 months, ≥ 1 relapse in past 12 months	110	Natalizumab 300 mg or placebo (1:1), every 4 weeks by IV, in addition to GA SC daily	Rate of new active lesion development on MRI: study complete, but results not available

Notes: All studies were randomized, double-blind, parallel-group, and placebo-controlled; ^aNew active lesions were defined as the sum of new Gd+ lesions on T1-weighted images and new or newly enlarging lesions observed on T2-weighted images; ^bTo qualify as an acute relapse, relapse symptoms must have been present within 24 hours but appeared no longer than 96 hours prior to receiving study medication, and the patient's EDSS score had to be >3.0 at the time of the acute relapse.

Abbreviations: EDSS, Expanded Disability Status Scale; FSS, functional system subscale; GA, glatiramer acetate; Gd+, gadolinium acetate; Gd+, gadolinium acetate; IM, intramuscular; IV, intravenous; MRI, magnetic resonance imaging; RRMS, relapsing-remitting multiple sclerosis; SC, subcutaneous; SPMS, secondary progressive multiple sclerosis.

found an increase in disease activity beyond the untreated state after stopping natalizumab treatment (Miller et al 2003; O'Connor et al 2006). Tubridy and colleagues (1999) concluded that natalizumab was superior to placebo in reducing the formation of brain lesions, but that the duration of the study was too short to detect possible differences in clinical outcomes.

A randomized, double-blind, placebo-controlled, multicenter trial assessed the effects of IV natalizumab 3 mg/kg (n = 68), natalizumab 6 mg/kg (n = 74), or placebo (n = 71) administered every 4 weeks for 6 months to patients with RRMS or SPMS (Miller et al 2003). All patients were followed for an additional 6 months. This study had a longer treatment period and enrolled more patients than the study by Tubridy and colleagues (1999). As with the previous study, the primary endpoints were evaluated by magnetic resonance imaging (MRI) measurements of brain lesions (Miller et al 2003). Secondary and tertiary endpoints were clinical measures such as relapses, disability progression, and patient well-being. During the 6-month treatment period, MRI data showed that natalizumab dramatically reduced the mean number of new Gd+ lesions compared with placebo (9.6 lesions per patient in the placebo group, 0.7 in the natalizumab 3 mg/kg group, and 1.1 in the natalizumab 6 mg/kg group; $p < 0.001$ for either natalizumab dose vs placebo). There was no statistically significant difference between the two natalizumab dose groups. Natalizumab also markedly reduced the mean number of persistent Gd+ lesions, the mean total volume of Gd+ lesions, and the mean number of new active lesions ($p \leq 0.01$ vs placebo for all comparisons). Clinical results showed that natalizumab reduced the number of patients who experienced a relapse by approximately half compared with placebo during the 6-month treatment period (19% for either active treatment group vs 38% in the placebo group; $p = 0.02$ for both comparisons). No statistically significant changes in disability, as measured by expanded disability status scale (EDSS), were observed in any group. A patient-assessed visual analogue scale showed improvements in the natalizumab treatment groups and a small worsening in the placebo group ($p \leq 0.04$, natalizumab vs placebo). The use of corticosteroids to ameliorate relapses was also significantly reduced in the natalizumab groups compared with placebo ($p \leq 0.001$), suggesting that relapse symptoms for patients treated with natalizumab were less intense than for patients receiving placebo. The main conclusions of this study were that natalizumab dramatically reduced lesion formation and relapses, and that longer-term studies were

needed to assess the effect of natalizumab on progression of disability (Miller et al 2003).

A subgroup analysis of the same study examined whether natalizumab could reduce the conversion of Gd+ lesions, which are associated with ongoing inflammation and demyelination, to more permanent T1-hypointense lesions (Miller et al 2003; Dalton et al 2004). Patients were included in the subgroup analysis if they had one or more new Gd+ lesions during months 0 to 6 of treatment and had at least 6 months of follow-up data (Dalton et al 2004). To improve statistical power, data from both natalizumab dose groups were pooled (n = 40) for analysis against placebo (n = 38) group data. At month 12, Gd+ lesions converted to T1-hypointense lesions in 26% of patients in the natalizumab group compared with 68% of those in the placebo group ($p < 0.01$) (Dalton et al 2004).

The clinical efficacy of natalizumab in treating acute MS relapses was investigated in a randomized, double-blind, placebo-controlled, multicenter trial of 180 patients with RRMS or SPMS (O'Connor et al 2004). This study assessed the effects of a single IV dose of natalizumab 1 mg/kg (n = 57), natalizumab 3 mg/kg (n = 60), or placebo (n = 63), administered 1 to 4 days after the start of an acute relapse, on clinical outcomes over 14 weeks. Patients did not receive corticosteroids, which typically would be prescribed in cases of relapse. No statistically significant differences in clinical endpoints were observed with natalizumab versus placebo. While post-hoc analysis revealed less of an increase in the mean volume of Gd+ lesions in the natalizumab groups compared with the placebo group at week 1 ($p = 0.021$ for combined natalizumab groups vs placebo) and at week 3 ($p = 0.024$ for combined natalizumab groups vs placebo), no differences were seen at week 14. These results suggested that natalizumab would not be appropriate for acute relapses, but rather showed more promise as preventative therapy (O'Connor et al 2004).

Phase 2b trial

Glatiramer acetate is a DMT used for the treatment of relapsing-remitting MS. Because the mechanism of action of GA may depend on Th2 lymphocytes entering the CNS (Aharoni et al 2000), a process blocked by natalizumab, concern arose about possible interference between the two therapies. To investigate the consequences of combining GA and natalizumab therapies, the GLANCE (Glatiramer Acetate and Natalizumab Combination Evaluation) study was conducted (Table 2) (Goodman et al 2005). This randomized,

double-blind, placebo-controlled, multicenter safety trial enrolled 110 patients with RRMS who had been treated with GA (≥ 20 mg/day) for at least 1 year and who had experienced at least one relapse during this time. All patients continued to receive GA and also received either placebo or natalizumab 300 mg, administered by IV infusion every 4 weeks for up to 20 weeks. The primary endpoint was the rate of new active lesions detected by brain MRI scans. The study has been completed, but the results are not yet available in the peer-reviewed literature.

Phase 3 trials

Two randomized, double-blind, placebo-controlled, multicenter, Phase 3 trials of natalizumab in patients with relapsing MS have been conducted: AFFIRM (Natalizumab Safety and Efficacy in Relapsing-Remitting MS) and SENTINEL (Safety and Efficacy of Natalizumab in Combination with Avonex® [IFN β -1a] in Patients with Relapsing-Remitting MS).

The AFFIRM study evaluated the long-term efficacy and safety of fixed-dose natalizumab 300 mg monotherapy ($n = 627$) versus placebo ($n = 315$), each administered by IV infusion every 4 weeks, in patients with RRMS (Polman et al 2006). Inclusion criteria required the patients to be aged 18 to 50 years, have MRI lesions consistent with MS, EDSS score of 0.0 to 5.0, and at least one relapse within the previous 12 months. Patients who experienced a relapse within 50 days before the first dose of study medication were excluded. The primary endpoints were the rate of clinical relapses at 1 year and the rate of sustained progression of disability at 2 years. Disability progression was defined as a ≥ 1.0 -point increase in EDSS score from a baseline EDSS score ≥ 1.0 (or a ≥ 1.5 -point increase in patients with a baseline EDSS score of 0) that was sustained for 12 weeks. At 1 year and over 2 years, natalizumab reduced the mean annualized relapse rate by 68% compared with placebo ($p < 0.001$). Over 2 years, the risk of sustained disability progression was reduced by 42% in the natalizumab group compared with the placebo group (hazard ratio [HR] 0.58; 95% confidence interval [CI] 0.43–0.77; $p < 0.001$). Natalizumab decreased the mean number of new or enlarging T2-hyperintense lesions by 83% over 2 years and the mean number of Gd+ lesions by 92% at 2 years, compared with placebo (both $p < 0.001$) (Polman et al 2006). Two-year data from AFFIRM are summarized in Table 3. Uniquely among studies of DMTs in patients with relapsing MS, treatment with natalizumab significantly improved quality of life from baseline to 2

years as compared with placebo on the mental and physical scales of the SF-36 (Ware and Sherbourne 1992; Rudick, Hutchinson, et al 2006).

The SENTINEL study evaluated the long-term efficacy and safety of natalizumab (same regimen as described for AFFIRM) when added to the standard regimen of IM IFN β -1a ($n = 589$), compared with IM IFN β -1a alone ($n = 582$), in patients with RRMS who had experienced breakthrough disease while on IFN β -1a therapy in the prior 12 months (Rudick, Stuart, et al 2006). To participate in SENTINEL, patients had to be 18 to 55 years of age, have MRI lesions consistent with MS, have an EDSS score of 0.0 to 5.0, and have at least one relapse within the previous 12 months, but not within 50 days before randomization. The primary endpoints were identical to those of AFFIRM. Natalizumab/IFN β -1a reduced the mean annualized relapse rate by 54% at 1 year and 55% at 2 years compared with IFN β -1a alone (both $p < 0.001$). Over 2 years, the risk of sustained disability progression, as defined in AFFIRM, was reduced by 24% in patients receiving combination therapy compared with monotherapy (HR 0.76; 95% CI 0.61–0.96; $p = 0.02$) (Table 3). In addition, natalizumab/IFN β -1a decreased the mean number of new or enlarging T2-hyperintense lesions by 83% over 2 years and the mean number of Gd+ lesions by 89% at 2 years, compared with IFN β -1a alone (both $p < 0.001$) (Rudick, Stuart, et al 2006). Treatment with natalizumab/IFN β -1a resulted in better quality of life than treatment with alone IFN β -1a, as measured with the SF-36; however, the difference was significant only for the physical scale (Ware and Sherbourne 1992; Rudick, Hutchinson, et al 2006).

Adverse effects of natalizumab from clinical studies

Safety and tolerability of natalizumab were evaluated during all Phase 1, 2, and 3 trials (Sheremata et al 1999; Tubridy et al 1999; Miller et al 2003; O'Connor et al 2004; Vollmer et al 2004; Polman et al 2006; Rudick, Stuart, and Calabresi 2006; Biogen Idec Data on File). Natalizumab was well tolerated in Phase 1 trials when administered alone (Sheremata et al 1999; Rudick and Sandrock 2004; Biogen Idec Data on File) or in combination with IM IFN β -1a (Vollmer et al 2004). In all Phase 2 trials, natalizumab was well tolerated and adverse events (AEs) were similar among patients receiving either natalizumab or placebo (Tubridy et al 1999; Miller et al 2003; O'Connor et al 2004). Miller and colleagues (2003) reported that levels of lymphocytes, monocytes, and eosinophils,

Table 3 Phase 3 studies of natalizumab: 2-year results

	Natalizumab (n = 627)	Placebo (n = 315)	P- Value
AFFIRM (Polman et al 2006)			
Clinical endpoints			
Annualized relapse rate, mean (95% CI)	0.23 (0.19, 0.28)	0.73 (0.62, 0.87)	<0.001
Sustained disability progression ^a , % of patients	17	29	<0.001
MRI endpoints (lesions per patient)			
No. of new or enlarging T2 lesions, mean ± SD	1.9 ± 9.2	11.0 ± 15.7	<0.001
No. of Gd+ lesions, mean ± SD	0.1 ± 1.4	1.2 ± 3.9	<0.001
	Natalizumab + IFNβ-1a (n = 589)	Placebo + IFNβ-1a (n = 582)	P- Value
SENTINEL (Rudick, Stuart, et al 2006)			
Clinical endpoints			
Annualized relapse rate, mean (95% CI)	0.34 (0.29, 0.39)	0.75 (0.67, 0.84)	<0.001
Sustained disability progression, % of patients	23	29	0.02
MRI endpoints (lesions per patient)			
No. of new or enlarging T2 lesions, mean ± SD	0.9 ± 2.1	5.4 ± 8.7	<0.001
No. of Gd+ lesions, mean ± SD	0.1 ± 0.6	0.9 ± 3.2	<0.001

Note: ^aDefined as either a ≥1.0-point increase in EDSS from a baseline of ≥1.0, or a ≥1.5-point increase in EDSS from a baseline of 0. The change was required to be sustained for at least 12 weeks and could not be confirmed during a relapse.

Abbreviations: CI, confidence interval; Gd+, gadolinium enhancing; IFN, interferon; MRI, magnetic resonance imaging; SD, standard deviation.

which express $\alpha_4\beta_1$ -integrin, were somewhat elevated during natalizumab treatment, but that mean levels remained within the normal range. The level of neutrophils, which do not express $\alpha_4\beta_1$ -integrin, was unaffected. One patient in each group (3/213), including the placebo group, developed an illness resembling serum sickness, and one patient in the 3 mg/kg group developed urticaria and bronchospasm that were reversed with antihistamines and corticosteroids (Miller et al 2003).

Analyses of 2-year safety data from the Phase 3 trials have recently been completed and support the excellent tolerability profile of natalizumab (Polman et al 2006; Rudick, Stuart, et al 2006; Yousry et al 2006). Patient withdrawal rates due to AEs were comparable in the different arms of the Phase 3 trials, suggesting that natalizumab was similarly well tolerated when compared with placebo or IFNβ-1a (Polman et al 2006; Rudick, Stuart, et al 2006). In AFFIRM, AE rates were not significantly different between the natalizumab and placebo groups, except for fatigue (27% vs 21%, respectively) and allergic reactions (9% vs 4%) (both $p < 0.05$). In SENTINEL, combination therapy was associated with a somewhat higher incidence of anxiety (12% vs 8% in patients receiving IFNβ-1a alone), pharyngitis (7% vs 4%), sinus congestion (6% vs 3%), and peripheral edema (5% vs 1%) (all $p \leq 0.05$) (Rudick, Stuart, et al 2006). In both AFFIRM and SENTINEL, infections and serious AEs occurred at a low and comparable incidence between

treatment groups, except that MS relapses were significantly reduced among patients receiving natalizumab (Polman et al 2006; Rudick, Stuart, et al 2006).

Two cases of progressive multifocal leukoencephalopathy (PML), a rare brain disorder; were diagnosed in patients with MS who received natalizumab, in combination with IFNβ-1a, in the SENTINEL study (Kleinschmidt-DeMasters and Tyler 2005; Langer-Gould et al 2005). A third case of PML, previously diagnosed as astrocytoma, was later identified post-mortem in a patient with Crohn's disease (CD) who had received immunosuppressive treatment in addition to natalizumab (Van Assche et al 2005). Natalizumab may allow the development of PML by reducing the transmigration of lymphocytes into the CNS and thus prevent or attenuate CNS immunosurveillance, however other immune mechanisms may be involved (Niino et al 2006). Natalizumab was withdrawn from the market in February 2005 and ongoing studies were suspended; patients who had received natalizumab were invited to participate in screening for other cases of PML. Based on this patient population, who received a mean of approximately 18 monthly doses of natalizumab, it was estimated that the incidence of PML was 1 case per 1000 patients over 18 months (95% CI 0.2–2.8) (Yousry et al 2006).

Immunogenicity

An immune response to protein therapeutic agents will lead to the development of neutralizing antibodies in a proportion

of patients; most natalizumab clinical studies assessed patients for the presence of natalizumab-reactive antibodies in serum (Sheremata et al 1999; Miller et al 2003; Vollmer et al 2004; Polman et al 2006; Rudick, Stuart, et al 2006). In the AFFIRM and SENTINEL Phase 3 studies, 6% of patients developed persistent antinatalizumab antibodies, which were associated with an increase in infusion-related AEs and a decrease in the efficacy of natalizumab (Polman et al 2006; Rudick, Stuart, et al 2006). In the AFFIRM study, antibodies were detected in 57 of 625 (9%) of natalizumab-treated patients: 20 (3%) were transiently positive and 37 (6%) were persistently positive. Persistently positive patients showed a loss of clinical efficacy as measured by disability progression ($p \leq 0.05$), relapse rate ($p = 0.009$), and MRI ($p \leq 0.05$) compared with antibody-negative patients. In transiently positive patients, full efficacy was achieved after approximately 6 months of treatment, the time when patients were becoming antibody negative. The incidence of infusion-related adverse events was significantly higher in persistently positive patients. Results of SENTINEL were similar to AFFIRM, except with regard to sustained disability progression (Calabresi et al 2007).

Clinical indications and patient support/disease management programs

Natalizumab is now approved for treatment of MS in both North America and the EU. In the EU, natalizumab is indicated as monotherapy for patients with relapsing-remitting MS who have high disease activity despite treatment with IFN β , and for patients with rapidly evolving severe relapsing-remitting MS. In the former case, patients should have had at least one relapse in the previous year while on therapy and have ≥ 9 T2 lesions or ≥ 1 Gd+ lesion on cranial MRI; in the latter case, patients should have had two or more disabling relapses in one year and ≥ 1 Gd+ lesion or an increase T2 lesion load relative to another recent cranial MRI scan. In the US, natalizumab is indicated as monotherapy for patients with relapsing forms of MS; it is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate MS therapies.

The relative benefits and risks of natalizumab therapy for a particular patient will depend on disease severity, treatment history, and factors that could cause immunocompromise. Risk minimization is achieved by promoting informed benefit–risk decisions, ensuring that natalizumab is not

prescribed to immunocompromised patients, and maintaining vigilance for PML and other adverse events. In the EU, prescribing will be limited to physicians experienced in the treatment of neurological diseases and with timely access to MRI, in facilities that are prepared to deal with any hypersensitivity reactions. Education directed to physicians will cover guidance on the appropriate patient population for treatment, algorithms for managing suspected cases of PML, and information on other risks.

Upon reintroduction of natalizumab for clinical use in the US, Biogen Idec implemented a comprehensive risk management plan, which is called Tysabri Outreach: Unified Commitment to Health (TOUCH). The purpose of TOUCH is to minimize known risks to patients and to continually reassess risks based on new data. Natalizumab will be made available in North America only to healthcare professionals and patients who meet requirements for inclusion in the TOUCH program. These requirements were chosen to ensure that prescribers and patients understand the risks of treatment with natalizumab, including PML and other opportunistic infections, and take advantage of several unique features of natalizumab distribution and administration. The enrolled prescriber counsels the patient on the risks and benefits of natalizumab therapy before an initial prescription is written. Administration of natalizumab is restricted to infusion centers where the staff has been educated about risks and appropriate use. During monthly infusion visits, members of the medical staff have regular opportunities to inform patients about PML risk and to screen for early symptoms of PML. Prescribing guidelines also state that an MRI scan should be obtained prior to treatment to help differentiate future MS symptoms from PML. Patient and physician data, after signed approval, are entered into a database maintained by Biogen Idec. The inclusion of all healthcare providers and patients in TOUCH will provide data for further defining the safety profile of natalizumab.

In addition, the safety of natalizumab is being further assessed in a 5000-patient registry cohort (the Tysabri Global Observation Program in Safety [TYGRIS] study) in the EU and North America, with 5-year follow-up for infections requiring hospitalization, cases of PML, malignancies, and all adverse events which are serious or medically significant. This study has an estimated 95% probability of detecting adverse events that occur at a frequency of at least 1 in 1500 patients. A comprehensive series of additional epidemiological, clinical, and nonclinical studies are either in progress or planned, including a redosing study, a registry

of approximately 300 pregnant patients, and examinations of immune function and vaccine response.

Support and information for patients with MS are also offered by national and international nonprofit, medical, and scientific organizations. These include the Multiple Sclerosis Association of America, the Multiple Sclerosis Foundation, the National Multiple Sclerosis Society, the Consortium of Multiple Sclerosis Centers, the International Multiple Sclerosis Support Foundation, and the Multiple Sclerosis International Federation.

Conclusions

Natalizumab fills an unmet medical need because of it provides a new level of efficacy in slowing disease progression and reducing relapses in MS patients. In addition, patient acceptance should be positively impacted by the convenience of dosing and long-term tolerability. These characteristics make natalizumab an important new therapeutic option for patients with relapsing MS. The efficacy and safety of natalizumab are supported by evidence from multiple, randomized, controlled clinical trials (Miller et al 2003; Polman et al 2006; Rudick, Stuart, et al 2006). A rapid and sustained treatment effect was observed in a large Phase 2 trial in patients with relapsing MS, in which natalizumab reduced relapses by 50% and the formation of Gd⁺ MRI lesions by approximately 90%, compared with placebo (Miller et al 2003). The large, controlled, Phase 3 trials (the AFFIRM and SENTINEL studies), which led to approval of natalizumab in the EU and US, are among the most rigorous and well-designed trials of DMTs to date, and are the most relevant indicators of likely performance in the general population of patients with relapsing MS. After 2 years in the AFFIRM study, patients treated with natalizumab monotherapy had an annualized relapse rate 68% lower than that of patients receiving placebo (Polman et al 2006); this is approximately double the reduction typically observed with IFNs or GA (IFNB 1993; Johnson et al 1995; Jacobs et al 1996; PRISMS 1998). In the same study, sustained disability progression was decreased by 42%, and the mean number of new brain lesions was reduced by 83 to 92% (Polman et al 2006). In the SENTINEL study of patients with continued disease activity despite receiving IFN β -1a therapy, the addition of natalizumab to the standard regimen of IFN β -1a decreased the annualized relapse rate by 55%, sustained disability progression by 24%, and the mean number of new lesions by 83 to 89%, compared with IFN β -1a alone (Rudick, Stuart, et al 2006). Uniquely, among

the trials of DMTs, significant efficacy was seen in nearly all primary, secondary, and tertiary endpoints, including the quality of life measurements. Although direct head-to-head comparisons have not been performed, the preponderance of data strongly supports the notion that natalizumab offers greater efficacy than existing DMTs. Clearly, since MS is a life-long illness, it is important to recognize that the benefits found on relatively short-term measures seen in clinical trials may not translate into long-term effects in the prevention of disability progression. Natalizumab is not a cure for RRMS but it is a significant improvement on current therapy and given its efficacy and tolerability, natalizumab fulfills an unmet medical need in the treatment of MS.

Disclosure of conflict of interest

Professor Hutchinson has received consulting fees from Biogen Idec and grant support from Serono, Schering AG, and Biogen Idec.

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