Natalizumab: α_4-integrin antagonist selective adhesion molecule inhibitors for MS

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Natalizumab (Antegren™, Elan Corp. plc.; Biogen Idec.) is the first α_4-integrin antagonist in the class of selective adhesion molecule inhibitors and is in Phase III clinical trials for the treatment of multiple sclerosis. After a 300 mg intravenous infusion, natalizumab has an elimination half-life of 6 to 9 days, but α_4-integrin receptors expressed on the surface of peripheral blood leukocytes are more than 80% saturated approximately 1 month postinfusion. Therefore, natalizumab is given as a 300 mg dose administered monthly. Preliminary efficacy results showed a marked reduction (~90%) in the formation of new gadolinium-enhancing lesions and reduced the number of patients with relapse by 50% in patients with relapsing–remitting or secondary progressive multiple sclerosis receiving natalizumab versus those receiving placebo over a 6-month period. In clinical studies, natalizumab has demonstrated a favorable safety profile. Pivotal Phase III studies of natalizumab as monotherapy and in combination with intramuscular interferon-β-1a are underway in patients with relapsing–remitting multiple sclerosis. Natalizumab may be an important addition to the therapeutic armamentarium for multiple sclerosis.

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Multiple sclerosis (MS) is a chronic disease of the CNS which causes various symptoms including sensory disturbances, unilateral optic neuritis, diplopia, limb weakness, clumsiness and gait ataxia [1]. Eventually, more troublesome complications such as cognitive impairment, spasticity, dysphagia, vertigo, pain, sensory loss and sexual dysfunction may also appear. The pathological hallmark of MS is multiple foci of inflammation accompanied by demyelination and varying degrees of axonal transection. The presence of gadolinium-enhancing (Gd+) lesions on magnetic resonance imaging (MRI) indicates current sites of presumed inflammatory demyelination [1].

Goals of pharmacotherapy in MS include symptom relief during acute relapses, and the prevention of future relapses and disease progression. Since a first clinical demyelinating event is associated with the development of clinically definite MS when MS-like lesions are present on brain MRI scans [2], early intervention is important and should be considered at the time of the first neurological event, especially in patients with an unfavorable prognosis [3]. Corticosteroids are standard therapy for the treatment of acute relapses due to their immunomodulatory and anti-inflammatory effects. They shorten the duration of the relapse and allow for faster recovery [3]. In the Optic Neuritis Treatment Trial, treatment with intravenous methylprednisolone (Medrone®, Pfizer Inc.) 1000 mg/day for 3 days followed by 1 mg/kg of oral prednisone for 11 days was associated with a significantly faster recovery compared with oral prednisone alone or placebo for 14 days [4,5]. After 2 years of follow-up, patients treated with intravenous methylprednisolone demonstrated a decreased risk of subsequent attacks compared with patients treated with prednisone alone [6]. However, it is unknown whether corticosteroids affect the long-term course of the disease [3].

Disease-modifying agents (DMAs) include interferon (INF)-β-1a (Avonex®, Biogen; Rebif®, Serono), IFN-β-1b (Betaseron®, Schering-Plough), glatiramer acetate (Copaxone®, Teva Pharmaceutical Industries) and mitoxantrone (Novantrone®, Lederle). These agents

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act to prevent or slow the primary events of MS [1,3], with varied effects on exacerbation rates, progression of disability, and inflammation in the brain as seen on brain MRI scans [7]. In the USA and Europe, IFN-β is used as first-line standard clinical therapy for relapsing–remitting MS, galatiramer acetate is also used, although not always as first-line therapy [1,8]. These agents have been shown to reduce the development of new Gd+ lesions on MRI and reduce the frequency of new relapses, and IFN-β has been shown to decrease the progression of disability [9–14].

Additional treatment options include immunoglobulin, azathioprine (Imurek®, GlaxoSmithKline), methotrexate, cyclosporin and cyclophosphamide (Endoxana®, Baxter Oncology), although none of these agents have received marketing approval for the treatment of MS from regulatory agencies. These drugs are generally considered for patients with relapsing–remitting disease who have not responded to IFN-β or glatiramer acetate therapy [3]. Many compounds are in development for MS treatment, including natalizumab (Antegren™, Elan Corp. plc.; Biogen Idec.; α_4-integrin antibody), alemtuzumab (MabCampath®, Schering-Plough; antileukocyte antibody), statins (currently used in lipid lowering) and extraneous estrogen [15].

There is little evidence on which to base treatment decisions for patients with continued MS disease activity despite the use of currently available DMAs. Although new therapies have been introduced in the last 10 years, additional effective treatments are needed to slow disease progression, reduce disability, and limit lesion evolution and irreversible tissue destruction [16].

Introduction to natalizumab

Adhesion molecules are involved in the inflammatory demyelination process in the CNS. Adhesion molecules and ligands expressed on endothelial cells and leukocytes (under the control of proinflammatory cytokines) mediate the entry of activated T- and B-lymphocytes and monocytes into the CNS [17]. The glycoprotein $\alpha_4\beta_1$ integrin (also known as very late antigen 4) is one such adhesion molecule and is expressed on lymphocytes, monocytes, mast cells, macrophages, basophils and eosinophils but not neutrophils [16]. The expression of $\alpha_4\beta_1$ integrin has been shown to be increased after T-cell activation [18]. The expression of vascular cell adhesion molecule (VCAM)-1, the major ligand for $\alpha_4\beta_1$ integrin, is increased in active CNS plaques [18].

Natalizumab is a recombinant humanized α_4-integrin antibody derived from a murine monoclonal antibody (mAb) to human $\alpha_4\beta_1$ integrin [19]. The murine mAb was humanized by complimentarity determining region grafting of the hypervariable region of the gene encoding the murine antibody onto a human immunoglobulin G4 framework (FIGURE 1) [19]. Natalizumab is the first α_4-integrin antagonist in the class of selective adhesion molecule (SAM) inhibitors.

Natalizumab binds to α_4-integrin on the surface of activated T-cells and other mononuclear leukocytes, preventing cellular adhesion between the T-cell and the endothelial cell. The disruption of cell adhesion molecule interactions results in the prevention of mononuclear leukocyte migration across the endothelium and into the parenchyma, with a subsequent reduction in proinflammatory cytokines [BIOGEN IDEC, DATA ON FILE]. A further mechanism of natalizumab may be the suppression of ongoing inflammatory reactions in diseased tissues by inhibiting the binding of α_4-positive leukocytes with osteopontin and fibronectin. There are three potential modes of action:

- Blockade of migration by blocking adhesion to endothelial cells and interaction with extracellular matric proteins (eg., fibronectin)
- Blockade of priming by interaction with osteopontin and VCAM expressed on microglial cells and monocytes *in situ*
- Induction of apoptosis by blocking interaction of α_4-integren bearing leukocytes with extracellualr matrix proteins (eg., fibronectin)

Thus, natalizumab may have dual anti-inflammatory effects: inhibition of recruitment of immune cells into inflamed tissue and suppression of existing inflammatory activity at the disease site. Since natalizumab inhibits the migration of leukocytes into gut tissue [BIOGEN IDEC, DATA ON FILE], it is also being investigated in inflammatory gastrointestinal conditions such as Crohn's disease and ulcerative colitis [20–22].

Pharmacokinetic & pharmacodynamic profile

Natalizumab consists of recombinant humanized α_4-integrin antibody and excipient materials (i.e., sodium chloride, sodium dibasic phosphate heptahydrate, sodium monobasic phosphate monohydrate and polysorbate 80). The current formulation of natalizumab is provided in a buffered solution at a concentration of 20 mg/ml. The product is stable for 30 months when stored at 2–8°C [BIOGEN IDEC, DATA ON FILE].

Pharmacokinetics

The pharmacokinetics of natalizumab were evaluated in a Phase I, randomized, placebo-controlled, dose-escalating trial involving 28 patients 19 to 55 years of age with stable relapsing–remitting or secondary progressive MS [19]. Patients were randomized to

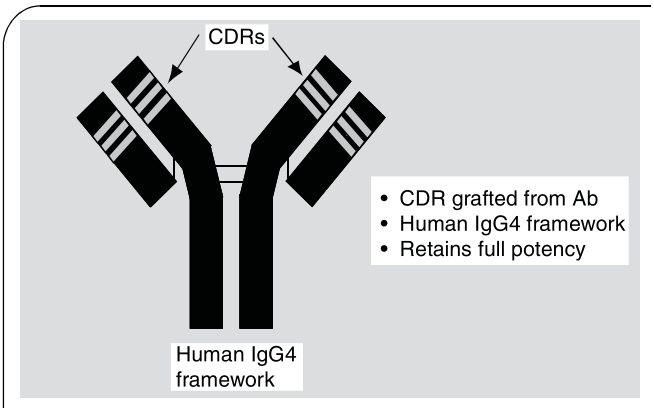

Figure 1. Protein structure of natalizumab.
Ab: Antibody; CDRs: Complementary-determining regions; Ig: Immunoglobulin.

natalizumab 0.03 mg/kg (n = 3), 0.1 mg/kg (n = 3), 0.3 mg/kg (n = 3), 1 mg/kg (n = 6), 3 mg/kg (n = 6) or placebo (n = 7). Maximum serum concentrations and area under the curve (AUC) values for natalizumab were generally proportional to the administered dose, although there was some indication of greater than proportional increases at the higher doses. At the lowest dose levels (0.03 and 0.1 mg/kg), serum natalizumab concentrations rapidly fell below detectable levels after the completion of the infusion. In contrast, patients receiving natalizumab 1 and 3 mg/kg had detectable concentrations for 3 to 8 weeks. At the 3 mg/kg dose, mean maximal drug concentrations (C_{max}) of 52.5 µg/ml were observed approximately 2 h after the dose. The drug concentration time curve was biphasic with a rapid distribution phase followed by a prolonged terminal phase. The elimination half-life of the 3 mg/kg dose was 4 to 5 days (108.0 ± 30.1 h) [19]. The pharmacokinetic parameters for the six patients receiving the highest natalizumab dose level are summarized in TABLE 1.

Similar results were obtained in another Phase I trial evaluating single doses of natalizumab 1, 3 and 6 mg/kg or placebo in 39 patients with relapsing–remitting or secondary progressive MS [BIOGEN IDEC, DATA ON FILE]. Natalizumab concentrations increased proportionally with the administered dose. Mean C_{max} concentrations were 22, 71 and 152 µg/ml for the 1, 3 and 6 mg/kg doses, respectively.

In a Phase II trial, 72 patients with relapsing–remitting or secondary progressive MS received two intravenous infusions of natalizumab 3 mg/kg or placebo 28 days apart [17, BIOGEN IDEC, DATA ON FILE]. There were no significant differences between the first and second doses with respect to pharmacokinetic parameters, indicating no significant accumulation of the drug. Similarly, in another Phase II study in which patients received natalizumab 3 or 6 mg/kg every 28 days for 6 months, there was minimal accumulation of the drug with multiple dosing as assessed by C_{max} and AUC values. However, the mean half-life was slightly higher for the 6 mg/kg dose (262 h) than for the 3 mg/kg dose (202 h) after multiple dose administrations.

The effect of coadministration of natalizumab and intramuscular IFN-β-1a on the pharmacokinetics and pharmacodynamics of both drugs was evaluated in an open-label study of 38 patients with relapsing–remitting MS [BIOGEN IDEC, DATA ON FILE]. Patients were required to have received intramuscular IFN-β-1a for at least 3 months and to be negative for antiIFN-β-1a antibodies. Patients received a single intravenous infusion of natalizumab 3 mg/kg (n = 15) or 6 mg/kg (n = 23). After coadministration of natalizumab and intramuscular IFN-β-1a, pharmacokinetic parameters (e.g., AUC, C_{max} and half-life) for natalizumab were similar to those observed in other pharmacokinetic analyses of natalizumab monotherapy. In addition, pharmacokinetic (AUC and C_{max}) and pharmacodynamic (β-2 microglobulin and neopterin) parameters for intramuscular IFN-β-1a before and after administration of natalizumab were not significantly different. These results suggest that the pharmacokinetics of natalizumab are not altered in the presence of intramuscular IFN-β-1a and that natalizumab does not affect the pharmacokinetics or pharmacodynamics of intramuscular IFN-β-1a.

Table 1. Pharmacokinetic parameters of natalizumab after a single intravenous 3 mg/kg dose in six patients with relapsing–remitting or secondary progressive multiple sclerosis [19].

Parameter	Value (mean ± standard deviation)
AUC_{∞} (µg•h/ml)	9899.00 ± 1285.00
AUC_{last} (µg•h/ml)	9778.00 ± 1380.00
C_{max} (µg/mL)	52.50 ± 12.00
T_{max} (h)	2.07 ± 1.25
Clearance (ml/h/kg)	0.30 ± 0.00
V_{SS} (ml/kg)	67.10 ± 17.10
Half-life (h)	108.00 ± 30.10

AUC: Area under the curve; C_{max}: Maximum plasma concentration; T_{max}: Time to maximum plasma concentration; V_{SS}: Volume of distribution at steady state.

Pharmacodynamics

Single natalizumab doses of 1 to 6 mg/kg produce maximal saturation (defined as >80% saturation) of α_4-integrin receptors on the surface of lymphocytes 24 h after administration [BIOGEN IDEC, DATA ON FILE]. Approximately 90% of patients achieve over 80% saturation of α_4-integrin receptors after natalizumab doses of 3 and 6 mg/kg. Receptor saturation is maintained for 1, 3–4 and 6 weeks with natalizumab 1, 3 and 6 mg/kg, respectively.

Development of antibodies against natalizumab was observed in both Phase I and II studies, as may be expected with a monoclonal antibody product [16,19]. Among the 21 patients receiving natalizumab in a dose-ranging study, none of the patients in the lowest dose levels (0.03, 0.1, 0.3, 1 mg/kg) developed antinatalizumab antibodies [19]. In contrast, three out of six patients receiving natalizumab 3 mg/kg developed low and transient antibody levels. In a Phase II trial, antibodies against natalizumab were detected in 15 out of 142 patients (11%) receiving natalizumab 3 or 6 mg/kg [16]. The clinical impact of binding or blocking antibodies against natalizumab is currently not known.

Natalizumab produced increased levels of circulating white blood cells (i.e., lymphocytes, monocytes and eosinophils) although the mean values did not exceed the normal range [16]. The increase began within the first month of treatment, persisted throughout the treatment period and subsided after treatment was discontinued. This effect is consistent with the mechanism of action of natalizumab-inhibition of the migration of leukocytes to areas of inflammation by binding to α_4-integrin receptors. The increase in white blood cells did not exceed the upper limit of the normal range and does not appear to adversely affect safety.

Pharmacokinetic modeling

A population pharmacokinetic modeling assessment determined that the clearance of natalizumab was only weakly

related to body weight over the range of 40 to 100 kg [BIOGEN IDEC, DATA ON FILE]. Pharmacodynamic data also indicate that the 3 and 6 mg/kg monthly doses maintain adequate saturation of the α_4-integrin receptor in approximately 90% of patients with MS. In addition, this analysis found that there is a plateau effect for efficacy at total doses of 300 mg or more. Based on these data, the mg/kg dosing schedules used in early clinical trials were considered unnecessary. Therefore, ongoing Phase III trials use a fixed 300 mg dose. In a pharmacokinetic study of a single dose of natalizumab 300 mg administered by intravenous infusion over 60 min in healthy volunteers (n = 65), mean concentration of natalizumab and α_4-integrin receptor saturation over time were similar to those observed with mg/kg dosing (FIGURE 2) [BIOGEN IDEC, DATA ON FILE].

Clinical trials

Phase I studies

Four dose-ranging Phase I studies were completed as part of the natalizumab MS clinical development program to gather data on the pharmacokinetic, pharmacodynamic and safety profile of the drug. One study was conducted in healthy volunteers while the other three evaluated natalizumab in patients with either relapsing–remitting or secondary progressive MS. Intravenous doses of natalizumab 0.03–6 mg/kg were assessed. A published Phase I study reported that natalizumab was well-tolerated, with no serious adverse events reported during the study [19]. Although the study was not designed to assess efficacy, there were no in-study disease exacerbations or any increase in disease activity as assessed by MRI.

Overall, Phase I trials found that natalizumab was very well-tolerated, with an overall adverse event profile that did not differ significantly from placebo. Pharmacokinetic and pharmacodynamic results from these studies also helped to identify the most appropriate natalizumab doses for use in subsequent Phase II and III MS trials.

Phase II studies

Overall, Phase II studies have demonstrated significant reductions in inflammatory lesions, as visualized by MRI, and fewer patients with relapse during natalizumab treatment compared with placebo. The results of the published Phase II trials are summarized in TABLE 2 [16,17].

In the first randomized, double-blind, placebo-controlled, parallel-group, Phase II study, the safety and efficacy of natalizumab was evaluated in 180 patients with relapsing–remitting or secondary progressive MS [BIOGEN IDEC, DATA ON FILE]. Patients were randomized to a single intravenous infusion of natalizumab 1 mg/kg (n = 57), 3 mg/kg (n = 60) or placebo (n = 63) during the early phase of an acute exacerbation (within 96 h of onset) and observed for 14 weeks post treatment. There was no significant difference in the rate or degree of recovery from the exacerbation, as measured by the Expanded Disability Status Scale (EDSS). This finding is not unexpected due to the short treatment period and is consistent with other studies showing that natalizumab does not affect the duration of enhancement in pre-existing lesions. A *post hoc* analysis showed a significant reduction in the volume of Gd+ lesions in the natalizumab 3 mg/kg group and the combined 1 and 3 mg/kg group compared with placebo. Given the role of α_4 integrins in T-cell migration and lesion formation and the MRI changes produced by natalizumab in this trial, further clinical studies evaluating multiple doses of natalizumab were considered warranted.

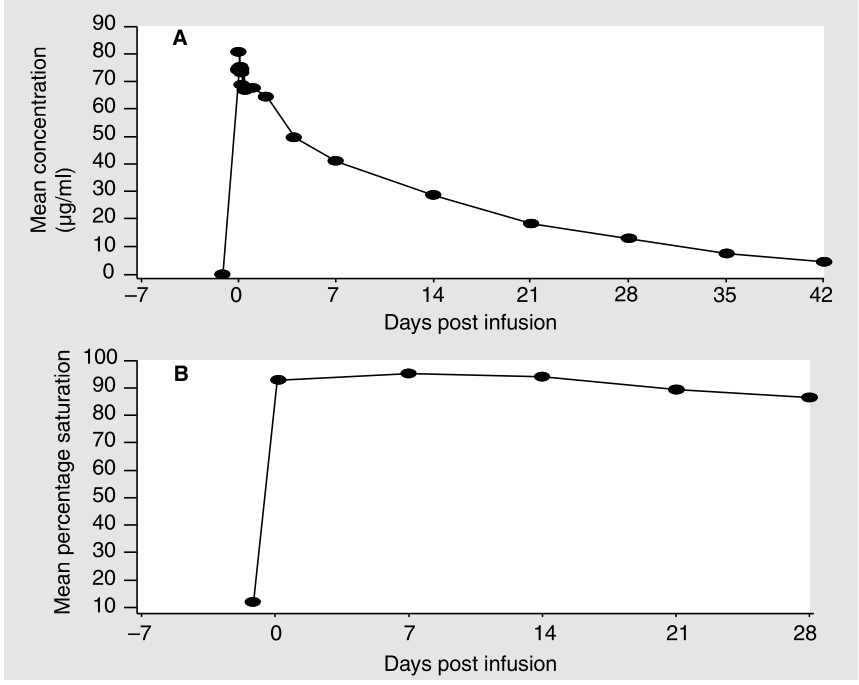

Figure 2. Mean serum concentration (A) and mean percentage saturation of α_4-integin receptors (B) over time in healthy volunteers (n = 65) after a single 60 min intravenous infusion of natalizumab 300 mg.

Tubridy and colleagues conducted a randomized, double-blind, placebo-controlled, parallel-group, Phase II study of the effect of natalizumab on brain lesion activity as detected by MRI in 72 subjects with active relapsing–remitting or secondary progressive MS. This study was described in the pharmacokinetics section [17, BIOGEN IDEC, DATA ON FILE]. Inclusion criteria included EDSS scores of 2.0 to 7.0, inclusive, two or more clinical exacerbations within the past 18 months and more than 4 weeks since onset of last exacerbation. Patients were excluded if they had used immunomodulating drugs within the past 6 months, used corticosteroids within the past 4 weeks or had a normal T2-weighted MRI scan at baseline. Patients were randomized to natalizumab 3 mg/kg (n = 37) or placebo

Table 2. Summary of randomizied, double-blind, placebo-controlled, Phase II clinical trials evaluating natalizumab in multiple sclerosis [16,17].

Study duration	Drug/dose	Efficacy					Ref.
		Timepoint	*Mean number of new active lesions*	*Mean number of new Gd+ lesions*	*Patients with no new Gd+ lesions (%)*	*Patients with relapses (%)*	
24 weeks	Placebo (n = 35)	12 weeks	3.6	3.3	73.1	NR	[17]
	Natalizumab 3 mg/kg every 28 days x2 (n = 37)	12 weeks	§1.8	§1.6	§83.6	NR	
24 weeks	Placebo (n = 71)	24 weeks	9.7	9.6	32.0	38	[16]
	Natalizumab 3 mg/kg every 28 days x6 (n = 68)	24 weeks	§§0.8	§§0.7	75.0	§19	
	Natalizumab 6 mg/kg every 28 days x6 (n = 74)	24 weeks	§§1.1	§§1.1	65.0	§19	

§p < 0.05.
§§p < 0.001.
GD+: Gadolinium-enhancing; NR: Not reported.

(n = 35), administered as two intravenous infusions 28 days apart and were observed for 24 weeks [17]. During the first 12 weeks post-treatment, the mean cumulative number of new active lesions (i.e., the number of new Gd+ lesions plus the number or new or newly enlarging T2 lesions – the primary outcome measure) was significantly reduced in patients receiving natalizumab versus those receiving placebo (1.8 vs. 3.6; p = 0.042). The mean number of new Gd+ lesions during the first 12 weeks was also lower in the natalizumab group than in the placebo group (1.6 vs. 3.3; p = 0.017). In addition, more natalizumab-treated patients experienced no new Gd+ lesions during the first 12 weeks of therapy compared with the placebo group (83.6 vs. 73.1%; p = 0.037). However, natalizumab did not appear to affect the duration of enhancement of lesions that existed prior to treatment.

There was no statistically significant difference between natalizumab and placebo groups in the incidence of MS exacerbations in the first 12 weeks of the study. However there was a difference in the latter 12 weeks of the study (weeks 12–24) in favor of placebo [BIOGEN IDEC, DATA ON FILE]. The discrepancy in the number of patients with relapse in the 12-week post-treatment phase was due to a reduction in relapses in the placebo group rather than a true increase in relapses in the Antegren group. Disability scales did not show consistent or marked differences for patients receiving natalizumab versus placebo. However, this is not surprising, as improvement in disability has generally not been observed in trials of DMAs after such a short treatment period [9–11].

Another randomized, double-blind, placebo-controlled Phase II(b) study was conducted in 26 clinical centers in the USA, Canada and the UK [16]. Inclusion criteria included EDSS scores of 2.0 to 6.5, inclusive, two or more relapses within the past 2 years and three or more T2 lesions on MRI. Patients were excluded if they had used immunomodulating drugs within the past 3 months or had an MS relapse, or used corticosteroids within 30 days of study entry. A total of 213 patients with relapsing–remitting or secondary progressive MS were randomized to monthly intravenous infusions of natalizumab 3 mg/kg (n = 68), natalizumab 6 mg/kg (n = 74), or placebo (n = 71) for 6 months. Patients were monitored for adverse events throughout the study and for 6 months after cessation of study therapy. There were no significant differences in baseline patient demographics or MRI parameters among the three treatment groups.

The mean number of new Gd+ lesions (the primary outcome measure) was 9.6, 0.7 and 1.1 in the placebo and natalizumab 3 and 6 mg/kg groups, respectively, over the 6 months of treatment (p < 0.001 for both natalizumab doses vs. placebo) [16]. This represented reductions in new lesions of 93% with natalizumab 3 mg/kg and 88% with natalizumab 6 mg/kg compared with placebo. The difference between natalizumab groups was not statistically significant. The decrease in new Gd+ lesions was evident both in patients with relapsing–remitting MS and in those with secondary progressive MS. Natalizumab also produced a significant reduction in the number of new active lesions (0.8 and 1.1 for natalizumab 3 and 6 mg/kg, respectively, vs. 9.7 for placebo; p < 0.001 for both natalizumab doses vs. placebo). In addition, both dose levels of natalizumab produced substantial reductions in total volume of enhancing lesions and in the percentage of scans showing inflammatory activity compared with placebo.

Although the study was not powered to detect statistically significant differences in clinical parameters, natalizumab demonstrated improvements in clinical outcomes. In the natalizumab groups, there was a reduction of approximately 50% in the number of patients experiencing a relapse compared with placebo (relapse experienced by 38% of patients in the placebo group and 19% in each treatment group, p = 0.02 for both natalizumab doses vs. placebo) [16]. Natalizumab 3 and 6 mg/kg also significantly improved patients' sense of

well-being (as measured by a visual analog scale) compared with placebo ($p = 0.04$ and 0.03, respectively). In addition, more patients receiving placebo (81%) required intravenous methylprednisolone for the treatment of relapse than those receiving natalizumab 3 mg/kg (38%; $p < 0.001$) or 6 mg/kg (50%; $p = 0.002$).

Additional analyses of these data [16] showed that natalizumab significantly suppresses the evolution of new Gd+ lesions to T1-hypointense lesions [23]. Specifically, compared with placebo, natalizumab (3 or 6 mg/kg) significantly decreased the proportion of patients with new Gd+ lesions that evolved to T1-hypointense lesions ($p = 0.01$), the proportion of new Gd+ lesions that became T1 hypointense ($p = 0.045$) and the odds ratio of converting from Gd+ into T1-hypointense lesions ($p = 0.031$).

Phase III studies

There are two ongoing Phase III clinical trials – AFFIRM and SENTINEL – designed to confirm the safety and efficacy of natalizumab alone (AFFIRM) or in combination with intramuscular IFN-β-1a (SENTINEL) in patients with relapsing–remitting MS. These 2-year trials are scheduled to be completed in late 2004 and early 2005, respectively.

AFFIRM is a double-blind, placebo-controlled, parallel-group, global study designed to evaluate the efficacy and safety profile of natalizumab over 2 years in patients with relapsing–remitting MS [24]. Patients 18 to 50 years of age with a diagnosis of MS (McDonald criteria, 1–4) [25], a baseline EDSS score 0.0–5.0 (inclusive), one or more relapse within the past 12 months and MRI lesions consistent with MS were eligible for inclusion. Exclusion criteria included primary progressive, secondary progressive or progressive relapsing MS, relapse within 50 days of randomization or unstable from prior relapse; treatment with IFN-β or glatiramer acetate for 6 months or more, treatment with IFN-β, glatiramer acetate, cyclosporin, azathioprine, methotrexate, or immunoglobulin within the past 6 months; and treatment with cyclophosphamide or mitoxantrone within the last year. A total of 942 patients were randomized (2:1) to natalizumab 300 mg or placebo intravenous infusion every 4 weeks for up to 116 weeks [24].

The primary efficacy outcomes of AFFIRM are the rate of clinical relapse at year 1 and sustained disability progression as assessed with the EDSS at year 2 [24]. Secondary measures at year 1 are the number of Gd+ lesions, the number of new or enlarging T2 hyperintense lesions and the proportion of relapse-free subjects. Secondary measures at year 2 are the rate of relapse, the number of T1 hypointense lesions, the volume of T2 hyperintense lesions and the progression of disability assessed with the Multiple Sclerosis Functional Composite (MSFC) scale [BIOGEN IDEC, DATA ON FILE]. Additional end points include the assessment of quality of life, cognitive changes and brain parenchymal fraction. Safety assessments include laboratory testing, physical examinations and adverse event monitoring.

SENTINEL is a double-blind, placebo-controlled, parallel-group, multicenter global study designed to determine the efficacy and safety of natalizumab when added to a standard regimen of intramuscular IFN-β-1a in a relapsing–remitting MS patient population that experienced breakthrough disease (defined as ≥1 relapse within 12 months of study enrollment) while on intramuscular IFN-β-1a therapy for at least 12 months [26]. A total of 1196 patients were randomized 1:1 to natalizumab 300 mg or placebo intravenous infusions every 4 weeks in addition to their current IFN-β-1a regimen (30 µg intramuscular weekly) for up to 116 weeks. Inclusion criteria included 18 to 55 years of age, an MS diagnosis (McDonald criteria, types 1–4) [25], a baseline EDSS score 0.0–5.0 (inclusive), treatment with intramuscular IFN-β-1a for 12 months or longer prior to randomization and MRI lesions consistent with MS. Patients with primary progressive, secondary progressive or progressive relapsing MS, those with relapse within 50 days of randomization or unstable from prior relapse and those receiving treatment with any IFN product aside from intramuscular IFN-β-1a within 12 months of randomization or treatment with oral glatiramer acetate within 3 months of randomization were excluded [26, BIOGEN IDEC, DATA ON FILE].

The primary efficacy outcomes of SENTINEL are the rate of clinical relapse at year 1 and sustained disability progression as assessed with the EDSS at year 2. Secondary measures at year 1 are the number of new or enlarging T2 hyperintense lesions, the number of Gd+ lesions and the proportion of relapse-free subjects. Secondary measures at year 2 are the rate of relapse, the volume of T2 hyperintense lesions, the number of T1 hypointense lesions and the progression of disability assessed with the MSFC scale [BIOGEN IDEC, DATA ON FILE]. Additional end points include the assessment of quality of life, cognitive changes and brain parenchymal fraction. Safety assessments include laboratory testing, physical examinations and adverse event monitoring.

Postmarketing surveillance, safety & tolerability

Natalizumab is not currently approved by any regulatory agency for human use. Therefore, it's use is restricted to clinical trials and no postmarketing data are available.

Currently, natalizumab has been administered to over 2800 patients, including healthy volunteers, patients with MS and those with inflammatory bowel disease [BIOGEN IDEC, DATA ON FILE]. In Phase I trials evaluating single intravenous doses of natalizumab, treatment was well-tolerated. There were no clinically apparent changes in vital signs, laboratory values, or electrocardiograph measurements. Most of the adverse events were mild in severity with headache and fatigue being the most frequently reported events. Only one serious adverse event was reported in Phase I trials (i.e., MS exacerbation and depression requiring hospitalization), although this event was considered unrelated to natalizumab. In Phase I trials with a placebo comparator, no differences were noted between placebo and natalizumab in the proportion of patients with an adverse event or a laboratory abnormality [19, BIOGEN IDEC, DATA ON FILE].

Table 3. Adverse events reported among patients with relapsing-remitting or relapsing secondary progressive multiple sclerosis receiving natalizumab 3, 6 mg/kg or placebo every 28 days for 6 months [16].

Adverse event	Placebo (n = 71)	Natalizumab 3 mg/kg (n = 68)	Natalizumab 6 mg/kg (n = 74)
Headache	38	40	27
Infection	15	22	19
Urinary tract infection	15	22	18
Accidental injury	17	16	18
Pharyngitis	11	15	22
Myasthenia	15	18	9
Paresthesia	13	13	16
Rash	8	10	11
Pruritis	10	12	5
Back pain	8	4	12
Diarrhea	6	10	3
Sinusitis	4	10	4

Similar results were reported in Phase II trials; natalizumab was well-tolerated, with no overall difference in the number of adverse events occurring in the placebo and natalizumab groups [16,17, BIOGEN IDEC, DATA ON FILE]. In one study involving patients receiving once-monthly infusions of natalizumab 3 mg/kg (n = 68), 6 mg/kg (n = 74), or placebo (n = 71) for a period of 6 months, the most frequently reported events were headache, infection, urinary tract infection, accidental injury, pharyngitis, myasthenia and paresthesia (TABLE 3) [16]. There were 20 serious adverse events among 15 participants in the study, including 11 events among seven patients in the placebo group, five events among five patients in the natalizumab 3 mg/kg group and four events among three patients in the natalizumab 6 mg/kg group. There were four immune-mediated events considered to be related to study medication but these events occurred in less than one out of 250 infusions. In the second published Phase II trial, there was no significant difference between patients receiving natalizumab or placebo with respect to any adverse event during the first 3 months of the study [17]. However, over the entire study period, fatigue and insomnia were more common in the natalizumab group compared with the placebo group (fatigue: 32 vs. 6%; $p = 0.047$; insomnia: 11 vs. 0%; $p = 0.05$).

Infusion-related events have been reported in a few patients receiving natalizumab. These can generally be classified as either early or delayed immune-mediated events [BIOGEN IDEC, DATA ON FILE]. Early immune-mediated events ranged from mild, nonserious allergic reactions to more serious events (e.g., anaphylactoid). Most of these events have occurred during the second infusion of the drug, typically within 60 min of administration. These resolved rapidly after discontinuation of natalizumab and appropriate treatment (e.g., antihistamine and corticosteroids). Delayed-type immune reactions (i.e., serum sickness) have been reported in two patients, accompanied by symptoms such as urticaria, erythema, cough, bronchospasm, sore throat, fever and sweats. The patients were treated with intravenous corticosteroids and/or antihistamines.

Regulatory affairs

Natalizumab has not been approved by the US Food and Drug Administration. The company submitted a Biologics Licensing Application on 24th May 2004 using the first year results from ongoing Phase III trials. This will allow the regulatory process to advance while the clinical trials continue.

Conclusions

Natalizumab is the first α_4-integrin antagonist in the new class of SAM inhibitors, acting to inhibit leukocyte migration into the CNS. Phase II trials have shown that natalizumab significantly reduces the development of new Gd+ lesions, reduces the volume of new lesions and increases the proportion of patients with no new Gd+ lesions [16,17]. Natalizumab also produces improvements in clinical outcome including a reduction in the proportion of patients experiencing a relapse and improvements in patient sense of well-being [16]. These studies indicate that natalizumab is generally safe and well-tolerated with an adverse effect profile generally similar to that produced by placebo [16,17].

Large ongoing trials are assessing the efficacy of natalizumab both as monotherapy and in combination with intramuscular IFN-β-1a. The Phase III combination therapy trial will test the hypothesis that combining therapies with different mechanisms of action will provide superior efficacy in MS. Results of these studies will contribute necessary information to determine the role of natalizumab in the treatment of patients with relapsing forms of MS.

Expert opinion

In Phase I and II trials, natalizumab was generally well-tolerated and effective in reducing Gd+ lesions, reducing relapse rate and improving patient perception of well-being. A major advantage of natalizumab is its ability to substantially reduce relapses; natalizumab was found to reduce relapses by approximately 50% compared with a reduction of approximately 30% with other DMAs [9,11,12,16]. Results of ongoing Phase III trials should provide definitive information on the safety and efficacy of natalizumab as monotherapy and in combination with intramuscular IFN-β-1a.

Natalizumab has an excellent tolerability profile. This is in contrast to IFN-β which is associated with a number of well-described adverse events (e.g., flu-like symptoms, fatigue and

myalgia) [9–11]. Administration of natalizumab is via intravenous infusion, with once-monthly dosing. Intravenous infusion is used for MS patients by neurologists who choose to treat with methylprednisolone for relapses and mitoxantrone or cyclophosphamide for disease progression. However, widespread use of intravenous infusion is not typical in neurologist practice settings. Therefore, this mode of administration represents a change for neurology practices and care providers may require additional training and equipment in order to administer natalizumab correctly. However, this change may be warranted depending on results of currently ongoing clinical trials.

An additional area to be explored is the clinical relevance of antinatalizumab antibodies. In a Phase II trial, 11% of patients receiving natalizumab developed binding antibodies [16]. Whether these antibodies have any effect on the clinical efficacy or duration of effect of natalizumab remains to be determined. In addition, the relative efficacy of natalizumab monotherapy compared with IFN-β-1a or glatiramer acetate monotherapy needs to be evaluated. The availability of an agent with a new mechanism of action may allow for the introduction of both mono- and combination therapy regimens in patients with MS.

The current hope for this new SAM inhibitor is that it will have a positive impact on the worldwide standard of MS treatment. The role of natalizumab in the treatment of MS will be determined only after Phase III trial results become available.

Five-year view

Ongoing investigations to develop new treatment strategies designed to improve outcomes in patients with MS include the evaluation of new agents with novel mechanisms of action, use of combination therapies and evaluation of new therapies. Research in these areas, especially in combination therapy, should produce regimens with greater efficacy in halting disease progression and managing symptoms. A limited number of studies evaluating the addition of an immunomodulating agent (i.e., azathioprine, methotrexate and cyclophosphamide) to IFN-β in MS have shown favorable results [27–30]. Although promising, these studies are small in size and nonrandomized. Larger controlled trials are required to determine whether combination therapies with different mechanisms of action will produce superior results in MS patients [27,30].

The development of small molecule inhibitors of $\alpha_4\beta_1$ integrin is another promising area of research [31]. In animal models, such inhibitors have been shown to induce lymphocytosis (a pharmacodynamic marker of activity) and produce improvements in experimental autoimmune encephalomyelitis. However, the safety and efficacy of these compounds in humans has not yet been evaluated.

There is increasing appreciation of the role of neurodegeneration as a mechanism of progressive neurologic disability in MS patients. Many experts believe that inflammation is a necessary and sufficient pathogenic process that leads to neurodegeneration. If this is true then natalizumab should be neuroprotective, particularly if administered early in the disease process. As the MS pathologic process unfolds, there is evidence to suggest that neurodegeneration becomes uncoupled from inflammation and proceeds in an autonomous fashion. This has led to increased interest in identifying neuroprotective strategies that will inhibit the late neurodegeneration that is seen in patients with long standing MS. The role of natalizumab in progressive neurodegeneration in this context will need to be determined.

Information resources

- National Multiple Sclerosis Society
  www.nationalmssociety.org
  (Accessed June 2004)
- MultipleSclerosis.com (sponsored by Berlex Laboratories)
  www.MultipleSclerosis.com
  (Accessed June 2004)
- Multiple Sclerosis International Federation (Sponsored by Schering AG):
  www.msif.org
  (Accessed June 2004)
- MS Active Source (sponsored by Biogen Idec, Inc.)
  www.msactivesource.com
  (Accessed June 2004)
- MS Thought Leaders (sponsored by Biogen Idec, Inc.)
  www.msleaders.org
  (Accessed June 2004)
- Biogen Idec website
  www.biogenidec.com
  (Accessed June 2004)
- Elan website
  www.elan.com
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Key issues

- Natalizumab is the first α_4-integrin antagonist in a new class of molecules referred to as selective adhesion molecule inhibitors that may disrupt the inflammatory cascade initiated by α_4-integrin-mediated adhesion. Following favorable results in Phase I and II trials in multiple sclerosis (MS), natalizumab is currently undergoing Phase III clinical trials.
- Natalizumab is a humanized α_4-integrin antagonist, derived from a monoclonal antibody against the human α_4-integrin, which blocks the crucial step of lymphocyte and monocyte migration into the CNS at sites of demyelination, the pathological hallmark of MS.
- In a Phase II study in MS, natalizumab reduced new gadolinium-enhancing lesions by approximately 90% and reduced the proportion of patients experiencing a relapse by approximately 50% [16]. These results indicate that interrupting leukocyte migration into the CNS may slow MS disease progression.
- Natalizumab has an elimination half-life of 6–9 days following a single dose and does not accumulate after multiple dosing.
- Based on receptor binding data, adequate saturation (≥80%) of the α_4-integrin receptor is achieved with either 3 or 6 mg/kg natalizumab in approximately 90% of patients. Body weight does not significantly influence clearance of natalizumab, thereby justifying the use of a fixed dose. In addition, it was found that there is a plateau for efficacy at doses of 300 mg or more. Based on these data, the mg/kg dosing schedules used in early clinical trials were considered unnecessary.
- In Phase III trials, natalizumab is administered monthly via intravenous infusion of a fixed 300 mg dose.
- In clinical trials, natalizumab was generally well-tolerated and showed an overall adverse event profile similar to that of placebo [16,17,19]. Hypersensitivity reactions (Type II [immediate and probably immunoglobulin-mediated] and Type III [delayed 'serum sickness']) have been observed in Phase II trials but were rarely serious (anaphylactoid).
- Two large, Phase III trials are underway. One of the trials will assess the efficacy of natalizumab in combination with intramuscular interferon-β-1a, thus testing the hypothesis that combining therapies with different mechanisms of action will provide superior efficacy in MS.
- Another trial is underway to test the safety of combining natalizumab with glatiramer acetate. The study is not powered to determine the efficacy of the combination but will provide important information for future studies testing natalizumab together with glatiramer acetate and for physicians who choose to add natalizumab in patients with suboptimal responses to glatiramer acetate.
- Based on available data, natalizumab may be an important addition to MS therapy.

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