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Relapse rates and enhancing lesions in a phase II trial of natalizumab in multiple sclerosis

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Background: *Natalizumab, a humanized monoclonal IgG4 antibody, is an α4-integrin antagonist, which inhibits the migration of inflammatory cells into the central nervous system, a key pathogenic mechanism in multiple sclerosis (MS). In a six month, phase II clinical trial of patients with relapsing MS, natalizumab significantly reduced the formation of new gadolinium-enhanced (Gd+) lesions and the number of clinical relapses.* ***Objective:*** *To investigate the relationship of historical relapse rate and new Gd+ lesion number with subsequent MS disease activity and natalizumab treatment in the phase II study.* ***Methods:*** *Patients who participated in the phase II study were stratified into subgroups according to: (i) the number of relapses in the two years prior to entry into the study: 2 relapses (*n *= 108), 3 relapses (*n *= 57), and >3 relapses (*n *= 48); (ii) the number of new Gd+ lesions at baseline (Month 0): 0 (*n *= 129), 1–2 (*n *= 50), and >2 (*n *= 33). Relapses and new Gd+ lesions during the treatment phase of the trial were determined and compared for each subgroup.* ***Results:*** *Both the prestudy relapse rate and number of new Gd+ lesions at baseline were related to the subsequent risk of a relapse; baseline number of Gd+ lesions was related to the likelihood of subsequent new Gd+ lesion formation. There was a lower proportion of subjects with an on-study relapse and fewer new Gd+ lesions in all natalizumab-treated subgroups when compared with their placebo counterpart; the difference was most apparent in the subgroups of patients with >3 relapses in the two years prior to study entry and >2 new Gd+ lesions at Month 0.* ***Conclusions:*** *There was a lower proportion of subjects with an on-study relapse in natalizumab-treated patients, particularly in those with a more active disease at study entry. Larger ongoing phase III studies will allow more definitive investigation of these preliminary subgroup findings.*
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Key words: *gadolinium-enhancing lesions; natalizumab; relapsing MS*

Introduction

Natalizumab is the first α4-integrin antagonist in the new class of selective adhesion molecule (SAM) inhibitors.[1] The interaction of α4β1 integrin expressed on lymphocytes and monocytes with its counter receptor, vascular cell adhesion molecule-1 (VCAM-1) expressed on endothelial cells, mediates the migration of lymphocytes and monocytes across the vascular endothelium and into the brain parenchyma. The migration of inflammatory cells across the blood–brain barrier (BBB) is thought to be a key step in the development of multiple foci of inflammation and demyelination within the white matter of the central nervous system (CNS) in patients with multiple sclerosis (MS).[2] By interfering with the pathogenic mechanism of adhesion and migration of inflammatory cells into brain parenchyma, natalizumab might be expected to lead to a reduction in the number of new active lesions.[3,4] The benefits of natalizumab on clinical and magnetic resonance imaging (MRI) outcomes in patients with relapsing MS were recently demonstrated in a phase II clinical trial.[5] Treatment with natalizumab for six months significantly reduced the proportion of patients with clinical relapses and the number of new gadolinium-enhancing (Gd+) lesions, an MRI measure suggestive of acute inflammatory changes associated with breakdown of the BBB.

In the present report, we divided the patients in this phase II trial into subgroups according to the extent of relapse-related or MRI activity prior to study entry. This was done in order to explore, in a post hoc analysis, the following questions: i) Is there an association between prestudy relapse rate or number of new Gd+ lesions at baseline and subsequent disease activity during the study period? and (ii) Are therapeutic effects apparent (comparing natalizumab versus placebo patients) in the subgroups selected according to prior disease activity?

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Patients and methods

Patients

The methods for the phase II study of natalizumab as well as the results of the primary analyses from this study have been published previously.[5] Men and women, 18–66 years of age (inclusive), with either relapsing–remitting MS (RRMS) or relapsing secondary progressive MS (SPMS) were included in the study. Eligible patients had ≥ 2 relapses in the previous two years, a baseline Kurtzke Expanded Disability Status Scale (EDSS)[6] score between 2 and 6.5, and ≥ 3 lesions on T2-weighted brain MRI. Patients were excluded from the study if they received immunosuppressive or immunomodulatory agents within three months before study entry, if they received systemic corticosteroids, or had a relapse within 30 days before study entry.

All patients randomized in the phase II study were included in the additional analyses presented here. Patients were stratified by prestudy relapse rate or number of new Gd+ lesions at baseline. For the purpose of the analyses presented here, the natalizumab treatment group includes all patients randomized to either active treatment group (i.e., combined data from the natalizumab 3 mg/kg and 6 mg/kg treatment groups). These treatment groups were combined because: i) a similar treatment effect was apparent in each group;[5] and ii) the larger combined cohort improved the power for statistical analysis.

Study design

This was a multicentre, randomized, double-blind, placebo-controlled, parallel-group study. Patients were randomized to receive an intravenous infusion of natalizumab 3 mg/kg, natalizumab 6 mg/kg, or placebo every 28 days for six months. Patients were followed for an additional six months post-treatment.

Gd+ T1-weighted MRI was used to determine the number of Gd+ lesions at baseline (one month before randomization at Month 0), immediately before each treatment, one month after the last treatment, and at Months 9 and 12. Patients were evaluated for relapses at various scheduled time points throughout the study and at unscheduled visits in the event of a suspected relapse. A relapse was defined as the occurrence of an acute episode of new or worsening symptoms of MS that lasted at least 48 h after a stable period of at least 30 days and was accompanied by an increase from baseline of at least one point in the score on the EDSS, at least one point on two functional system scores, or at least two points on one functional system score. Neurologic symptoms that did not meet the aforementioned criteria for relapse but were judged to constitute a relapse by the treating neurologist were also recorded as a relapse. Relapses reported here include both defined relapses and neurologist-judged relapses.

MRI

Precontrast proton density (PD) and T2-weighted spin echo (SE) scans and Gd+ T1-weighted SE images were acquired during the screening phase (Month −1), immediately before each treatment (Months 0–5), one month following the last treatment (Month 6), and during safety follow-up at Months 9 and 12. The following parameters were used: repetition time (TR) = 2–2.5 s; short echo time (TE) = 30–40 ms; long TE = 80–100 ms. Also at each of these visits, a T1-weighted SE was acquired 5–7 min after the administration of 0.1 mmol/kg gadolinium diethylenetriamine pentaacetate [Gd-DTPA] (TR = 500–700 ms, TE = 5–25 ms). For all of the MRI sequences, 46 axial oblique, contiguous, interleaved slices were acquired with a matrix of 256×256 and a slice thickness of 3 mm. Repositioning for all follow-up MRI scans was achieved by using a protocol based on identification of standardized anatomical landmarks.[7]

MRI analysis

All MRI studies performed at the individual centres were archived onto hard copy film and electronic media and transported to the MRI Analysis Center (Institute of Neurology, University College London, Queen Square, London, UK), where analyses were performed by staff blinded to the clinical details.

On hard copy scans, two experienced observers identified and counted the number of new and persisting T1 Gd+ lesions at Months 0, 1, 2, 3, 4, 5, 6, 9 and 12 (results previously published),[5] as well as new and enlarging T2 hyperintense lesions and new T1 hypointense lesions at Months 6 and 12.

Statistical analyses

Only relapses and new Gd+ lesions during the treatment phase (Months 1–6) were included in these subgroup analyses. The association between treatment and the proportion of subjects with an on-study relapse, stratified by the number of relapses in the two years prior to study entry, was evaluated using a logistic regression model. The number of relapses in the two years prior to study entry was categorized as: 2 relapses, 3 relapses and >3 relapses. Covariates in the model were treatment group (natalizumab versus placebo) and number of relapses in the two years prior to study entry. The number of relapses in the past two years was included in the logistic model as an ordered categorical covariate. A separate logistic model evaluated the interaction between treatment group and number of relapses in the two years prior to study entry. For this model, a covariate for the treatment group and number of relapse interaction was added.

Similar analyses using a logistic regression model were conducted for the association between treatment and the proportion of subjects with an on-study relapse, stratified by the number of new Gd+ lesions at Month 0. These were defined as new Gd+ lesions detected on the baseline MRI (Month 0), i.e., lesions that were not present on the screening MRI, obtained one month prior to baseline. The number of new Gd+ lesions at Month 0 was categorized into three groups: 0 Gd+ lesions; 1–2 Gd+ lesions; and >2 Gd+ lesions. Treatment group and the number of new Gd+ lesions were included as covariates in the model. A separate model evaluated the interaction between treatment groups by number of new Gd+ lesions.

The association between new Gd+ lesions at Month 0 and the median number of new Gd+ lesions during Months 1–6 was evaluated using the Kruskal–Wallis test. The proportion of patients with RRMS was stratified both by number of relapses in the two years prior to study entry and by number of new Gd+ lesions at Month 0.

Results

A total of 213 patients were randomized in the phase II trial of natalizumab. Of these, 68 received 3 mg/kg natalizumab, 74 received 6 mg/kg natalizumab, and 71 received placebo. For the analyses presented here, the natalizumab treatment group ($n=142$) included all patients treated with natalizumab (3 mg/kg and 6 mg/kg) in the phase II trial. Demographic and baseline disease characteristics were similar between the natalizumab and placebo groups (Table 1), as were the proportions of each subgroup stratified by prior relapse or baseline MRI activity (Table 2).

Stratification by number of previous relapses

In both placebo and natalizumab subgroups, it was apparent that the proportion of patients experiencing relapses on study increased with increasing number of relapses in the two years prior to study entry (Figure 1). Natalizumab reduced the proportion of patients with an on-study relapse compared with placebo, regardless of the number of relapses during the two years prior to study entry ($P=0.004$, Figure 1). Although the test for a treatment group by baseline relapse interaction was not quite statistically significant ($P=0.061$), a strong trend for a decreased likelihood of a relapse in the natalizumab group that had experienced >3 relapses during the two years prior to study entry was identified. Among these patients, the percentage of patients who experienced an on-study relapse was 23% in the natalizumab group versus 71% in the placebo group.

Table 1 Patient demographics and baseline disease characteristics

Characteristic	*Natalizumab* (n = *142*)	*Placebo** (n = *71*)
Sex, *n* (%)		
Female	106 (75)	46 (65)
Male	36 (25)	25 (35)
Mean age, years	44	43
Category of MS, *n* (%)		
Relapsing–remitting	99 (70)	45 (63)
Secondary progressive	43 (30)	26 (37)
Mean disease duration, years	12	10
No. of relapses in past two years		
Mean	3	3
2, *n* (%)	74 (52)	34 (48)
3, *n* (%)	37 (26)	20 (28)
>3, *n* (%)	31 (22)	17 (24)
No. of new Gd+ lesions at Month 0		
Mean	1.4	1.3
0, *n* (%)	81 (57)	48 (68)
1–2, *n* (%)	38 (27)	12 (17)
>2, *n* (%)	23 (16)	10 (14)

*MRI scans were not available for one patient in the placebo group.

Table 2 Proportion of patients by the number of relapses in the two years prior to study entry and the number of new Gd+ lesions at baseline (Month 0) by disease type

	Natalizumab		*Placebo*	
	RRMS (n = *99*)	*SPMS* (n = *43*)	*RRMS* (n = *45*)	*SPMS* (n = *26*)
No. of relapses				
2, *n* (%)	50 (51)	24 (56)	19 (42)	15 (58)
3, *n* (%)	27 (27)	10 (23)	15 (33)	5 (19)
>3, *n* (%)	22 (22)	9 (21)	11 (24)	6 (23)
No. Gd+ lesions				
0, *n* (%)	57 (58)	24 (56)	32 (71)	16 (64)
1–2, *n* (%)	26 (26)	12 (28)	6 (13)	6 (24)
>2, *n* (%)	16 (16)	7 (16)	7 (16)	3 (12)

Stratification by number of Gd+ lesions at baseline

Compared with the placebo group, a lower proportion of patients in the natalizumab group had an on-study relapse, regardless of the number of new Gd+ lesions at baseline ($P=0.003$, Figure 2). A separate logistic regression model suggested that there was an interaction between the number of new Gd+ lesions at baseline and treatment ($P=0.033$), with the decrease in the proportion of patients with a relapse most apparent in the subgroup of patients who had >2 new Gd+ lesions at Month 0 (4% of patients in this natalizumab subgroup experienced a relapse on study versus 60% in the placebo subgroup).

Patients in the placebo group who had a greater number of new Gd+ lesions at Month 0 had a greater number of

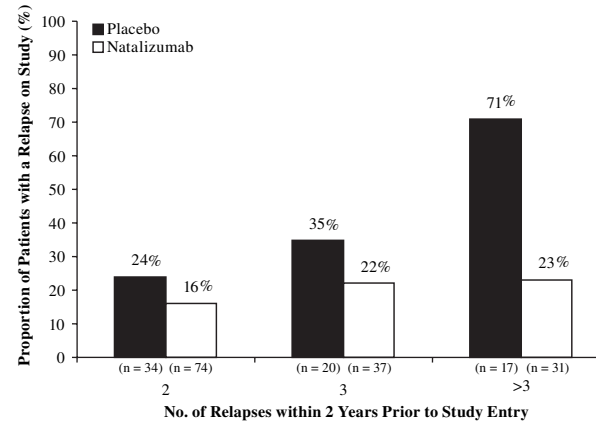

Figure 1 *Proportion of patients with a relapse on study (Month 6) by number of relapses in the two years prior to study entry. The number of relapses in the two years prior to study entry was categorized as: 2 relapses, 3 relapses and >3 relapses, and evaluated using ordinal logistic regression. Covariates in the model were treatment group (natalizumab versus placebo), and number of relapses in the two years prior to study entry. The number of relapses in the past two years was included in the model as an ordered categorical covariate.*

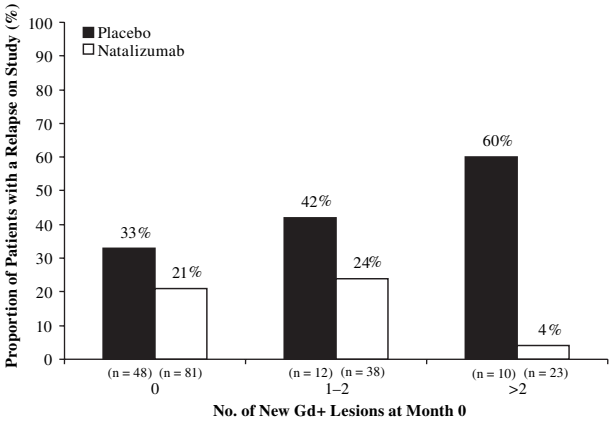

Figure 2 *Proportion of patients with a relapse on study (Month 6) stratified by the number of new Gd+ lesions at Month 0. The number of new Gd+ lesions at Month 0 was categorized into three groups: 0 Gd+ lesions, 1–2 Gd+ lesions, and >2 Gd+ lesions. Treatment group and the number of new Gd+ lesions were included as covariates in the model.*

new Gd+ lesions on study (Figure 3; $P < 0.001$, Kruskal–Wallis). In the placebo group, the median number of new Gd+ lesions during Months 1–6 was 1 for the patients who had 0 new Gd+ lesions at Month 0, 4.3 for patients who had 1–2 new Gd+ lesions at Month 0, and 17.4 for the subgroup of patients who had >2 new Gd+ lesions at Month 0. Among patients in the natalizumab group, the median number of new Gd+ lesions during Months 1–6 was 0 for the patients who had 0 or 1–2 new Gd+ lesions at Month 0, and 1 for the subgroup of patients who had > 2 new Gd+ lesions at Month 0. Therefore, the median number of new on-study Gd+ lesions was similarly low across the groups (0–1) after natalizumab treatment and the reduction in lesion activity was most apparent in the highest lesion activity group at baseline.

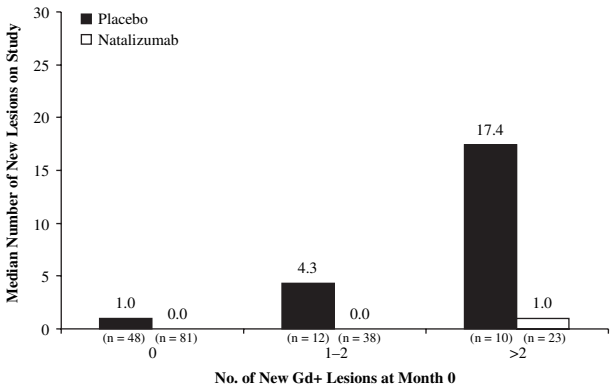

Figure 3 *Median number of new Gd+ lesions between Months 1 and 6 by number of new Gd+ lesions at Month 0. The association between new Gd+ lesions at Month 0 and the median number of new Gd+ lesions during Months 1–6 was evaluated using the Kruskal–Wallis test.*

Discussion

In this post hoc subgroup analysis of data from a phase II trial, we found that: (i) relapse and Gd+ lesion rate during the study were related to the level of such activity observed prior to study entry; and (ii) the reductions in relapses and Gd+ lesions previously observed and reported in the whole cohort[5] were particularly apparent in the subgroup with the highest level of relapse and MRI lesion activity prior to study entry. These findings will be discussed in turn.

The observation that patients with a higher rate of relapse prior to entering the study continued to experience a higher rate of relapse while on study is perhaps not surprising, given the selection of the study population with active relapsing disease and the relatively short duration of the study. A similar relationship between pre-study and on-study relapse activity has been previously observed in another study of natalizumab in acute MS relapses.[8] The relationship observed between the number of new Gd+ lesions at entry and the number of relapses during the next six months is in accordance with results of other studies.[9,10] In a meta-analysis of 307 patients with RRMS and secondary progressive MS, the mean number of Gd+ lesions in monthly scans obtained during the first six months predicted the relapse rate in the first year with moderate ability (relative risk per five lesions = 1.13, $P = 0.023$).[10] It is less clear whether a relationship exists between Gd+ lesions and the development of clinical disability, and the present study duration of only six months precluded any meaningful investigation of this relationship in any of the preselected subgroups or the treatment arms.

The previously reported decrease in relapse rate reported in the whole cohort for natalizumab versus placebo-treated patients[5] was apparent in all the subgroups studied in the present report, but appeared to be most evident in those who had the greatest extent of clinical or MRI activity prior to study entry (i.e., patients experiencing ≥ 4 relapses in the prior two years or exhibiting ≥ 3 new Gd+ lesions at baseline). This finding, which was most certain regarding prestudy MRI activity, may reflect a higher chance of detecting an effect when there are more disease activity events to measure. It may also reflect a potential for the therapeutic effects of natalizumab to be greater in patients with more active disease, a finding that could not have been predicted *a priori*. The treatment effects did not appear to differ between RRMS and SPMS patients. Natalizumab prevents α4-integrin-mediated migration of inflammatory cells across the vascular endothelium and into the parenchymal tissue of the brain,[1] and would therefore be expected to inhibit the development of new inflammatory lesions resulting from disruption of the BBB. Therefore, the findings may also be consistent with the mechanism of action of natalizumab in that a patient with a higher level of inflammatory activity (leukocyte migration) in the CNS may be more responsive to leukocyte migration inhibition; however, this has not been studied directly.

We would emphasize that our therapy observations in the defined subgroups should be seen as exploratory because they are based on a cohort size and study duration that was not powered to definitively investigate the clinical outcomes of a putative MS disease-modifying therapy. Phase III clinical trials are currently underway to define the effect of natalizumab therapy with regard to relapse rates and clinical disability.[11]

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Appendix A

In addition to the authors, the following investigators participated in the International Natalizumab Multiple Sclerosis Trial (principal investigators are in boldface type): *Institute of Neurology, London (MRI Analysis Center), UK* – G.J. Barker, D.G. MacManus, C. Webb, C. Middleditch, S. Lewis, T. Pepple, E. Riddle, C. Coombs; *University of California at Davis, Sacramento* – **M. Agius,** D. Richman, J. Adams, M. Buonocore; *University of Nebraska Medical Center, Omaha* – **J. Al-Omaishi,** K. Markopoulou, K. Healey, P. Sorensen; *Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom* – **D. Bates,** J. Forsyth, J. Curlis, P. English; *University Hospital Queens Medical Centre, Nottingham, United Kingdom* – **L. Blumhardt,** V. Orpe, T. Jaspen; *University of Washington, Seattle* – **J. Bowen,** M. Chang, H. Lew, M. Burke, T. Richards; *Mayo Clinic, Scottsdale, AZ* – **J.L. Carter,** D. Dodick, J. Takata, M. Malikowski, K. Nelson; *Washington University School of Medicine, St. Louis, MO* – **D.A.H. Cross,** J. Trotter, D. Derrington, J. Lauber, C. Martinez, G. Foster, T. Conturo; *University of British Columbia, Vancouver, Canada* – **V. Devonshire,** J. Oger, L. Wang, W. Morrison, L. Costley; *North Staffordshire Royal Infirmary, Stoke on Trent, United Kingdom* – **C. Hawkins,** C. Mathews, C. Gibson; *Hospital for Joint Diseases, New York, NY* – **J. Hebert,** I. Rozentsvit, L. Capolino, J.P. Kelly; *Carolinas Medical Center, Charlotte, NC* – **M. Kaufman,** S. Putman, A. Diedrich, R. Follmer, S. Dombrowski, C. Graves, B. Harwick; *Wayne State University, Detroit, MI* – A.C. Tselis, M. Din, C. Caon, M. Cochran, Z. Latif, R.P. Lisak, M. Zvartau-Hinds; *Foothills Hospital, Calgary, Alberta, Canada* – **L. Metz,** J. Scott, D. Patry, M. Yeung, J. Heuser, C. Wallace, S. Curtis; *Maimonides Medical Center, Brooklyn, NY* – **A. Miller,** E. Drexler, M.J. Keilson, K. Bruining, A. Schneider, R. Wolintz, L. Sciarra, H. Oltazewska; *Rocky Mountain Multiple Sclerosis Center, Englewood, CO* – **R.S. Murray,** A. Bowling, R.E. Kramer, K. Bracht, C. O'Brien, L. Seeberger, J. Leitch, E. Prenger, R. Gagnon; *St. Michael's Hospital, Toronto, Ontario, Canada* – **M. Hohol,** T. Gray, E. Viara, B. Gray, L. Lewin, J. Rainford; *Radcliffe Infirmary, Oxford, UK* – **J. Palace,** A. Cavey, V. Moody; *Texas Neurology, Dallas* – **J.T. Phillips,** A. Martin, D. Hietzman, S. O'Leary, J. Phillips, M. Newsome; *Lehigh Valley Hospital, Allentown, PA* – **A. Rae-Grant,** J.E. Castaldo, G. Mackin, N.J. Eckert, E. Shoemaker, L. Fowler-Blatt; *University of Chicago, IL* – **A. Reder,** B. Arnason, A. Noronha, P. Manning, V. Edmonds, B. Jamison, R. Ladsaria; *London Health Science Center, London, Ontario, Canada* – P. Mandalfino, D. Wingerchuk, M. Nicolle, M. Hopkins, D. Lee, E. Buchner, K. Kennedy; *Guy's Hospital, London, UK* – **M. Sharief,** K. Wilson, S. Soudain, J. Bingham, P. Graves; *University of Miami School of Medicine, Miami, FL* – **A. Minegar,** M. Martinez, G. Calabro, S. Falcone; *Ninewells Hospital, Dundee, UK* – **R. Swingler,** S. Wilson, W. Milne; *Yale University School of Medicine, New Haven, CT* – **T. Vollmer,** M.A. Rizzo, M. Carrithers, G. Blonco, H. Sarofin; *Walton Centre for Neurology and Neurosurgery, Liverpool, UK* – **C. Young,** L. Owens, C. Dickinson.