The efficacy of natalizumab in patients with multiple sclerosis according to level of disability: results of an observational study

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Abstract

Background: Little is known about how the level of disability at the start of treatment with natalizumab affects its efficacy.
Objectives: The aim of this study was to investigate the effect of natalizumab on relapses in patients with different levels of baseline disability associated with MS.
Methods: This single-centre observational study collected demographic data for patients followed prospectively and who were scheduled to start natalizumab therapy due to the presence of disease activity. The annualized relapse rate (ARR) and Kurtzke Expanded Disability Status Scale scores were analysed for the previous year, on starting treatment (baseline) and 1 year after starting therapy.
Results: Seventy-seven patients (mean age: 39.0 years, mean disease duration: 12.4 years) were included. The difference between ARR before and after starting treatment was 0.92 for baseline Expanded Disability Status Scale ::;3.5 ($p < 0.0005$), 0.70 for Expanded Disability Status Scale 4.0–6.0 ($p < 0.007$) and 0.57 for Expanded Disability Status Scale ?:6 (p ¼ 0.386). Expanded Disability Status Scale did not vary during the study. One patient discontinued treatment due to an adverse event and nine patients discontinued due to positive anti-natalizumab antibodies.
Conclusions: The findings support the efficacy of natalizumab in reducing ARR in the year after starting treatment in patients with baseline Expanded Disability Status Scale ::;6.

Keywords

natalizumab, relapsing–remitting multiple sclerosis, secondary–progressive multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic debilitating disease, with an estimated prevalence of 83 per 100 000 inhabitants and an incidence of 4.3 cases per 100 000 in Europe, though with marked regional variations.[1] The natural history of the disease is highly variable; most patients are initially diagnosed with the relapsing–progression of disability.[4] Annualized relapse rates in patients with RRMS have been shown to be reduced by the current mainstay therapies, such as interferon (IFN)b-1b,[5] subcutaneous IFNb-1a,[6] intramuscular IFNb-1a[7] and glatiramer acetate.[8] These therapies are

remitting form of the disease (RRMS), characterized by relapses or exacerbations with subsequent remis- sions.[2] In some patients, this form of the disease converts relatively quickly, in a matter of years, to the secondary–progressive form, whereas in others no sig- nificant progression in disability is noted after decades.[3] Disease-modifyintherapy is generally aimed at reducing the annualized relapse rate and slowing

also thought to slow the progression of the disease, although the effect is less clear.[9]

Natalizumab has been approved as second-line therapy for use in patients who are responding poorly to the more traditional agents. The pivotal clinical trials for initial licensing were conducted in patients who received natalizumab as first-line treatment,[10] although subsequent observational studies point to the effectiveness of natalizumab in the second-line setting.[11–13]

How the effectiveness of these disease-modifying therapies varies at different degrees of disability is unclear. Of the aforementioned therapies, IFNb-1b and IFNb-1a by the subcutaneous route are approved for use in patients with active secondary–progressive multiple sclerosis (SPMS), that is, progressive disease with exacerbations. Little is known about the effects of these therapies in patients with more advanced disease and greater disability. The objective of this study was therefore to investigate the efficacy of natalizumab in patients with active multiple sclerosis (defined by the presence of clinical exacerbations) in spite of previous therapy and, in particular, to compare data on the efficacy of the drug at reducing relapses and disease progression in patients with different baseline Expanded Disability Status Scale scores in a clinical practice setting.

Patients and methods

This was an observational study of the use of natalizumab in a standardized clinical practice setting. Patients were followed prospectively at a single centre (Hospital Regional Universitario Carlos Haya, Malaga, Spain). Patients who were to start treatment with natalizumab were asked whether they wanted to participate in the present study. All patients agreed, and, after signing informed consent, were included in the study. Patients who were participating in other clinical trials or studies at the time of consultation [except for the TYSABRI® Global Observational Program in Safety for Rest of World (TYGRIS) and the Safety of TYSABRI Re-Dosing and Treatment (STRATA) study, which are observational post-marketing studies of natalizumab] were excluded. Prior participation in clinical trials was permitted. In addition, data from patients included in the active treatment arms of previous randomized clinical trials with natalizumab could also be included in the analysis provided that all the information to be collected for the present study was available. Data from patients initially on placebo in these studies who then received natalizumab in the extension studies were also eligible for analysis. These data from patients from the clinical trials with natalizumab were pooled with data from patients from the clinical practice setting. Data were always obtained under the same conditions. Patients were included at least 1 month after their latest attack, in order to be confident that the baseline Expanded Disability Status Scale score was not calculated during a disease exacerbation.

The following data were recorded in the database: demographic data (sex, age), past medical history, history of multiple sclerosis (including date of onset of first symptoms of MS and diagnosis, presenting symptoms, number of relapses and Expanded Disability Status Scale score in the year prior to starting treatment with natalizumab, prior use of disease-modifying drugs, whether immunomodulators or immunosuppressants, and history of natalizumab use), baseline Expanded Disability Status Scale score, number of relapses and Expanded Disability Status Scale after 1 year of therapy, follow-up laboratory tests, status of natalizumab treatment after 12 months (including the reason for withdrawal if applicable), concomitant medication, pregnancy and adverse events. All these variables were recorded prospectively and extracted from the patient records at the end of the study. For the purposes of this study, a relapse was defined as the appearance of symptoms of neurological dysfunction that lasted more than 24 h (and more than 1 month apart) and that affected different parts of the central nervous system (CNS).[14]

This was an observational study that in no way interfered in the care received by the patients and was approved by the ethics committee of the Hospital Regional Universitario Carlos Haya.

Outcome variables and study groups

The main outcome measure was the difference in annualized relapse rate (ARR) between the year before and the year after starting therapy with natalizumab. The secondary outcome measure was the difference in Expanded Disability Status Scale between the start of natalizumab therapy and after 1 year of therapy.

Statistical analysis

For continuous variables, measures of central tendency and dispersion were calculated. For discrete variables, absolute and relative frequencies were calculated. Patients were stratified according to baseline Expanded Disability Status Scale, and the means compared using the paired Student *t* test. All statistical analyses were performed using the SSPS 11.0 program.

Results

A total of 77 patients were included in the analysis. Of these, 64 (83.1%) had started taking natalizumab in a commercial setting, eight (10.4%) had been

included in the active-treatment arm of a placebo-controlled trial of natalizumab[10] and five (6.5%) had started natalizumab after being included in the placebo arm of the aforementioned trial.

The mean age at onset of the disease was 26.3 years (range, 10–55 years) and the mean age on starting natalizumab therapy was 39.0 years (range, 23–63 years). The mean disease duration was 12.4 years (range, 1–32 years). Fifty of the patients were women (71.4%). Pyramidal symptoms were the most common predominant symptom at onset [29 patients (37.7%)], followed by sensory symptoms [20 patients (26.0%)] and brainstem symptoms [16 patients (20.8%)]. Sixty-four patients (83.1%) had a monosymptomatic disease presentation. The baseline distribution of Expanded Disability Status Scale scores is summarized in Figure 1. The mean ARR (±SD) in the year prior to natalizumab treatment was 0.96 ± 0.98. The mean Expanded Disability Status Scale (±SD) 1year before starting natalizumab treatment was 3.18 ± 1.9. At the start of treatment, the mean Expanded Disability Status Scale score was 3.25 ± 2.0. Natalizumab was the first disease-modifying treatment in four patients who were considered to have extremely active disease at onset. More than half the patients [45/77 (58.4%)] had received a single disease-modifying therapy prior to starting natalizumab treatment, while 14/77 (18.2%) had received two drugs. The remaining patients had received three or more prior disease-modifying therapies (maximum, six different prior disease-modifying therapies). The most common prior therapy was interferon beta (used by 81% of the patients), followed by glatiramer acetate (15%). The median number of administrations of natalizumab at the time of data collection was 14.7 (range, 1–58).

Effect of natalizumab treatment on relapse rate and EDSS

The ARR (±SD) in the year before and the year after starting treatment with natalizumab, and the differences, are shown in Table 1, with stratification according to various different baseline Expanded Disability Status Scale scores. The ARR before and after treatment was significantly different for all strata of baseline Expanded Disability Status Scale scores or cutoffs, except Expanded Disability Status Scale ?:6. Table 2 shows the change in Expanded Disability Status Scale (±SD) from start of treatment with natalizumab until 1 year afterwards according to baseline Expanded Disability Status Scale. In this case, no significant differences were found for any of the baseline Expanded Disability Status Scale scores or cutoffs.

Discontinuations and safety data

Thirteen patients withdrew before the end of the year of therapy (16.8%). The most common reason for discontinuation was development of positive neutralizing antibodies to natalizumab (three patients from clinical trials withdrew after developing neutralizing antibodies in one determination and six patients receiving natalizumab commercially discontinued treatment after developing neutralizing antibodies in two successive determinations). In addition, one patient withdrew due to an adverse drug reaction (an allergic reaction which resolved after treatment with methylprednisolone and permanent discontinuation of natalizumab; she had persistent neutralizing antibodies), two because they wished to become pregnant and two for unspecified personal reasons. In general, natalizumab was

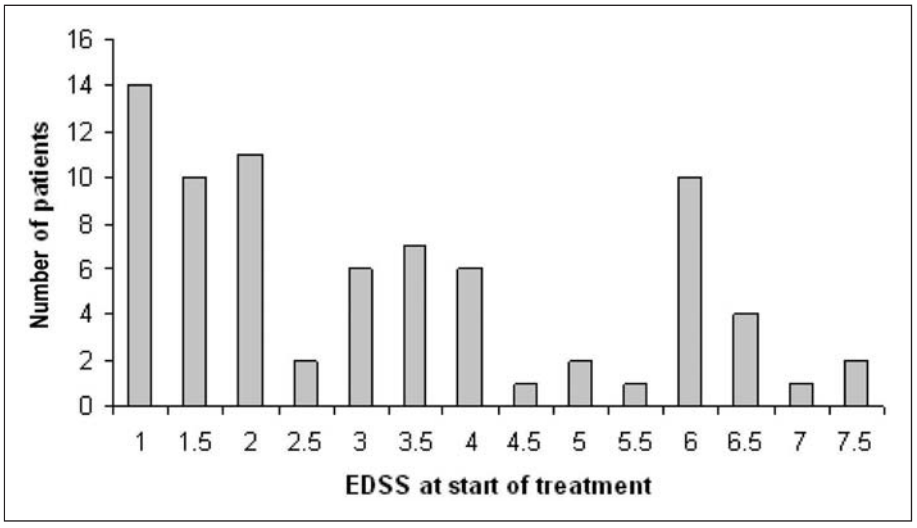

Figure 1. Expanded Disability Status Scale (EDSS) scores of the patients at baseline prior to starting treatment.

Table 1. Change in annualized relapse rate (ARR) between the year before and the year after treatment with natalizumab by baseline Expanded Disability Status Scale

Baseline Expanded Disability Status Scale	*N*	ARR before treatment (mean ± SD)	ARR after treatment (mean ± SD)	ARR before – ARR after (Difference ± SD)	95% CI	*p*
::;3.5	50	1.04 ± 0.91	0.12 ± 0.48	0.92 ± 1.13	0.59 to 1.24	<0.0005
4–6	20	0.85 ± 0.98	0–15 ± 0.48	0.70 ± 1.03	0.22 to 1.18	0.007
?:6	7	0.71 ± 1.49	0.14 ± 0.37	0.57 ± 1.61	0.93 to 2.07	0.386

ARR: annualized relapse rate, CI: confidence interval, SD: Standard Deviation.

Table 2. Change in Expanded Disability Status Scale from start of treatment with natalizumab until 1 year afterwards by baseline Expanded Disability Status Scale

Baseline Expanded Disability Status Scale	*N*	Baseline Expanded Disability Status Scale (mean ± SD)	Expanded Disability Status Scale at 1 year (mean ± SD)	Expanded Disability Status Scale baseline - Expanded Disability Status Scale at 1 year (Difference ± SD)	95% CI	*p*
::;3.5	50	1.96 ± 0.88	1.94 ± 1.06	0.02 ± 0.46	−0.114 to 0.155	0.761
4–6	20	5.20 ± 0.90	5.15 ± 1.20	0.05 ± 0.53	−0.201 to 0.301	0.681
?:6	7	6.85 ± 0.47	6.85 ± 0.47	0	-	-

CI: confidence interval, SD: Standard Deviation.

well tolerated. The most common adverse reaction was headache, reported in 16% of patients, followed by urinary tract infection, reported in 10% of patients.

Discussion

Prototypic multiple sclerosis can be divided into two types according to the presence of relapses and disease progression, namely, RRMS and SPMS.[2] At onset of the disease, patients will have the relapsing–remitting form, which eventually converts to the secondary–progressive form. There is no exact definition of when transition occurs, although some authors have suggested it takes place when the score on the Expanded Disability Status Scale reaches 4.[3] In our study, we applied the definition of Lublin and Reingold[2] (initial relapsing–remitting disease course followed by progression, with or without occasional relapses, minor remissions and plateaus).

Natalizumab has been tested in RRMS (70% of patients) together with SPMS with exacerbations up to Expanded Disability Status Scale 6.5 (30% of patients) in a phase II trial,[15] with positive results in MRI for both disease phases. These results encouraged us to investigate the effect of this agent on the annualized relapse rate in a patient population with a wide range of baseline Expanded Disability Status Scale scores.

The principal finding of our study was that there was a reduction in the annualized relapse rate between the year prior to starting natalizumab and the year following the start of therapy, even for patients with high baseline Expanded Disability Status Scale scores indicative of the transition, or really the advance to the secondary progressive phase of the disease, if exacerbations were still present. This reduction was apparent up to baseline Expanded Disability Status Scale scores of 6. At Expanded Disability Status Scale scores greater than 6, no significant differences were observed, but we must take into account that only seven patients had an EDSS above 6, and this number is too small to perform a meaningful statistical analysis of the efficacy of natalizumab on the annualized relapse rate in these patients.

Natalizumab is thought to exert its beneficial effect principally by interfering in the interaction between very late activation antigen-4 (VLA-4) and the vascular adhesion molecule-1 (VCAM-1).[16] This hinders leukocyte adhesion and migration across the blood–brain barrier to the CNS, thereby alleviating CNS inflammation. Given that the relapsing–remitting phase is characterized by limited focal lesions resulting from inflammation in which immune cells migrate across the blood–brain barrier, natalizumab would be expected to be effective in this phase. In view of its known mechanism of action, natalizumab would not be expected to be so effective in the secondary–progressive, more neurodegenerative phase. However, relapse-type inflammatory events still occur, albeit less frequently, and agents such as natalizumab may still be beneficial.

Natalizumab is indicated as second-line treatment in patients with a poor response to first-line disease

modifying therapy (an IFNb or glatiramer acetate). The pivotal trials for natalizumab were largely conducted using the drug as first-line therapy, although subsequent observational studies have pointed to the efficacy of the drug as second-line treatment.[11–13] The results of our study, in which the overall relapse rate in the year after starting natalizumab therapy decreased by 0.83 in absolute terms (86.5%) compared with the year before, further add to the growing body of evidence that natalizumab is effective after discontinuing first-line therapy with an IFNb or glatiramer acetate.

Natalizumab has been linked with rare but potentially serious and occasionally fatal adverse drug reactions. Opportunistic infections and progressive multifocal leukoencephalotahy (PML) in particular are a concern,[16] and the European Medicines Evaluation Agency has urged patients and prescribers to be vigilant to this possibility.[17,18] In our study, natalizumab was well tolerated and only one patient had to discontinue due to a severe adverse event. The most common reason for discontinuation was, in fact, development of antibodies against natalizumab. In the pivotal Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) study, the incidence of persistent antibodies against natalizumab was 6% and their presence was associated with reduced clinical efficacy.[19] In our study, 9/77 patients (11.6%) withdrew due to the presence of anti-natalizumab antibodies, although in three of these only one determination was positive and so these antibodies would not be considered as persistent.

Our study is clearly limited by the retrospective design. However, given that information on the disease was extracted from medical records and data collected prospectively rather than by patient recall, this should help limit systematic bias. In addition, there was no separate comparator used in our study. Essentially, patients acted as their own comparator, with the year before treatment serving as the comparator in the case of annualized relapse rate and Expanded Disability Status Scale at baseline as the comparator for Expanded Disability Status Scale at 1 year. While these limitations, which would be inherent to most observational studies of this type, should be recognized when interpreting the results, we believe that observational studies outside the tightly controlled setting of interventional clinical trials can provide valuable information of interest to physicians working in clinical practice. In the particular case of the present study, the results provide evidence that natalizumab is effective in patients with Expanded Disability Status Scale scores up to 6.

In conclusion, the present study provides further evidence of the effectiveness of natalizumab at reducing the annualized relapse rate in MS patients with a range of different Expanded Disability Status Scale scores when used as second-line therapy. The drug was well tolerated and no particular safety concerns were identified.

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