An observational study of the effectiveness and safety of natalizumab in the treatment of multiple sclerosis

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Aim. To analyse the safety and effectiveness of natalizumab in the treatment of multiple sclerosis in a real clinical practice setting and according to the approved indications.

Patients and methods. All patients with multiple sclerosis treated with natalizumab in our centre were evaluated. The clinical and radiological disease activity during the first year of treatment was analyzed in patients who received at least 12 doses of the drug. The data regarding moderate and severe adverse events in the entire study sample was also evaluated.

Results. A total of 112 patients were included in the study, of which 110 had been previously treated with other drugs and 76 had received at least 12 doses of natalizumab. In this group, the annualized relapse rate was reduced by 89% compared to the preceding year and 80% of patients were free from relapses after one year of treatment. Nine percent of patients exhibited 3-month confirmed disability progression. At month 12, the mean number of gadolinium-enhancing lesions on brain MRI was decreased by 99% compared to the pre-treatment MRI. During the first year of treatment, 76% of patients remained free from clinical activity and 33% remained free from both clinical and radiological disease activity. Twenty-nine percent of patients had at least one moderate or severe adverse event, which led to treatment discontinuation in 6%. Four percent of patients experienced immediate hypersensitivity reactions.

Conclusion. This study suggests that natalizumab is effective in reducing disease activity in patients with relapsing multiple sclerosis and inadequate response to other therapies, with a favorable risk-benefit ratio.

Key words. Immunomodulatory treatment. Magnetic resonance imaging. Monoclonal antibody. Multiple sclerosis. Natalizumab. Observational study.

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Introduction

Natalizumab, an α_4 integrin inhibitor, is the first monoclonal antibody approved for the treatment of relapsing-remitting multiple sclerosis (MS). Natalizumab probably exerts its therapeutic effect by blocking the interaction between the leukocyte integrin $\alpha_4\beta_1$ and its endothelial receptor VCAM-1, thus inhibiting the transmigration of leukocytes across the blood-brain barrier into the central nervous system parenchyma [1]. The efficacy of natalizumab for the treatment of MS has been evaluated in four Phase II and two Phase III clinical trials [2-7]. In the AFFIRM study, a Phase III clinical trial in patients with relapsing-remitting MS, natalizumab in monotherapy reduced the risk of sustained disability progression by 42% and the relapse rate by 68% after two years of treatment, as compared with placebo [6]. In the same study, natalizumab also reduced the number of new or enlarging lesions on T_2-weighted sequences by 83% and the number of gadolinium-enhancing (Gd+) lesions by 92%, as detected by brain magnetic resonance imaging (MRI).

Despite its considerable efficacy, the use of natalizumab has been restricted due to several reports of progressive multifocal leukoencephalopathy, a serious opportunistic infection of the central nervous system, in patients who were receiving the drug [8]. The risk of this complication is currently estimated at 0.8 to 1.3 cases per 1,000 patients treated with the drug for 12 to 24 months, respectively [9]. In Europe, the approved therapeutic indications limit the use of natalizumab to patients with relapsing-remitting MS with high disease activity despite treatment with interferon β (IFNβ), and to those with rapidly evolving severe relapsing-remitting MS [10]. However, no clinical trials have adequately evaluated the efficacy of natalizumab as a second-line therapy or

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in aggressive forms of the disease. In addition, no studies have been conducted to compare the efficacy of natalizumab in monotherapy with other available disease-modifying drugs. The objective of the present study was to investigate the safety and effectiveness of natalizumab in routine clinical practice and according to the approved indications.

Patients and methods

Sample

The present study included all consecutive patients with MS who started treatment with natalizumab at the Multiple Sclerosis Centre of Catalonia since its authorisation in 2006 by the Spanish Agency of Medicines and Health Products, until December 2009.

According to the criteria established by the General Directorate of Health Resources of the Department of Health of the Government of Catalonia, natalizumab is indicated as monotherapy in patients of 16 years or older with relapsing-remitting MS and a score of 0 to 5.5 on the Kurtzke's expanded disability status scale (EDSS), who have suboptimal response to treatment with IFNβ, as defined by two or more relapses and an increase of 1.0 on the EDSS in the preceding year. These patients must also have at least nine lesions consistent with demyelination on T_2-weighted sequences or one Gd+ lesion on brain MRI. Treatment is also indicated for patients with rapidly evolving severe relapsing-remitting MS. This is defined by the occurrence of two or more disabling relapses (increase of 1.0 or more on the EDSS from a baseline score less than 3.5, or an increase of 0.5 or more from a baseline score of 3.5 to 5.5) in the preceding year and, within the same period, the presence of one or more Gd+ lesions on brain MRI or more than two new lesions on T_2-weighted sequences compared with a previous brain MRI. Informed consent was obtained from all patients before administration of the drug. In addition, the treatment was authorized by the Advisory Committee of the General Directorate of Health Resources in all cases, except for those in which natalizumab was administered on a compassionate-use basis. The treatment was authorized for some patients who did not meet all of the above mentioned criteria after individual consideration of each case.

Study design

An observational study was conducted to determine the characteristics and clinical course of a cohort of patients with longitudinal follow-up during natalizumab treatment. For this purpose, we reviewed our database, in which follow-up data from these patients is stored in an encoded format. This data includes: past medical history, date of first relapse and diagnosis, previously used disease-modifying drugs, and number of relapses and EDSS scores from the preceding three years. As part of a routine follow-up protocol, we conducted a monthly control visit and additional visits for patients with worsening disease, a quarterly neurological examination with EDSS scoring, and a quarterly laboratory analysis, including complete blood count and renal and liver function tests. A brain MRI was obtained within three months before treatment initiation (pretreatment MRI) and every 12 months after treatment initiation. The patients and their relatives were instructed to report any new symptoms without delay. The established recommendations were applied in patients with a worsening neurological condition [11].

Clinical and radiological disease activity during the first year of follow-up was analyzed in patients who completed at least 12 months of treatment. For this analysis, two clinical and two radiological parameters of disease activity were evaluated. Relapses and sustained disability progression were considered clinical parameters of disease activity. Relapses were defined as new or recurrent neurological symptoms not associated with fever or infection and accompanied by new neurological signs on the physical examination, that lasted longer than 24 hours and subsequently improved or resolved. The level of disability was measured using the EDSS, a rating that ranges from 0 to 10, with higher scores indicating more severe disease. Sustained disability progression was defined as an increase of 1.0 o more on the EDSS from a baseline score of 1.0 or higher, or an increase of 1.5 or more from a baseline score of 0, that was maintained for at least three months. Sustained disability improvement was defined as a reduction of 1.0 or more on the EDSS that was maintained for at least three months. The following were considered radiological parameters of disease activity: the presence and number of Gd+ lesions on the brain MRI performed after 12 months of treatment, and the presence and number of new lesions on T_2-weighted sequences on the brain MRI performed after 12 months of treatment as compared with the pretreatment brain MRI. All brain MRI studies were obtained with a 1.5 T scanner, using a standardized technique and with an appropriate repositioning [12], which allowed the comparative visual analysis of the scans obtained from the same pa-

tient (detection of new Gd+ lesions and new lesions on T_2-weighted sequences at the 12-month MRI study compared to the pretreatment MRI study).

The adverse events that occurred during natalizumab treatment in any of the patients included in the study were also evaluated. For practical reasons, only moderate or severe adverse events were registered in the database. Adverse events were defined as any adverse medical occurrence or alteration in the paraclinical tests that was identified during treatment with natalizumab, even if it was not causally related to the treatment. Moderate adverse events were defined as those that were bothersome enough to interfere with the patient's normal daily activities. Severe adverse events were defined as those that required admission or prolongation of hospital stay; were life-threatening or resulted in death or permanent or severe disability; or could result in congenital anomaly or malformation. Other adverse events that were considered medically relevant were also recorded as severe, even when they did not meet these criteria.

Statistical analysis

Statistical analysis was performed using SPSS software v. 15.0. The annualized relapse rate for a defined period was calculated as the number of relapses in that period divided by the duration of the period in years. Numerical variables were analysed using descriptive statistics, and data were expressed as percentages or means ± standard deviation, unless otherwise specified. To compare the basal characteristics of the patients who were included in the study with the subgroup of patients who were treated for at least 12 months, the Mann-Whitney *U* test was used for numerical variables, and Pearson's chi-square test or Fisher's exact test was used for categorical variables. To compare the measures of disease activity before and after treatment with natalizumab, the Wilcoxon rank-sum test was used for numerical variables, and the McNemar test was used for categorical variables. The statistical significance level was set at $p < 0.05$. The Kaplan-Meier method was used to estimate the probability of remaining free from relapses during the first year of treatment.

Results

Baseline characteristics

A total of 112 patients were included in the study. Their baseline clinical and demographic character-

Table I. Baseline characteristics of the patients.

	All patients (*n* = 112)	Treatment ≥ 12 months (*n* = 76)	*p*
Age (years)			
Mean	34.4 ± 7.8	34.7 ± 7.9	0.834
Range	19-59	20-57	
Sex			
Female	79 (70.5%)	54 (71.1%)	0.939
Male	33 (29.5%)	22 (28.9%)	
Disease subtype			
Relapsing-remitting MS	104 (92.9%)	72 (94.7%)	0.765
Secondary progressive MS	8 (7.1%)	4 (5.3%)	
Disease duration (years)			
Mean	10 ± 6.5	10.2 ± 6.6	0.933
Range	0.4-32.7	0.4-32.7	
Relapsing-remitting MS	9.98 ± 6.5	10.1 ± 6.8	0.992
Secondary progressive MS	10.9 ± 6.3	11.7 ± 2.2	0.552
EDSS score			
1-1.5	9 (8%)	6 (7.9%)	
2-2.5	20 (17.9%)	13 (17.1%)	
3-3.5	16 (14.3%)	9 (11.9%)	
4-4.5	29 (25.9%)	19 (25%)	
5-5.5	20 (17.9%)	16 (21.1%)	
≥ 6	18 (16.1%)	13 (17.1%)	
Mean	4 ± 1.6	4.1 ± 1.5	0.699
Median	4	4	
Annualized relapse rate			
Previous year	2.25 ± 1.1	2.25 ± 1.2	0.853
2 previous years	1.68 ± 0.8	1.73 ± 0.9	0.806
3 previous years	1.45 ± 0.6	1.49 ± 0.7	0.694
No. of gadolinium-enhancing lesions			
0	44 (39.3%)	29 (38.2%)	
1-5	40 (35.7%)	26 (34.2%)	
≥ 6	28 (25%)	21 (27.6%)	
Mean	4.3 ± 7.1	4.8 ± 7.8	0.732
Median	1	1	
No. of T_2 lesions			
< 9	3 (2.7%)	2 (2.6%)	1
≥ 9	109 (97.3%)	74 (97.4%)	

EDSS: Kurtzke's Expanded Disability Status Scale; MS: multiple sclerosis.

Table II. Clinical and radiological activity during the first year of treatment.

	Period from –12 to 0 months [a]	Period from 0 to 12 months [b]	*p*
Clinical	*n* = 76	*n* = 76	
No. of relapses			
0	1 (1.3%)	61 (80.3%)	< 0.001
≥ 1	75 (98.7%)	15 (19.7%)	
Annualized relapse rate			
Mean	2.25 ± 1.2	0.24 ± 0.5	< 0.001
Median	2	0	
EDSS score			
1-1.5	6 (7.9%)	11 (14.5%)	
2-2.5	13 (17.1%)	12 (15.8%)	
3-3.5	9 (11.9%)	12 (15.8%)	
4-4.5	19 (25%)	17 (22.4%)	
5-5.5	16 (21.1%)	13 (17.1%)	
≥ 6	13 (17.1%)	11 (14.5%)	
Mean	4.1 ± 1.5	3.9 ± 1.6	0.038
Median	4	4	
Sustained change in disability			
No change		56 (73.7%)	
Improvement		13 (17.1%)	
Progression		7 (9.2%)	
Radiological	*n* = 67	*n* = 67	
No. of gadolinium enhancing-lesions			
0	25 (37.3%)	65 (97.0%)	< 0.001
≥ 1	42 (62.7%)	2 (3.0%)	
Mean	4.73 ± 7.9	0.04 ± 0.3	< 0.001
Range	0-40	0-2	
No. of new T_2 lesions			
0		31 (46.3%)	
1		11 (16.4%)	
2		9 (13.4%)	
≥ 3		16 (23.9%)	
Mean		1.9 ± 3.4	
Range		0-23	

EDSS: Kurtzke's Expanded Disability Status Scale. [a] During the 12 months before treatment initiation; [b] During the 12 months after treatment initiation.

istics are summarized in Table I. The reasons for initiating treatment with natalizumab were: relapsing-remitting MS with suboptimal response to other therapies (107 patients, 95.5%); rapidly evolving severe relapsing-remitting MS since the beginning of the disease (2 patients, 1.8%); and intolerance to other drugs (3 patients, 2.7%). In eight patients (7.1%), the treatment was authorised in a compassionate-use basis. All patients received the standard regimen consisting of natalizumab 300 mg, administered by continuous intravenous infusion over one hour, every four weeks. The mean number of doses administered was 15.8 ± 8.2 (median: 17; range: 1-32), and the mean follow-up time from the beginning of treatment was 15.6 ± 8.7 months (median: 16.8; range: 0-31.9).

Except for two patients, all of them had received other disease-modifying drugs before natalizumab treatment, with a median number of previous treatments of one (range: 0-6). Thirty-seven patients (33%) had been treated with intramuscular IFNβ-1a, 55 (49.1%) with subcutaneous IFNβ-1a, 42 (37.5%) with subcutaneous IFNβ-1b, 25 (22.3%) with glatiramer acetate, and 2 (1.8%) with azathioprine. Fifteen patients (13.4%) had received mitoxantrone, and the median time between the last dose of this drug and natalizumab administration was 25.2 months (range: 5.3-64.5). Four patients (3.6%) had received daclizumab during a clinical trial. The median cumulative time of treatment with previous drugs was 4.3 years (range: 0.4-14.1), and the median time of treatment with the last drug prior to natalizumab was 21 months (range: 0.3-161.5).

Effectiveness of natalizumab

At the time of the study, 76 patients (67.9%) had been treated with natalizumab for at least 12 months, and 22 patients (19.6%) had been treated for at least 24 months. Clinical and radiological disease activity was analyzed during the first year of follow-up in the subgroup of patients who had completed 12 months of treatment. No significant differences were observed in the baseline clinical and demographic characteristics of this subgroup of 76 patients compared with the total of 112 patients who were included in the study (Table I). At month 12 of the study, brain MRI results were available for 67 of the 76 patients analyzed.

After 12 months of treatment, there was an 89% relative reduction in the annualized relapse rate and an 80% decrease in the proportion of patients who had one or more relapses, as compared with the 12-month pretreatment period ($p < 0.001$ for

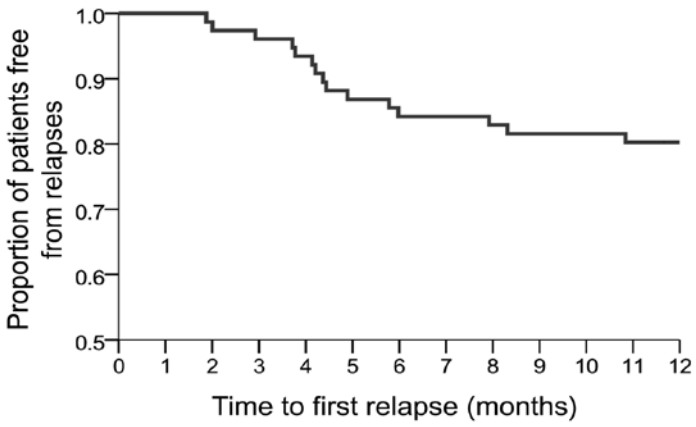
both comparisons) (Table II). The proportion of patients free from relapses as a function of time is shown in Figure 1. At month 12, 80% of the patients remained free from relapses. Among the patients who had relapses, the median time until the first relapse was 4.4 months (range: 1.9-10.8) over the first year of treatment. During this period, six patients (7.9%) had eight relapses that required treatment with intravenous corticosteroids.

A 5% relative reduction in the mean EDSS score compared with that at baseline was observed at month 12 ($p < 0.05$) (Table II). The median EDSS score did not change over the course of the study. During the first year of treatment, 9.2% of patients experienced sustained disability progression confirmed at three months, whereas 17.1% of patients experienced disability improvement. No sustained changes in the EDSS score were observed in the remaining 73.7%.

A 99% relative reduction in the mean number of Gd+ lesions was observed on the 12-month brain MRI compared with the pretreatment brain MRI ($p < 0.001$). In addition, there was a 95% relative reduction in the number of patients with one or more Gd+ lesions ($p < 0.001$). The mean number of new lesions on T_2-weighted sequences at month 12 was 1.9 ± 3.4 (Table II).

The analysis of disease activity during the first 12 months of treatment showed that 76.3% of patients remained free from clinical activity (relapses or sustained disability progression) and that 46.3% of patients did not present signs of radiological activity (new lesions on T_2-weighted sequences or Gd+ lesions on brain MRI) (Figures 2a and 2b). Overall, 32.8% of patients exhibited neither clinical nor radiological activity, and 53.7% of patients exhibited only one parameter of disease activity (Figures 2c and 2d).

Figure 1. Kaplan-Meier curve showing the probability of remaining free from relapses during the first 12 months of treatment with natalizumab ($n = 76$).



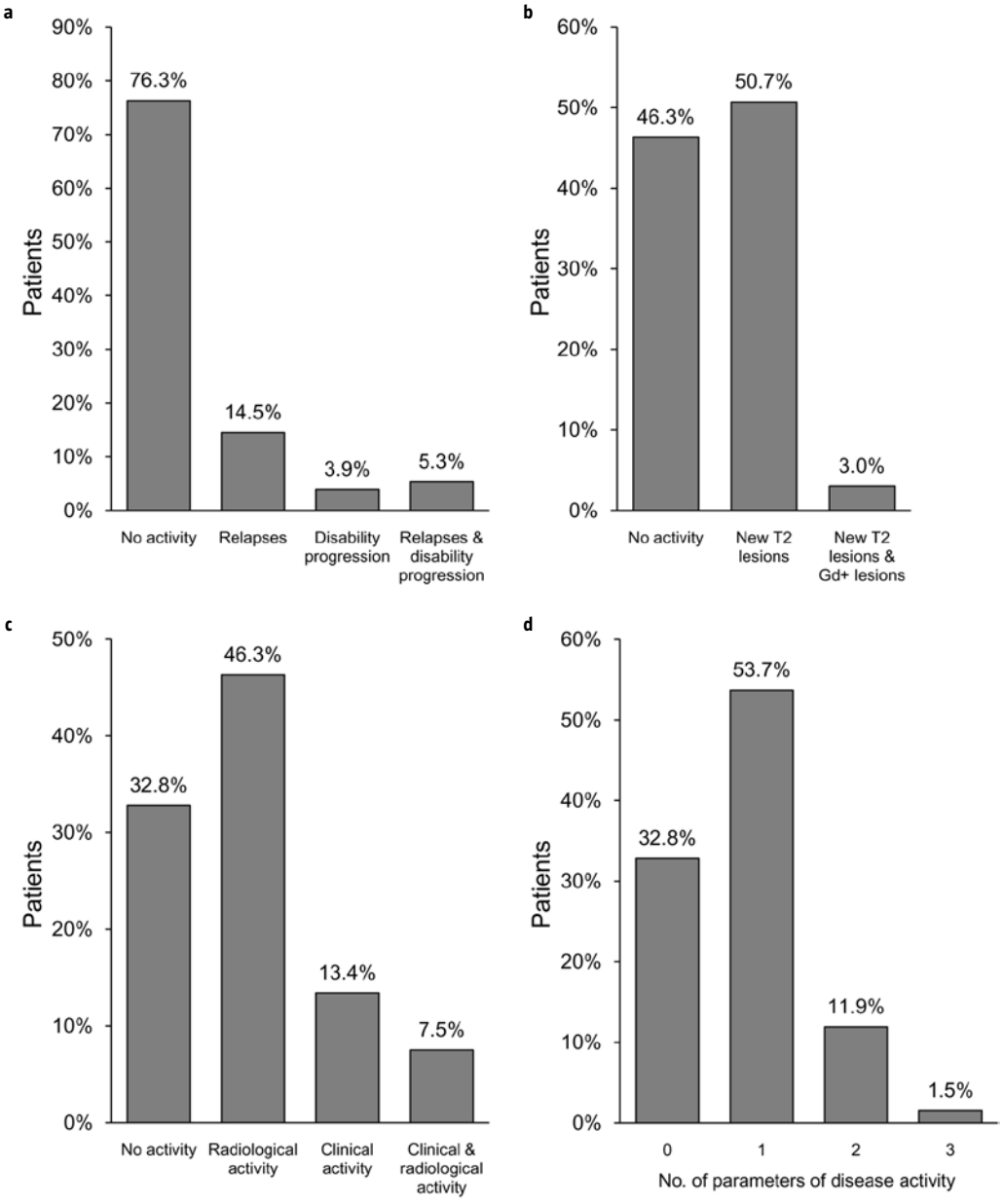
Tolerability and safety

Thirty-two patients (28.6%) presented at least one moderate or severe adverse event during follow-up (Table III). Five patients (4.5%) exhibited immediate hypersensitivity reactions, and four of these reactions were considered to be severe (anaphylactic reaction; 3.6%). Three of these four patients exhibited mild symptoms, such as pruritus or a localized rash, during the administration of the previous dose. Immediate hypersensitivity reactions occurred between the second and the fourth natalizumab infusion in four patients. In the remaining patient, the reaction occurred when treatment was resumed after a long interruption due to pregnancy. Two patients (1.8%) exhibited a delayed hypersensitivity reaction that persisted for the first five to seven infusions and was characterized by headache, arthralgia, and myalgia, with or without fever or pruriginous rash.

Other adverse events are shown in Table III. Four patients (3.6%) reported arthralgias, which were generalized in two cases. Two patients (1.8%) presented oral candidiasis, and another two patients (1.8%) developed subcutaneous cellulitis following cutaneous injury. One case of exacerbation of psoriasis and one case of livedo reticularis were observed after the first and third infusion of natalizumab, respectively. One patient with previous history of epilepsy experienced a generalized tonic-clonic seizure during natalizumab administration; other causes were excluded by brain MRI and cerebrospinal fluid analysis. Two patients were diagnosed with malignancies that had not been previously detected (ovarian serous cystadenoma and basal-cell carcinoma); both of them were treated successfully. One patient with previous history of multiple abdominal surgical interventions had an intestinal subocclusion. There were no cases of progressive multifocal leukoencephalopathy.

Adverse events led to permanent treatment discontinuation in seven patients (6.3%): in five patients (4.5%) due to hypersensitivity reactions; in one (0.9%) due to a severe orchiepididymitis following recurrent urinary tract infections; and in one (0.9%) due to a low-grade astrocytoma. In this last case, the review of previous brain MRI scans con-

Figure 2. Clinical and radiological disease activity during the first 12 months of natalizumab treatment (*n* = 67). a) Clinical activity: The absence of activity was defined as the absence of relapses or sustained disability progression confirmed at 3 months; b) Radiological activity: The absence of activity was defined as the absence of gadolinium-enhancing lesions or new lesions on T_2-weighted sequences on brain MRI at month 12; c) Combined analysis of clinical and radiological activity; d) Distribution of patients according to the total number of clinical or radiological activity parameters. None of the patients had simultaneously four parameters.



firmed that the lesion existed before natalizumab administration and that it had remained unchanged since then. The median number of natalizumab doses before treatment discontinuation due to adverse events was 4 (range: 2-25).

Natalizumab administration was interrupted in four patients (3.6%) because of a desire for pregnancy. These patients had received a median number of 20 doses (range: 13-29) before treatment was stopped. Other reasons for treatment discontinua-

Table III. Adverse events (AEs) (*n* = 112).

All AEs	
At least one AE	32 (28.6%)
At least one serious AE	10 (8.9%)
AEs leading to treatment discontinuation	7 (6.3%)
Moderate AEs	
Hypersensitivity reaction	
Immediate	1 (0.9%)
Delayed	2 (1.8%)
Perfusion reaction	
Headache	1 (0.9%)
Infection	
Pneumonia	1 (0.9%)
Urinary tract infection	1 (0.9%)
Cellulitis/subcutaneous abscess	3 (2.7%)
Influenza	3 (2.7%)
Oral candidiasis	2 (1.8%)
Intraoral herpes	1 (0.9%)
Skin disorder	
Exacerbation of psoriasis	1 (0.9%)
Livedo reticularis	1 (0.9%)
Psychiatric disorder	
Depression	4 (3.6%)
Rheumatologic disorder	
Arthralgia	4 (3.6%)
Neoplasm	
Basal-cell carcinoma	1 (0.9%)
Others	
Generalized epileptic seizure	1 (0.9%)
Biliary colic	1 (0.9%)
Renal colic	1 (0.9%)
Metrorrhagia	1 (0.9%)
Weight loss	1 (0.9%)
Fever and headache	1 (0.9%)
Severe AEs	
Hypersensitivity reaction	
Immediate	4 (3.6%)
Infection	
Pneumonia	2 (1.8%)
Orchiepididymitis	1 (0.9%)
Neoplasm	
Low-grade astrocytoma	1 (0.9%)
Ovarian serous cystadenoma	1 (0.9%)
Others	
Intestinal subocclusion	1 (0.9%)

tion were: moving abroad (one patient; 0.9%), concern of side effects (one patient; 0.9%), recurrent relapses (one patient; 0.9%), and transition to a secondary progressive phase (two patients; 1.8%).

Discussion

Evaluation of the efficacy of a drug should be based on data obtained through controlled clinical trials. However, after a drug becomes commercially available, studies are needed to evaluate its effectiveness and safety when administered in real-life situations. The objective of these studies is to complement the information obtained during the clinical development of the drug, prior to its approval, and to establish whether and to what extent the expected risks and benefits observed in the clinical trials are achieved. These studies are particularly useful when the approved therapeutic indications differ from those evaluated in controlled clinical trials, as it occurs with natalizumab. The current study shows a consistent and significant effectiveness of natalizumab when used in routine clinical practice, as well as its favourable safety profile.

According to the therapeutic indications approved by the European Medicines Agency, natalizumab is an option for patients who have inadequate response to other immunomodulatory drugs [10]. However, the efficacy of this therapeutic strategy has not been specifically evaluated in clinical trials. In the AFFIRM study, previous treatment with IFNβ or glatiramer acetate for more than six months, or treatment with mitoxantrone within the previous year, were exclusion criteria [6]. In contrast, in the present study, 98% of patients had re-

Table IV. Basal characteristics and disease activity during the first year of treatment in the present study and the AFFIRM study.

	Present study (*n* = 76)	AFFIRM (*n* = 627)
Basal		
Age (years)	34.7 ± 7.9	35.6 ± 8.5
Disease duration (years) [a]	9.1	5.0
EDSS score	4.1 ± 1.5	2.3 ± 1.2
Annualized relapse rate in the previous year	2.25 ± 1.2	1.53 ± 0.91
Absence of gadolinium-enhancing lesions	38%	49%
No. of gadolinium-enhancing lesions	4.8 ± 7.8	2.2 ± 4.7
Clinical (one year)		
Annualized relapse rate	0.24 ± 0.5	0.27
Absence of relapses	80%	80%
Sustained disability progression [b]	9.2%	17%
Radiological (one year)		
No. of gadolinium-enhancing lesions	0.04 ± 0.3	0.1 ± 1.3
Absence of gadolinium-enhancing lesions	97%	96%
No. of new T_2 lesions [c]	1.9 ± 3.4	1.2 ± 4.7
Absence of new T_2 lesions [c]	46%	61%

EDSS: Kurtzke's Expanded Disability Status Scale. [a] Median; [b] AFFIRM study: sustained disability progression at two years; [c] New or enlarging T_2 lesions in the AFFIRM study.

ceived at least one immunomodulatory or immunosuppressive drug for a median of 4.3 years before natalizumab, and the reason for starting this treatment was a suboptimal response to other drugs in 96% of the cases. Therefore, the data on disease activity in our cohort mainly reflect the effectiveness of natalizumab as a second-line therapy.

After one year of treatment, the annualized relapse rate was reduced by 89% in the present study and by 82% in the AFFIRM study [6]. The proportion of patients without clinical activity (relapses or sustained disability progression confirmed at three months) in both studies was also similar (75% and 76%, respectively) [13]. After one year, the percentage of patients without radiological activity was 46% in the present study and 63% in the AFFIRM study, which explains the different proportion of patients who exhibited neither clinical nor radiological activity during the same period (33% and 47%, respectively) [13]. This difference resulted from the greater number of patients with new lesions on T_2-weighted MRI in our cohort (Fig. 2b), which may be in part related to a greater pretreatment disease activity (Table IV). Despite these differences, our results suggest that a significant proportion of patients with MS who have a suboptimal response to other drugs achieve complete disease remission during the first year of treatment with natalizumab.

The effectiveness data from the present study are also consistent with those from other postmarketing observational studies conducted in various European centres [14-19]. Taken together, these indicate that natalizumab is used as a second-line therapy in 88% to 94% of patients, and that, after 11 to 19 months of treatment, 60% to 80% of patients remain free from relapses and 90% to 93% do not experience sustained disability progression.

The main limitation of the present study is the absence of a control group, so it cannot be ruled out that the observed reduction in the activity parameters may be due to the natural course of the disease or to regression to the mean. Both the magnitude of the change and the trends observed, as well as the similarity of the present findings to those previously reported, suggest a favourable effect of natalizumab in our cohort. However, the sample size and the follow-up duration preclude us from making any definitive conclusions. The clinical course of all patients was prospectively documented, which adds to the reliability of the data despite the retrospective design of the study. To minimise any potential selection bias, all consecutive patients who started treatment with natalizumab in our centre were included in the study. The subgroup of patients available for the analysis of disease activity at 12 months was representative of the whole sample (Table I).

The limited sample size, the follow-up duration, and the absence of a control group do not allow us to draw definitive conclusions about the tolerability and safety of natalizumab. However, treatment with natalizumab was generally well tolerated, and its safety profile was similar to that previously reported. In line with former studies [1,6], 4.4% of patients experienced immediate hypersensitivity reactions. These occurred between the second and fourth infusions and, in one case, when the treatment was resumed after a long interruption. Two patients exhibited delayed hypersensitivity reactions, which were mainly characterised by headache, arthralgia, and myalgia. This type of delayed reaction has been observed in the postmarket experience, and type III hypersensitivity has been proposed as the underlying mechanism [20-22]. Two additional patients re-

ported generalized arthralgia, which may represent a milder form of delayed hypersensitivity.

The majority of infections were moderate in severity and resolved with medical treatment without complications. In some patients, natalizumab administration was temporarily interrupted until the process was resolved. Infections requiring hospital admission occurred in 2.7% of patients, including two cases of pneumonia and one case of orchiepididymitis. No cases of progressive multifocal leukoencephalopathy were observed.

In conclusion, and despite the methodological limitations, the results of the present study suggest that the administration of natalizumab to patients with relapsing forms of MS and suboptimal response to other immunomodulatory treatments is effective in reducing the clinical and radiological disease activity, with a similar degree of therapeutic benefit to that observed in randomized clinical trials and with a favourable risk-benefit ratio. These results should be confirmed in controlled clinical trials specifically designed to evaluate the efficacy of natalizumab as a second-line therapy as well as in aggressive forms of the disease.

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Estudio observacional sobre la efectividad y seguridad del natalizumab en el tratamiento de la esclerosis múltiple

Objetivo. Analizar la seguridad y efectividad del natalizumab en el tratamiento de la esclerosis múltiple según las indicaciones autorizadas en nuestro ámbito y en condiciones de uso real.

Pacientes y métodos. Evaluamos todos los pacientes con esclerosis múltiple tratados con natalizumab en nuestro centro. Se analizó la actividad clínica y radiológica de la enfermedad durante el primer año de tratamiento en los pacientes que

recibieron 12 o más dosis. Se evaluó la información relativa a los acontecimientos adversos moderados y graves en toda la muestra.

Resultados. Se incluyeron 112 pacientes, de los que 110 habían sido tratados anteriormente con otros fármacos y 76 habían recibido 12 o más dosis de natalizumab. En este grupo, la tasa anualizada de brotes se redujo un 89% respecto al año previo y el 80% de los pacientes permaneció libre de brotes después de un año de tratamiento. El 9% de los pacientes presentó progresión de la discapacidad confirmada a los tres meses. En el mes 12, el número medio de lesiones que realzaban con gadolinio en la resonancia magnética cerebral disminuyó un 99% respecto a la resonancia magnética pretratamiento. Durante el primer año de tratamiento, el 76% de los pacientes no presentó actividad clínica y el 33% no presentó actividad clínica ni radiológica. Se observó al menos un acontecimiento adverso moderado o grave en el 29% de los casos, que obligó a interrumpir el tratamiento en el 6%. El 4% de los pacientes tuvo reacciones de hipersensibilidad inmediata.

Conclusión. Este estudio sugiere que el natalizumab es efectivo en la reducción de la actividad de la enfermedad en pacientes con formas recurrentes de esclerosis múltiple con respuesta inadecuada a otras terapias, con una relación beneficio-riesgo favorable.

Palabras clave. Anticuerpo monoclonal. Esclerosis múltiple. Estudio observacional. Natalizumab. Resonancia magnética. Tratamiento inmunomodulador.