The efficacy and safety of natalizumab for the treatment of multiple sclerosis in Portugal: a retrospective study

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Introduction. Studies have shown that natalizumab is an effective treatment for relapsing-remitting multiple sclerosis (RRMS). To date, no data are available in Portuguese patients.

Aim. To determine the efficacy and safety of natalizumab in patients with RRMS in routine clinical practice in Portugal.

Patients and methods. Clinical data for adult patients with RRMS treated with natalizumab at specialist neurology centres in Portugal were entered retrospectively into a database for analysis between October 2010 and February 2012. Changes in annualized relapse rates (ARR), Expanded Disability Status Scale (EDSS) scores and disability status were analysed.

Results. A total of 383 patients from 20 centres were included. Prior to starting natalizumab, the baseline median EDSS score was 4.0 and the mean ARR was 1.64. Most patients had previously received multiple sclerosis treatment (93.0%). Median natalizumab treatment duration was 12 months. Natalizumab treatment was associated with significant ($p < 0.001$) reductions from baseline in the mean ARR and EDSS scores in patients treated with natalizumab for ≥ 12 months ($n = 288$) and for ≥ 24 months ($n = 160$). Natalizumab was more effective in patients with less disability (EDSS < 3.0) and in those who had not previously received disease-modifying treatments. Two cases of progressive multifocal leukoencephalopathy were reported. No new unexpected adverse events occurred.

Conclusion. Natalizumab is well tolerated, and is effective in reducing relapse rate and stabilising disease in patients with RRMS in the clinical practice setting in Portugal. Its efficacy persists with continued treatment, and it may be particularly effective in patients with less disability and without prior disease modifying therapy.

Key words. Demyelinating autoimmune diseases. Multiple sclerosis. Natalizumab. Progressive multifocal leukoencephalopathy. Relapse rate. Retrospective study.

Introduction

Natalizumab is an α4-integrin antagonist, the first of a new class of selective adhesion molecule inhibitors approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). In Europe, natalizumab is indicated for the treatment of patients who have failed first-line –i.e. interferon (IFN)-β and glatiramer acetate– therapy or who have an aggressive form of the disease [1].

A number of randomized-controlled trials have demonstrated the efficacy of natalizumab in reducing the annualized relapse rate (ARR) and limiting disease progression [2-4]. For example, in the AFFIRM (Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis) study by Polman et al [4], natalizumab significantly reduced the rate of clinical relapse by 68% at 1 year in adult patients with RRMS. The risk of disability progression was also significantly reduced over 2 years versus placebo.

Real-world studies of natalizumab in Europe provide evidence of its efficacy and safety in everyday clinical practice [5-17]. Natalizumab treatment was generally associated with a low ARR across most of these studies, and Expanded Disability Status Scale (EDSS) scores remained stable suggesting a lack of disability progression. Preliminary findings from the on-going, multinational, open-label, observational Tysabri Observational Program (TOP) study confirm the positive effect of natalizumab on relapse rates and disease stability, with a safety profile consistent with that known of natalizumab [18]. Interim analysis of 4434 patients currently enrolled in TOP suggest that ARR was significantly reduced from baseline regardless of prior treatment history, and that EDSS scores remained stable over long-term treatment (up to 4 years) [18].

Natalizumab has been available in Portugal since June 2007. To date, no studies have investigated the efficacy and safety of natalizumab specifically in

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Conflicts of interest:
L.S. has received fees from Novartis Pharma, Biogen Idec, Merck Serono, Sanofi-Aventis, Allergan, Bayer Schering and Teva for participating on advisory boards or as lecturers. J.d.S. received consultation fees for participating on advisory boards sponsored by Biogen Idec, Ipsen Pharma, Novartis Pharma, and speaker honoraria for participating in symposia from Teva, Novartis, and Biogen Idec. M.J.S. has received research support from Bayer Schering, Bial, Biogen Idec, Fundação Schering Lusitana, Merck Serono, Sanofi-Aventis, Schering-Plough and Octapharma; speaker honoraria from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis; and consultation fees for participating on scientific advisory boards from Bayer Schering, Biogen Idec, CSL Behring, Merck Serono and Novartis. J.J.C. has received research support from Fundação Bial and Biogen Idec and honoraria from Bayer Schering, Biogen Idec and Novartis as lecturer or for participating as consultant on advisory boards. A.M.S. has received research support from Bayer Schering, Biogen Idec, Merck Serono and Octapharma; speaker honoraria from Biogen Idec, Merck Serono, Novartis, Sanofi-Aventis and Pfizer; and consultation fees for participating on scientific advisory boards from Biogen Idec and Novartis.

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Portuguese patients. The aim of this multicentre, retrospective study was to investigate the safety and effectiveness of natalizumab in routine clinical practice in Portugal and to compare the patient and disease characteristics with that of a similar study in Spain [6].

Patients and methods

Twenty-eight specialist neurology departments or units across Portugal were invited to participate in this study. Patients were assessed for eligibility by participating neurologists, and patient data were collected at a single time point in a 2-month period after the approval of the Ethics Committee of each hospital. Data collection started in October 2010 and ended in February 2012. Patients aged ≥ 18 years who had received at least one dose of natalizumab and who gave informed consent were eligible. The study was approved by the Portuguese Data Protection Authority.

Participating neurologists completed a web-based electronic form for each patient using retrospective data from patients' clinical records. Data collected were: demographic data (gender, age), MS history (date of symptom onset, date of diagnosis, number of relapses in the 12 months prior to starting natalizumab treatment), ARR, EDSS score at the time of natalizumab initiation (i.e. 'baseline' score), prior MS treatments (disease modifying treatments –DMTs–; for each treatment: date of initiation and of discontinuation), natalizumab use (date of initiation, reason for use, date and reason for discontinuation –if applicable–), clinical data after starting natalizumab (number of relapses during natalizumab treatment –to calculate ARR– and last recorded EDSS score while on natalizumab treatment). Safety data during natalizumab treatment were also collected (adverse events, hypersensitivity/infusion reactions, and neutralizing antibodies).

Study endpoints

Study endpoints included the proportion of patients with at least one relapse before and after initiating natalizumab treatment and change in disability status (improvement, stability or worsening) during natalizumab treatment according to change in EDSS score from baseline. The change was as defined by Fernandez et al. [6], where improvement was defined as a decrease of ≥ 1 point, stability defined as a change of < 1 point, and worsening defined as an increase of ≥ 1 point. Subgroup efficacy analyses were conducted according to natalizumab treatment duration (≥ 12 months vs ≥ 24 months, and ≤ 12 months vs 13-23 months vs ≥ 24 months) for selected efficacy endpoints before and after natalizumab treatment. Comparisons of reduction in mean ARR according to baseline EDSS score (EDSS < 3.0 vs EDSS ≥ 3.0) and according to baseline treatment history (DMT-naïve vs ≥ 1 DMT) were also performed.

Statistical analysis

Descriptive statistics were used for patient data. Nonparametric tests (Mann-Whitney and Kruskal-Wallis tests) were used for comparisons of numerical variables. Before versus after comparisons were always performed using the appropriate paired-sample nonparametric test (McNemar or Wilcoxon tests). The Kolmogorov-Smirnov test was used to test for normality assumptions. The Chi-square test and Fisher's exact test were used for comparison of categorical variables.

The ARR before treatment was the number of relapses in the 12-month period prior to treatment initiation; ARR after natalizumab initiation was calculated as the number of relapses during the natalizumab treatment period divided by treatment duration (treatment duration calculated from treatment initiation date and date of discontinuation or date of last recording, as appropriate). ARR 95% confidence intervals (95% CI) were estimated using Poisson regression. CIs for EDSS and for before-after differences were calculated using the usual normal (Gaussian) approximations.

Analyses compared various patient subpopulations: those who had received natalizumab for at least 12 months vs at least 24 months (not mutually exclusive), and those who had received natalizumab for less than 12 months vs 13 to 23 months vs at least 24 months.

The level of significance used was $\alpha = 0.05$. *P* values were calculated from a negative binomial model adjusted for treatment duration, baseline EDSS score and baseline treatment history. Statistical analysis was performed using SPSS v. 20.0.

Results

Data capture

Twenty of 28 neurology centres in Portugal participated in this study (i.e. 71.4% of all Neurology

centres in Portugal). Data were available for 383 patients, corresponding to 97.5% of the total number of patients ever treated with natalizumab in the 20 participating centres (n = 393). Data for the remaining 10 patients were not included due to incomplete information in patient records. Reasons for non-participation of eight centres were as follows: one hospital executive committee refused to participate because they do not approve any observational study; four hospitals did not collect any data from their patients during the study period; and three hospitals had issues with patient medical records, making it difficult to retrieve old data.

Patient characteristics and prior treatments

Most patients (69.2%) were female, and the mean patient age was 41 years (Table I). Patients had relatively severe disability although mostly were still ambulatory when they began treatment with natalizumab (median EDSS score of 4.00; range: 0.00-8.50). Approximately 80% (301/379) of patients had an EDSS score ≥ 3 at baseline, while 24.5% (93/379) had an EDSS ≥ 6. Most patients had relapsed at least once in the year prior to natalizumab treatment (324/383; 84.6%) and more than half had experienced ≥ 2 relapses (216/383; 56.4%) with a median ARR of 2.0 (range: 0.0-5.0). In the 15.4% of patients that had no relapses in the previous 12 months, the reasons for natalizumab treatment included increasing MRI activity and disability in the context of previous unresponsiveness to other disease modifying treatments.

The majority of patients had previously received MS treatment (93.0%), of which the most common was IFN-β 1b (42.6%). Several patients had received a prior immunosuppressive drug: mitoxantrone 15.7% (n = 60); azathioprine 8.4% (n = 32); cyclosporine 0.5% (n = 1); cyclophosphamide 8.1% (n = 31); mycophenolate 2.1% (n = 8); fingolimod 1.3% (n = 5); methotrexate 1.0% (n = 4). Only a small proportion of patients received only immunosuppressant therapy (1.3%; n = 5). The majority of patients had received ≥ 2 prior MS treatments at baseline (215/383; 56.1%) with one patient receiving seven previous drugs (Table I).

Treatment with natalizumab

The majority of patients were switched to natalizumab because of a lack of efficacy with prior treatment(s), in particular 80.7% (309/383) of previously treated patients switched due to a subopti-

Table I. Patient demographic and disease characteristics at baseline (n = 383).

Sex	Female	265 (69.2%)
	Male	118 (30.8%)
Age at time of inclusion in survey (years)	Mean ± standard deviation	40.50 ± 10.50
	Median	40 (range: 18-68)
Disease duration (years) [a]	Mean	8.16 ± 5.70
	Median	7.08 (IQR: 4.17-11.25)
Number of multiple sclerosis relapses in year prior to treatment	0	59 (15.4%)
	1	108 (28.2%)
	≥ 2	216 (56.4%)
Annualized relapse rate in year prior to treatment	Mean ± standard deviation	1.64 ± 1.07
	Median	2.00 (range: 0-5.00)
EDSS score in year prior to treatment [b]	Mean ± standard deviation	4.21 ± 1.68
	Median	4.00 (range: 0-8.50)
EDSS score [b]	< 3	78 (20.6%)
	≥ 3	301 (79.4%)
	< 6	286 (75.5%)
	≥ 6	93 (24.5%)
Number of prior treatments (median)		2.00 (IQR: 1.00-3.00)
Prior multiple sclerosis treatments	No [c]	27 (7.0%)
	Yes	356 (93.0%)
	IFN only	155 (40.5%)
	Glatiramer acetate only	21 (5.5%)
	Switched between glatiramer acetate and IFN	64 (16.7%)
	Immunosuppressant only [d]	5 (1.3%)
	Other treatment combinations [e]	111 (29.0%)
Prior drug use [f]	0	20 (5.2%)
	1	148 (38.6%)
	2	108 (28.2%)
	3	56 (14.6%)
	4	29 (7.6%)
	5	13 (3.4%)
	6	8 (2.1%)
	7	1 (0.3%)

[a] Disease duration was defined as the time between multiple sclerosis diagnosis and the first natalizumab infusion; data missing for 12 patients (n = 371). [b] Data missing for 4 patients (n = 379). [c] Therapy-naïve patients were defined as those who had not previously received any treatment or who had previously received only corticosteroids. [d] Immunosuppressants included mitoxantrone, azathioprine, cyclosporine, cyclophosphamide, mycophenolate, fingolimod and methotrexate. [e] Included patients exposed to combinations of IFN, glatiramer acetate and immunosuppressants. [f] Drugs included intramuscular IFN β-1a, subcutaneous IFN β-1a, IFN β-1b, glatiramer acetate, intravenous immunoglobulin, plasmapheresis, mitoxantrone, azathioprine, cyclosporine, cyclophosphamide, mycophenolate, fingolimod, methotrexate. EDSS: Expanded Disability Status Scale; IFN: interferon; IQR: interquartile range.

Table II. Efficacy of natalizumab treatment in patients with relapsing remitting multiple sclerosis in Portugal.

		≥ 12 months treatment (*n* = 288)			≥ 24 months treatment (*n* = 160)		
		Baseline	After/during treatment	Change from baseline (*p*) [a]	Baseline	After/during treatment	Change from baseline (*p*) [a]
Number of relapses	Mean ± SD	1.61 ± 1.09	0.34 ± 0.86	Not available	1.64 ± 1.13	0.43 ± 0.95	Not available
	Median (IQR)	2.00 (2.00-5.00)	0	Not available	2.00 (1.00-2.00)	0	Not available
Annualized relapse rate	Mean ± SD	1.61 ± 1.09	0.16 ± 0.49	–1.45 ± 1.15 (< 0.001)	1.64 ± 1.13	0.16 ± 0.37	–1.48 ± 1.14 (< 0.001)
	Median (IQR)	2.00 (2.00-5.00)	0		2.00 (1.00-2.00)	0	
EDSS score	Mean ± SD	4.31 ± 1.67	4.04 ± 1.92	–0.27 ± 0.94 (< 0.001)	4.32 ± 1.73	4.03 ±1.93	–0.29 ± 0.98 (< 0.001)
	Median (IQR)	4.00 (3.00-6.00)	4.00 (2.50-6.00)		4.00 (3.00-6.00)	4.00 (5.20-6.00)	

[a] Wilcoxon test for difference prior to and after natalizumab treatment. EDSS: Expanded Disability Status Scale; IQR: inter-quartile range; SD: standard deviation.

mal response to IFN-β or glatiramer acetate, defined as two or more relapses over 1 year, a severe relapse in the previous year or a mild relapse with significant changes evident on the MRI.

Median natalizumab treatment duration was 1.75 years (range: 0-4.33 years). Most patients had received natalizumab for at least 12 months (75.2%; 288/383); 41.8% received natalizumab for at least 24 months (160/383) and 11.5% of patients had received natalizumab for ≥ 3 years (44/383).

During the study, 85 patients discontinued natalizumab, with the majority of these being due to a lack of efficacy (43.5%; 37/85). Lack of efficacy was determined by no improvement or stabilisation based on the impression of the treating physician using their clinical judgement in view of the relevant medical information available (physical examination, MRI, EDSS score and relapse). Adverse events (n = 18), JC virus (JCV) positive serology (*n* = 15), the presence of natalizumab antibodies (*n* = 2), pregnancy (*n* = 2), disease progression (*n* = 2) and non-compliance (*n* = 1) were other reasons for discontinuing natalizumab therapy.

Efficacy outcomes

The mean ± standard deviation (SD) ARR after treatment with natalizumab was 0.23 ± 0.90 compared with 1.64 ± 1.07 in the year prior to natalizumab treatment (p < 0.001). Disability also improved after natalizumab, with the mean ± SD EDSS score reduced to 3.96 ± 1.90 from 4.21 ± 1.68 (p < 0.001). Natalizumab treatment was associated with a reduction in the mean number of relapses, ARR and EDSS scores in patients treated for at least 12 or 24 months (Table II). Figure 1 shows the change in disability as measured via EDSS score according to length of treatment (≤ 12 months, 13-23 months, or ≥ 24 months).

The proportion of patients with relapses decreased from 84.6% (324/383) in the year before natalizumab to 17.5% (67/383) during natalizumab treatment.

When patients were grouped by baseline EDSS score (Fig. 2), the reduction in mean ARR was significantly greater in patients with less disability at baseline (Δ –1.85 vs –1.30 in patients with a baseline EDSS < 3 and EDSS ≥ 3, respectively; p < 0.001).

Analysis of change in ARR by prior DMT status showed that patients who had not received any prior DMT responded better than those with prior DMT, with a greater reduction in mean ARR; however, the difference between treatment-naïve and DMT-experienced patients in ARR mean change from baseline was not significant (–1.39 vs –1.71; *p* = 0.841) (Fig. 3).

In terms of disability status, 22.6% (82/379) of patients improved, 75.2% (285/379) had stable disease and only 3.2% (12/379) experienced worsening of their disability. Data were not available for 4 patients.

Safety data: discontinuation of treatment and adverse events

Natalizumab was generally well tolerated. The most frequently reported adverse events were infection

Figure 1. Expanded Disability Status Scale (EDSS) scores before and after natalizumab treatment as a function of natalizumab treatment duration. Subgroups are mutually exclusive.

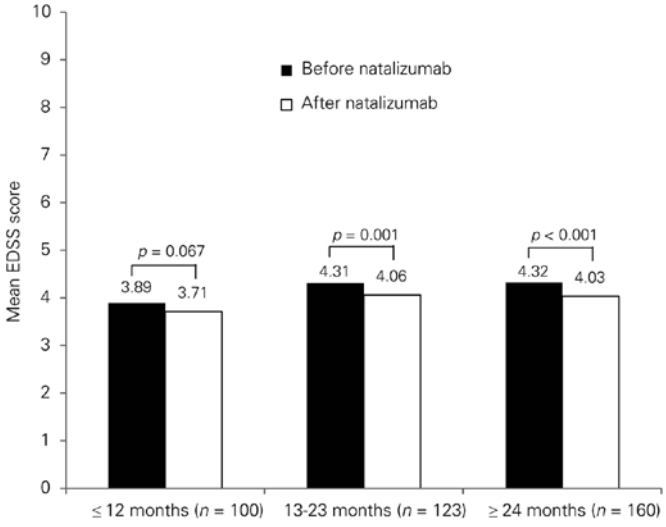
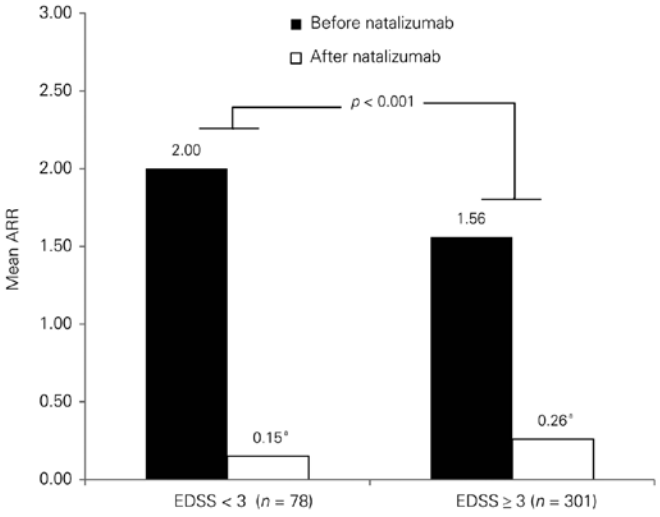


Figure 2. Mean annualized relapse rate (ARR) by baseline Expanded Disability Status Scale (EDSS) score (< 3.0 vs ≥ 3.0). [a] $p < 0.001$ vs before natalizumab.



(3.1%) and allergic reaction (2.6%). Most adverse events (94.7%) were mild in severity with only one classified as severe (a myocardial infarction in a 68-year-old woman). The majority of cases clinically resolved (83.3%) with three reported as unresolved (infection, visual and memory/attention symptoms and numbness/altered sensitivity in one side of the body). Eighteen patients (21.2%) discontinued therapy with natalizumab due to an adverse event: allergic reaction ($n = 8$), infection ($n = 2$), progressive multifocal leukoencephalopathy (PML; $n = 2$), myocardial infarction ($n = 1$) or other ($n = 5$).

The two cases of PML occurred in female patients; both discontinued therapy. One, 53 years of age, was diagnosed with MS 9 years before (prior to natalizumab treatment and PML diagnosis), and had been treated with IFN-β 1b and mitoxantrone prior to natalizumab. This patient received 28 doses of natalizumab. The other patient diagnosed with PML was 51 years old, was diagnosed with MS 12 years before, and had received IFN-β 1a SC, IFN-β 1a intramuscular and glatiramer acetate prior to receiving 28 doses of natalizumab. Both patients had detectable JCV DNA in their CSF as tested by JC virus ultra-sensitive real time PCR (Focus Diagnostics, California, USA), as tests for anti-JCV antibodies, such as the Stratify JCV assay (Biogen Idec, Portugal), were not available at the time.

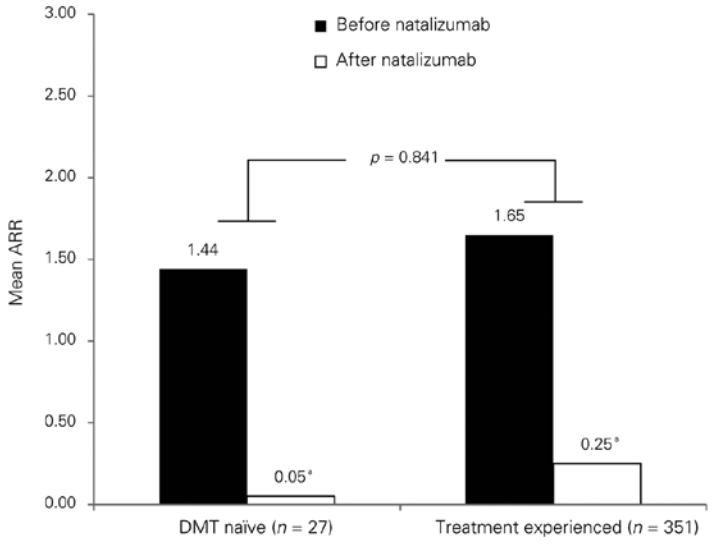
Discussion

This retrospective study of patients with RRMS treated at MS centres across Portugal shows that the monoclonal antibody natalizumab is effective and generally well tolerated. Most patients in this study received natalizumab after having received prior MS treatments (93.0%).

Natalizumab treatment was associated with reductions in the ARR and a small improvement in disability status as assessed by the EDSS. Analysis of efficacy by treatment duration indicated that natalizumab efficacy remained constant with treatment continuation, i.e. there was a consistent effect of natalizumab throughout treatment: the mean ARR was 0.16 in both the ≥ 12 months and ≥ 24 months' treatment duration subgroups.

Natalizumab appears to have better efficacy in patients with less baseline disability, and in those who had not previously received DMTs, according to analyses of ARR by baseline EDSS score and prior DMTs, respectively. These results are in line with those from the on-going TOP study [18], where ARRs were lower in patients with a baseline EDSS score of < 3.0, compared with those with a score of ≥ 3.0 (0.26 vs 0.32; $p < 0.0001$), and lower in treatment-naïve patients compared with those previously treated with two or more DMTs (0.17 vs 0.30)

Figure 3. Mean annualized relapse rate (ARR) by baseline treatment history: disease-modifying treatment (DMT) naïve vs treatment experienced. [a] $p < 0.001$ vs before natalizumab.



[18]. However, it is important to note that in our study, the observed difference in ARR between patients with a baseline EDSS score of < 3.0 than those with a score of ≥ 3.0 may have been due to a significantly higher baseline ARR in the EDSS < 3.0 patient group. It should also be noted that in our study, many patients had severe disability at baseline: median EDSS score 4 (range: 0-8.5), 80% with EDSS score ≥ 3, and a quarter with EDSS ≥ 6. The high baseline disability of our patients can be explained by the huge unmet medical need before natalizumab was approved in Portugal, resulting from the inadequate effectiveness of interferons and glatiramer acetate in many patients and the lack of viable alternatives. Indeed, in our study, 56.1% of patients had not responded to ≥ 2 DMTs before starting natalizumab. The study included patients that were initiated on natalizumab immediately after its approval in Portugal, some of whom would have been in the progressive phase of the disease.

Study results regarding the efficacy of natalizumab generally confirm those reported in other retrospective or open-label observational studies of natalizumab in patients with MS in various European countries [5-17]. As in many of these other studies [6,8,10-16], the current study included patients with greater clinical disease activity prior to initiating natalizumab therapy than in the pivotal natalizumab AFFIRM trial [4]. In fact, most patients had received prior therapy with DMTs and were still experiencing relapses. Nevertheless, natalizumab induced a greater reduction in ARR than that in the AFFIRM trial (reduction of 86% in current study vs 68%).

In particular, it is worth comparing the results of the current study with those of a recent similarly-designed Spanish study by Fernandez et al [6] (Table III). Both studies were retrospective, multicentre, and included RRMS patients –either exclusively (current study) or in the great majority –Spanish study–). Both studies reported relapse rates in the year prior to initiating natalizumab therapy and EDSS scores at treatment initiation (i.e. 'baseline' EDSS). However, the Spanish study collected efficacy outcome data at specified time points after initiation of natalizumab (6 and/or 12 months), and then reported results for the subpopulation who had been treated for at least 12 months. In comparison, the current study did not collect outcomes data at specified time points after natalizumab initiation but during natalizumab treatment up to the last available assessment (either at discontinuation or date of data collection). Nevertheless, key efficacy data were reported from both studies for patients who received natalizumab for at least 12 months; in both, these patients experienced improved clinical disease activity and disability symptoms, and most had stabilized disease (Table III).

No unexpected safety results were reported in this study. Two cases of PML occurred, both in female patients who had received 28 doses of natalizumab. The risk of PML with natalizumab treatment was initially identified in pivotal clinical trials; clinicians prescribing natalizumab should make their patients aware of the risk of PML, and that this risk increases with longer treatment duration, if they have previously taken immunosuppressant therapy or if they are already anti-JCV antibody positive prior to natalizumab treatment initiation [19,20].

Study limitations include the inherent potential for bias in any retrospective study and the potential for regression to the mean since our study lacked a control group. In any multicentre retrospective study, it is possible that data collection methods vary among the centres involved and this could be a source of bias; however, in this study, all patients followed a standard protocol and received natalizumab infusion in the hospital and so all relevant complications or side effects should have been captured by a healthcare professional. Despite inherent limitations, data analyses from the routine clinical practice setting are useful for examining treatment response in a

broad range of patients not bound by strict inclusion criteria as occurs in clinical trials, and for providing 'real-life' data based on use of the drug following local prescribing and clinical practice guidelines.

In conclusion, natalizumab monotherapy for patient with RRMS, most of whom had received prior MS treatments, stabilized the disease and reduced relapse rates over a 1- and 2-year period in patients who remained on treatment. Natalizumab appeared to have better efficacy in patients with less disability and those who were DMT-naïve. Further research on when natalizumab therapy is best initiated is required to confirm these observations.

Table III. Comparison of key outcomes after natalizumab treatment for patients with multiple sclerosis between the current study in Portugal and the previous study in Spain [6].

		Current study (n = 383)		Spanish study (n = 1364)	
Gender (female)		69.2%		69.3%	
Age (mean ± SD) [a]		40.5 ± 10.50 years		39.2 ± 8.95 years	
Time since diagnosis	Mean ± SD	8.16 ± 5.70 years		9.62 ± 5.65 years	
	Median (IQR)	7.08 (4.17-11.25) months		NR	
Prior multiple sclerosis treatments	No	7.0%		7.0%	
	Yes	93.0%		93.0%	
	1 treatment	38.6%		44.2%	
	2 treatments	28.2%		31.6%	
	> 2 treatments	27.9%		17.1%	
		All patients (n = 383)	Patients treated ≥ 12 months (n = 288)	All patients (n = 1364)	Patients treated ≥ 12 months (n = 825-839) [b]
ARR, mean ± SD or mean (95% CI)	Before natalizumab	1.64 ± 1.07	1.61 ± 1.09	NR	2.01 (1.92-2.11)
	After natalizumab	0.23 ± 0.90	0.16 ± 0.49	NR	0.25 (0.21-0.29)
EDSS, mean ± SD or mean (95% CI)	Before natalizumab	4.21 ± 1.68	4.31 ± 1.67	NR	3.71 (3.60-3.82)
	After natalizumab	3.96 ± 1.90	4.01 ± 1.92	NR	3.37 (3.25-3.49)
Change in disability status after natalizumab	Improved	22% c	NR	NR	24% [d]
	Stabilized	75% c	NR	NR	70% [d]
	Worsened	3% c	NR	NR	6% [d]

[a] Age at inclusion of survey (current study) or starting natalizumab (Spanish study). [b] Number of evaluable patients for baseline and after natalizumab ARR were 826 and 825, respectively, and for baseline/after natalizumab EDSS, 839 patients. [c] n = 379. [d] n = not reported. ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale; IQR: interquartile range; NR: not reported; SD: standard deviation.

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Estudio retrospectivo de la eficacia y seguridad del natalizumab en el tratamiento de la esclerosis múltiple en Portugal

Introducción. Los estudios han demostrado que el natalizumab constituye un tratamiento eficaz contra la esclerosis múltiple remitente recurrente (EMRR). Hasta la fecha, no había datos de pacientes portugueses.

Objetivo. Determinar la eficacia y la seguridad del natalizumab en pacientes con EMRR atendidos en la práctica clínica ordinaria en Portugal.

Pacientes y métodos. Los datos clínicos de adultos con EMRR tratados con natalizumab en centros especializados de neurología en Portugal se introdujeron de forma retrospectiva en una base de datos para llevar a cabo un análisis entre octubre de 2010 y febrero de 2012. Se analizó el cambio en la tasa anualizada de brotes (TAB), en las puntuaciones de la escala ampliada de discapacidad (EDSS) y en el estado de discapacidad.

Resultados. Se admitió un total de 383 pacientes atendidos en 20 centros. Antes de iniciar el tratamiento con natalizumab, la mediana inicial de la EDSS era de 4,0 y la TAB media, de 1,64. La mayor parte de los pacientes ya había recibido tratamiento contra la esclerosis múltiple (93,0%). La duración media del tratamiento con natalizumab era de 12 meses. El tratamiento propició reducciones significativas ($p < 0,001$) de los valores iniciales de la TAB media y de las puntuaciones EDSS en los tratados con el anticuerpo durante ≥ 12 meses ($n = 288$) y durante ≥ 24 meses ($n = 160$). El natalizumab resultó más eficaz en los pacientes que presentaban un menor grado de discapacidad (EDSS < 3,0) y en los que no habían recibido ningún tratamiento modificador de la enfermedad. Se notificaron dos casos de leucoencefalopatía multifocal progresiva. No hubo efectos adversos inesperados.

Conclusión. El natalizumab presenta una tolerabilidad satisfactoria y se muestra eficaz en la reducción de las recidivas y la estabilización de la EMRR en el marco de la práctica clínica ordinaria en Portugal. Conserva su eficacia con el tratamiento continuado y podría ser eficaz especialmente en los pacientes con menos discapacidad y en aquellos que no han recibido ningún tratamiento modificador de la enfermedad hasta el momento.

Palabras clave. Enfermedades autoinmunitarias desmielinizantes. Esclerosis múltiple. Estudio retrospectivo. Leucoencefalopatía multifocal progresiva. Natalizumab. Tasa de brotes.