

Efficacy of Natalizumab and Fingolimod in Relapsing Remitting Multiple Sclerosis in Real World Clinical Setting

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Abstract

Objective: The aim of this study was to compare the efficacy of natalizumab and fingolimod in relapsing-remitting multiple sclerosis patients in real-world clinical setting.

Methods: We enrolled 391 patients starting either natalizumab or fingolimod for relapsing-remitting multiple sclerosis, referred to four multiple sclerosis centers between March 2007 and July 2013. Cumulative proportion of patients free from any disease activity, as defined by freedom from relapse, Expanded Disability Status Scale (EDSS) progression, new or newly enlarging T2 lesions, and gadolinium enhancing lesions at magnetic resonance imaging (MRI) was assessed at 12-month follow-up.

Results: Out of 391 patients, 197 were treated with natalizumab and 194 with fingolimod. The cumulative proportion of patients free from any disease activity was 72.0% in the natalizumab and 59.1% in the fingolimod group ($P=0.014$). This proportion was lower in fingolimod patients with prior natalizumab exposure compared to those without (51.7% vs. 61.8%; $P=0.008$). Moreover, the cumulative proportion of patients free from new MRI lesions was 87.5% in the natalizumab vs. 70.0% in the fingolimod group ($P<0.001$); the cumulative proportion of patients free from clinical relapse was 82.5% in the natalizumab vs. 81.3% in the fingolimod group ($P=0.739$); 93.5% of patients on natalizumab were free from EDSS progression compared to 89.6% of patients on fingolimod ($P=0.186$).

Conclusions: Results from 1-year follow-up of treatment suggest higher efficacy of natalizumab compared to fingolimod in terms of proportion of patients free from any disease activity.

Keywords: Multiple sclerosis; Natalizumab; Fingolimod; Post-marketing study; Efficacy

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system and the second leading cause of neurological disability in young adults. During the past decades substantial effort has been made to broaden the MS treatment armamentarium with the approval of second line drugs effective in breakthrough disease.

To date, second line treatment options available include fingolimod, natalizumab and, to lesser extent, mitoxantrone. Both natalizumab and fingolimod provide a significant control in highly active disease.

Natalizumab is a $\alpha 4$ -integrin antagonist that blocks adhesion and diapedesis of leukocytes into the CNS. Two pivotal trials, the AFFIRM (natalizumab vs. placebo) and SENTINEL (natalizumab + interferon beta-1a vs. interferon beta-1a alone) studies proved natalizumab to be effective as monotherapy as well as add-on therapy with first line agents, leading to its final approval as second line treatment for relapsing remitting multiple sclerosis (RRMS) [1,2]. Nevertheless, the

risk of progressive multiple leukoencephalopathy raised concern about potential safety issues of natalizumab in so-called "triple risk" patients (previous immunosuppressive agents, positive JCV serology, two-year treatment duration) [3].

Fingolimod is the first oral agent approved for the treatment of multiple sclerosis. Fingolimod acts as a sphingosine 1 phosphate receptor modulator and exerts its mechanism of action preventing lymphocyte egress from lymphoid tissues. Two phase III studies, TRANSFORM and FREEDOMS trials, demonstrated fingolimod as an highly effective treatment in lowering relapse rate and disability progression in relapsing-remitting multiple sclerosis [4,5]

Adverse events associated with its use are first dose symptomatic bradycardia and atrio-ventricular block, macular oedema, hypertension and malignancy.

European Medical Agency (EMA) eligibility criteria for either fingolimod and natalizumab include highly active disease despite first-line therapies or breakthrough disease at onset, thus prompting a careful balancing between potential risks and efficacy profiles.

To date, few observational studies compared efficacy between natalizumab and fingolimod in real clinical setting, while there are still no head-to-head trial comparing efficacy of these drugs, which would eventually improve clinical decision making after switching to second line therapies.

The aim of our study was to assess the efficacy at 1-year follow-up in a cohort of patients treated with either fingolimod or natalizumab in real world clinical practice.

Materials and Methods

We report data from 391 patients, diagnosed with RRMS according to McDonald Criteria, collected routinely in four multiple sclerosis centers throughout Central and Southern Italy. All patients starting either natalizumab or fingolimod between March 2007 and July 2013 were included. All patients had at least 1-year follow-up period of observation.

Patients were included in accordance to Italian Drug Agency (AIFA) eligibility criteria for reimbursement of the drug. Natalizumab eligibility criteria included: patients on previous immunomodulant treatment for at least 12 months who had experienced either two relapses in the last year or a single relapse with incomplete recovery and residual disability (EDSS \geq 2.0), with at least 9 T2 lesions at MRI, or an increased lesion burden, or at least 1 gadolinium-enhanced lesion; patients with severe MS with a fast evolution, even if not previously treated with immunomodulant treatments, with \geq 2 relapses with increased disability during the last year (EDSS \geq 2.0), and with new T2 or gadolinium-enhanced lesions on MRI, compared with a previous MRI examination performed during the previous 12 months.

Fingolimod eligibility criteria included: patients on previous immunomodulant treatment for at least 12 months who have experienced at least one relapse in the last year with at least 9 T2 lesions at MRI, or an increased lesion burden, or at least 1 gadolinium-enhanced lesion; patients with severe MS with a fast evolution, even if not previously treated with immunomodulant treatments, with \geq 2 relapses with accumulation of disability during the last year, and with new T2 or gadolinium-enhanced lesions on MRI, compared with a previous MRI examination conducted during the previous 12 months.

Patients switching from natalizumab to fingolimod were also included and started treatment after a wash-out period of three months. All these patients discontinued natalizumab due to safety concerns for positive JCV status and overall treatment duration longer than 24 months, despite being clinically and radiologically stable under natalizumab treatment.

Patients treated with fingolimod underwent complete cardiac evaluation before starting fingolimod in order to exclude heart rate and atrio-ventricular conduction abnormalities. Moreover, a continuous electrocardiographic monitoring for at least six hours after the administration of the first dose was performed in all patients. Every hour, arterial pressure values were also recorded. Ophthalmologic evaluation with optical coherence tomography was performed at baseline, at 3, 6, and 12 months, in order to monitor potential adverse events such as macular oedema. Neurological examination and EDSS assessment were performed at baseline and during follow-up visits. EDSS was registered at baseline, at 6 and 12 months. Serious adverse events were recorded at each scheduled visit or whenever they occurred.

MRI scans were obtained at baseline and 12 months. Imaging data were collected at MRI facilities of the participating sites and reviewed by experienced neuroradiologists. MRI imaging was performed at 1.5T and at least axial FLAIR, T2 weighted and T1 gadolinium enhanced sequences were obtained for all exams. MRI scans were analyzed for new or newly enlarging T2 lesions and gadolinium enhancing lesions.

Patients were treated with fingolimod 0.5 mg once daily or natalizumab 300 mg every 28 days.

The study was approved by the Azienda Sanitaria Locale Avezzano-Sulmona-L'Aquila Ethics Committee.

The main end point was the proportion of patients free from any disease activity as defined by freedom from clinical relapses; from confirmed EDSS progression, as defined by sustained increase of \geq 1.0 point in the EDSS score (or \geq 1.5 points if the baseline was $<$ 1.0) confirmed after 12 weeks; from new or newly enlarging T2 lesions and/or gadolinium enhancing lesions.

As additional end-points, we also considered each single disease activity measure independently and ARR variations at 6 and 12 months with respect to values in the year prior the start of treatments. In the fingolimod group previously treated with natalizumab the ARR of year preceding treatment start was assumed equal to that in the year prior the natalizumab start.

Statistical analysis

Continuous variables were reported as means, standard deviations and range while discrete data were reported in contingency tables as absolute and relative frequencies.

The comparisons between groups (fingolimod vs natalizumab and fingolimod previously treated with natalizumab vs fingolimod not previously treated with natalizumab vs natalizumab) were performed using negative binomial regression and Paired Samples t-test. Multivariate analysis was carried out by negative binomial regression model corrected by covariates. Time to first relapse, time to first EDSS worsening and time to first new MRI lesions were evaluated using Kaplan-Meier analysis and curves. Groups (fingolimod vs natalizumab and fingolimod previously treated with natalizumab vs fingolimod not previously treated with natalizumab vs natalizumab) were compared using the log-rank test. Multivariate analysis of survival was carried out by Cox Regression model corrected by covariates.

	Natalizumab (N=197)	Fingolimod (N=194)	p-value	Total
Women (n,%)	134(68.0%)	130(67.0%)	0.831	67.50%
Age	34.5 \pm 9.39	38.9 \pm 9.34	$<$ 0.001	36.7 \pm 9.61
Duration of disease	9.0 \pm 7.00	10.1 \pm 7.32	0.121	9.6 \pm 7.17
EDSS in the year preceding treatment	2.3 \pm 0.95	2.5 \pm 1.14	0.099	2.43 \pm 1.05
ARR in the year preceding treatment	1.9 \pm 0.72	1.1 \pm 0.74	$<$ 0.001	1.5 \pm 0.84
Patients with MRI activity at baseline (n,%)	190(96.4%)	135(70.7%)	$<$ 0.001	325(83.8%)

Table 1: Demographic and clinical characteristics of study population (Data are mean \pm SD unless otherwise indicated, EDSS-Expanded Disability Status Scale; ARR-Annualized relapse rate)

A significance level of 0.05 was used for each test. For all the analysis, IBM SPSS Statistics for Windows, Version 20.0, was used.

Results

Out of 391 patients included, 265 patients were women and 127 men. One-hundred-ninety-seven patients were treated with natalizumab and 194 with fingolimod. Out of 194 patients who started with fingolimod, 52 were previously treated with natalizumab.

Complete demographic and clinical characteristic were reported in the Table 1. As shown in the table, patients who started natalizumab

were significantly younger (34.5 ± 9.39 years vs. 38.9 ± 9.34 years; $P < 0.001$), had a higher annualized relapse rate (ARR) (1.9 ± 0.72 vs. 1.1 ± 0.74 ; $P < 0.001$), and a higher proportion of patients with disease activity at MRI (96.4% vs. 70.7%; $P < 0.001$) compared to patients who started fingolimod.

Table 2 shows cumulative proportion of patients free from disease activity in natalizumab and fingolimod groups at 1-year follow-up.

	Natalizumab	Fingolimod	P*	Fingolimod		P**
				Without prior natalizumab exposure	With prior natalizumab exposure	
Proportion of patients free from any disease activity	72.0%	59.1%	0.014	61.8%	51.7%	0.008
Proportion of patients free from MRI lesions	87.5%	70.0%	<0.001	74.5%	68.3%	<0.001
Proportion of patients free from relapse	82.5%	81.3%	0.739	86.3%	68.2%	0.01
Proportion of patients free from EDSS progression	93.5%	89.6%	0.186	92.2%	82.5%	0.06

Table 2: Cumulative proportion of patients free from disease activity at 1-year follow-up (*Comparison between natalizumab and fingolimod groups; **Comparison between natalizumab, fingolimod without prior natalizumab exposure, and fingolimod with prior natalizumab exposure; EDSS-Expanded Disability Status Scale; MRI-Magnetic Resonance Imaging)

In detail, the cumulative proportion of patients free from any disease activity was 72.0% in natalizumab and 59.1% in fingolimod group (long rank test; $P = 0.014$). This proportion was 51.7% in the group of patients treated with fingolimod and previously treated with natalizumab whereas the proportion was 61.8% in the fingolimod group not previously treated with natalizumab (long rank test; $P = 0.008$) (Figure 1).

Cox regression analysis showed that patients in the fingolimod group previously treated with natalizumab had a greater risk of disease activity (HR 2.15, 95%CI 1.15-4.01, $P = 0.016$).

The cumulative proportion of patients free from new MRI lesions was 87.5% in natalizumab and 70.0% in fingolimod group (long rank test; $P < 0.001$). This proportion was 74.5% in the group of patients treated with fingolimod and previously treated with natalizumab whereas the proportion was 68.3% in the fingolimod group not previously treated with natalizumab (long rank test; $P < 0.001$).

Cox regression analysis showed that patients treated with fingolimod previously treated with natalizumab had a greater risk of new MRI lesions than patients treated with natalizumab (HR 0.42, 95%CI 0.23-0.74, $P = 0.005$).

The cumulative proportion of patients free from clinical relapse was 82.5% in natalizumab group and 81.3% in fingolimod group (long rank test; $P = 0.739$).

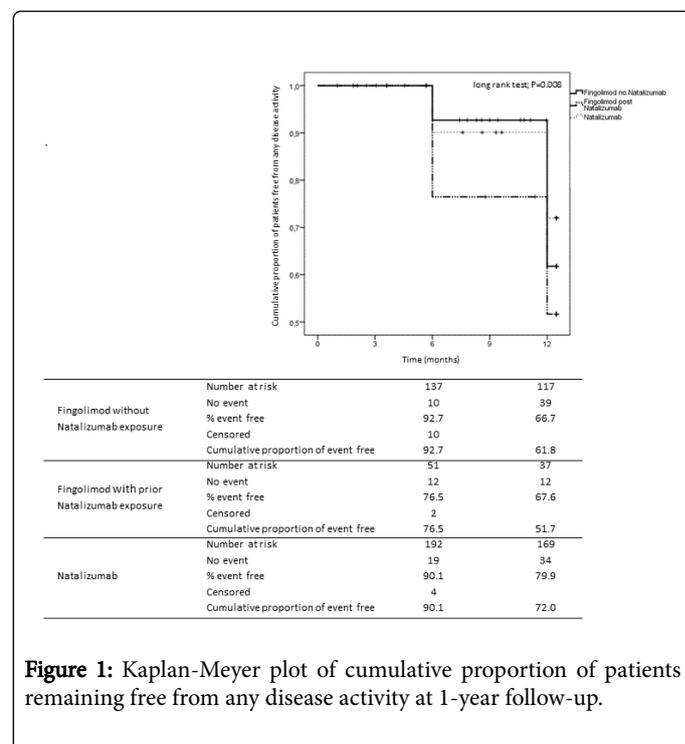


Figure 1: Kaplan-Meier plot of cumulative proportion of patients remaining free from any disease activity at 1-year follow-up.

This proportion was 68.2% in the group of patients treated with fingolimod and previously treated with natalizumab whereas the

proportion was 86.3% in the fingolimod group not previously treated with natalizumab (long rank test; $P=0.011$).

Multivariate regression analysis showed that both at 6 and 12 months of follow-up the risk of new relapse was significantly associated with the ARR ($P=0.001$ and $P=0.015$, respectively) and the MRI activity ($P=0.0001$ and $P=0.0001$, respectively) in the year preceding the start of treatment.

Cox regression analysis showed that patients who started fingolimod after treatment with natalizumab had a greater risk of new relapses with respect to patients treated with fingolimod not previously treated with natalizumab (HR 3.28, 95%CI 1.47-7.34, $P=0.004$) and patients treated with natalizumab (HR 2.83, 95%CI 1.27-6.27, $P=0.011$).

Finally, the cumulative proportion of patients free from EDSS progression was 93.5% in natalizumab group and 89.6% in fingolimod group (long rank test; $P=0.186$). This proportion was 82.5% in the fingolimod group with prior natalizumab exposure whereas the proportion was 92.2% in the fingolimod group not previously treated with natalizumab (long rank test; $P=0.060$).

Multivariate regression analysis showed that both at 6 and 12 months of follow-up the risk of EDSS progression was significantly associated with the number of previous disease modifying treatments ($P=0.013$ and $P=0.021$, respectively).

Cox regression analysis showed that the number of previous disease modifying treatments (HR 2.00, 95%CI 1.26-3.17, $P=0.003$) and age (HR 1.04, 95%CI 1.00-1.09, $P=0.039$) were significantly associated with EDSS progression.

ARR significantly lowered after treatment with natalizumab or fingolimod. In the natalizumab group values decreased from 1.88 in the year prior treatment start to 0.20 at 6 months ($P<0.001$) and 0.21 at one year ($P<0.001$) of treatment. In the fingolimod group values decreased from 1.06 to 0.30 at 6 months ($P<0.001$) and 0.23 at one year ($P<0.001$) of treatment. In the fingolimod group not previously treated with natalizumab ARR decreased from 1.13 to 0.18 ($P<0.001$) at 6 months and 0.14 at one year ($P<0.001$). In the fingolimod group previously treated with natalizumab ARR decreased from 0.85 to 0.62 ($P=0.308$) at 6 months and 0.46 at one year ($P=0.038$).

No PML cases or other serious adverse events were reported during the 12-month study period.

Discussion

Over the past two decades, treatment options for relapsing remitting multiple sclerosis have broadened out hugely. Fingolimod and natalizumab have both proven effective in relapsing remitting multiple sclerosis thus being offered as second-line treatments after failure of prior immunomodulatory drugs or in breakthrough disease.

Phase III trials comparing natalizumab and fingolimod to placebo were the AFFIRM and FREEDOMS trial, respectively. In the AFFIRM trial natalizumab reduced the ARR by 68%, lesion burden accumulation by 83% and the risk of sustained disability progression by 42%. In the FREEDOMS trial fingolimod reduced the ARR by 54%, accumulation of new or newly enlarging lesions by 74% and the risk of sustained disability progression by 30%. Yet, evidence coming from head-to-head trials is still lacking. Thus far, direct comparative data still come from few observational studies trying to address their relative efficacy in real world setting. Thus, the purpose of this study

was to evaluate the 1-year follow-up clinical and radiological outcomes in a cohort of patients prescribed with either fingolimod or natalizumab.

Baseline characteristics of the study population were similar between groups except for baseline disease activity as defined by MRI activity and ARR in the year preceding study enrolment. Different enrolment times can partly account for higher disease activity in the natalizumab group since many patients were enrolled before 2011 when fingolimod was not yet available. Besides, therapeutic trend shifted towards increasingly early treatment switch in unresponsive disease thus providing patients with lower disease activity with second line treatment options.

In our study a significant greater proportion of patients receiving natalizumab remained free from any disease activity compared with fingolimod treated patients. Higher efficacy was largely driven by a greater impact of natalizumab on radiological disease activity measures, namely lesion burden and gadolinium enhancing lesions. The potent anti-inflammatory effect of natalizumab and the sensitivity of MRI in detecting inflammatory changes in active MS may partly account for these differences.

Even if the proportion of patients free from EDSS progression and clinical relapse did not significantly differ between groups, except for a higher relapse risk in the fingolimod group with prior natalizumab exposure, longer follow-up is needed to ascertain clinical benefit of natalizumab treatment over time.

Both groups had a similar proportion of patients with stable EDSS and subgroup analysis in the fingolimod group did not show any statistically significant difference regardless prior natalizumab exposure. Of further note, the only independent factor associated with EDSS progression was the number of previous disease modifying treatments. This finding backs the hypothesis of longer disease duration and higher disease activity as the underlying cause of disability progression despite second-line therapy. The lack of an outstanding greater efficacy of natalizumab treatment on EDSS is not surprising since the beneficial effect on disability progression lags behind its impact on MRI measures of disease activity. Therefore only prospective, longitudinal studies might disclose relative efficacies of both natalizumab and fingolimod in halting disability progression over long periods of time.

So far, data from literature failed to prove compelling evidence of superiority of natalizumab over fingolimod or vice versa [6]. Recently observational studies showed lower relapse risk and new gadolinium enhancing lesions in natalizumab treated patients vs. fingolimod group, with a follow-up ranging from 18 to 20 months [7-9]. Yet, a study conducted in a German outpatient cohort revealed similar clinical efficacy in either cohorts in terms of EDSS, relapse free and progression free probability [10]. Furthermore, several post-marketing studies have attempted to address efficacy of fingolimod or natalizumab in real clinical setting [11-24]. Hersh et al. reported clinical practice data from a cohort of patients prescribed with fingolimod from 2010 to 2011 with a mean follow-up of 12 months [25]. Compared to our cohort of patients on fingolimod, freedom from relapse or new gadolinium enhancing lesions was achieved in a higher proportion of patients. Many possible confounding factors can undermine this difference such as selection bias. Following the Food and Drug Administration (FDA) fingolimod approval as first line treatment for RRMS, in the aforementioned study only a small proportion of patients were prescribed with fingolimod for

breakthrough disease (24.9%) whereas the majority switched because of patient preference (47.6%) thus reflecting a higher disease activity in our population.

We did not find statistically significant difference between groups in terms of cumulative proportion of patients free from clinical relapse. Nevertheless, the subgroup analysis in the fingolimod cohort disclosed a significant difference in the proportion of patients being relapse free among those without natalizumab prior treatment as compared with those switching from natalizumab to fingolimod (86.3% and 68.2%, respectively) and with the natalizumab group as well (82.5%).

Studies have also assessed the outcomes of patients switching from natalizumab to fingolimod in real world setting [26-31]. The expected higher relapse risk up to 6 months after therapeutic switch is largely borne out by results of many observational studies, the higher risk being related to longer wash out period (2-4 months) and higher number of relapse in the previous 6 months [29]. Some authors argued that ARR in patients with prior natalizumab exposure drops after 12 months of treatment with no statistically significant difference with fingolimod naïve patients. One could infer that higher relapse risk up to 6 months after therapeutic shift is underpinned by rebound of disease activity after natalizumab withdrawal and that a shorter wash out period up to 8 weeks would be advisable to prevent disease recurrence early after fingolimod start [32]. In our cohort 31.8% of fingolimod patients with prior natalizumab exposure relapsed at 1-year follow-up. This result is consistent with findings from previous literature reporting clinical relapses after therapeutic switch ranging from 20%, at 6 months, up to 41%, at 10 months [26,27]. The aim of this study was to provide an insight from real life efficacy data. To this end we included in the analysis both fingolimod naïve patients and those with prior natalizumab exposure. Nevertheless, direct comparison between natalizumab group and fingolimod naïve patients did not show any statistically significant difference in terms of relapse risk, EDSS progression. Yet, natalizumab proved to be more efficacious in avoiding new MRI lesions as compared to fingolimod. The cumulative proportion of patients free from new MRI lesions was still lower in the fingolimod group when analysed for possible confounder such as prior natalizumab exposure therefore prompting a higher natalizumab efficacy on radiological measures.

In conclusions, results from the present observational study suggest greater efficacy of natalizumab over fingolimod in a real-world setting. In our study, a higher proportion of patients treated with natalizumab showed absence of combined clinical and radiological disease activity being largely driven by radiological outcome parameters. These results are not at odds with previous findings from literature. Since direct comparison coming from head-to-head studies is still lacking, long-term follow-up real world studies are warranted to attempt filling this gap.

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