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Use of Natalizumab in Patients with Active Relapsing-Remitting Multiple Sclerosis in Kuwait

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Key Words
Multiple sclerosis · Natalizumab · Magnetic resonance imaging · Expanded Disability Status Scale

Abstract
Objective: To evaluate the outcomes of patients with multiple sclerosis (MS) who were treated with natalizumab in Kuwait. ***Materials and Methods:*** A retrospective study using the MS registry to identify patients who were treated with natalizumab was conducted. Patients' demographics, clinical characteristics and treatment parameters were collected at baseline and last follow-up visit. Primary outcome was the proportion of relapse-free patients at the last follow-up while secondary outcomes were the change in the mean annual relapse rate, Expanded Disability Status Scale (EDSS) and the proportion of patients with magnetic resonance imaging (MRI) activity at the last follow-up visit. Forty-four patients were included in the study. ***Results:*** Of the 44 patients, 27 (61.4%) were females and the remaining 17 (38.6%) males. Mean age of patients and mean disease duration were 29.05 ± 7.25 and 5.71 ± 3.37 years, respectively. The mean number of natalizumab infusions was 18.14. The proportion of relapse-free patients significantly increased from 11.36 to 90.91% ($p < 0.0001$). The EDSS significantly improved from 4.76 to 3.15 ($p < 0.0001$) over the observational period. There was no significant difference between patients with EDSS <3 compared to those with EDSS ≥3 ($p < 0.67$). The proportion of patients with MRI activity was significantly reduced from 95.5 to 18.2% ($p < 0.0001$) at their last visit. Six patients discontinued the drug, 5 due to positive JC virus and 1 due to pregnancy. ***Conclusions:*** Natalizumab induced a suppression of disease activity and was responsible for a significant improvement in disability status in highly active MS patients.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune and neurodegenerative disease of the central nervous system associated with irreversible progression of disability. It affects up to 2.5 million people worldwide [1]. The etiology of MS is unknown; however, more recent studies [2, 3] have highlighted how MS arises from a combination of genetic susceptibility and environmental exposures acting from gestation to early adulthood. Vitamin D deficiency, season of birth, Epstein-Barr virus infection, and smoking behavior are strongly implicated and able to influence genetic predisposition to MS [2, 3].

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Natalizumab (Tysabri®, Biogen Idec, USA) is the first humanized monoclonal antibody indicated for the therapy of relapsing-remitting multiple sclerosis (RRMS) and is now recognized as an effective disease-modifying therapy (DMT) in MS [4, 5]. Natalizumab belongs to a new class of selective adhesion-molecule inhibitors, binds to the α4 subunit of α4β1 and α4β7 integrins and blocks binding to their endothelial receptors (VCAM-1 and mucosal addressin cell adhesion molecule-1), thereby attenuating inflammation [6]. It appears to be more effective than current first-line DMTs, as suggested by results of a phase III study [4], which demonstrated a reduction in relapse rate of approximately 68% compared with placebo, and a reduction in risk of sustained disability progression by 42% over 2 years. There are no head-to-head trials with first-line DMTs or any class A evidence comparative data. However, postmarketing studies indicated superiority of escalation to natalizumab [7, 8]. Natalizumab is considered a second-line therapy for patients who have failed first-line agents [9, 10] because of safety concerns – most notably the increased risk of progressive multifocal leukoencephalopathy, a rare but opportunistic infection of the brain, which can be fatal. A novel oral drug (fingolimod) was approved as a DMT for MS in the United States and Europe in 2010 and 2011, respectively, based on phase III results [11, 12]. A subgroup analysis revealed that fingolimod has been shown to have comparable efficacy in highly active MS [13]. The aim of our study was to evaluate the outcomes of MS patients who have been treated with natalizumab in Kuwait.

Materials and Methods

This is a retrospective observational study using the MS registry in Al-Amiri Hospital and Dasman Diabetes Institute, Kuwait. All patients who had been prescribed natalizumab were identified. Patients were diagnosed with MS according to the revised 2005 McDonald criteria [14]. All patients received natalizumab 300 mg i.v. every 4 weeks. According to hospital protocols, patients had to have at least 2 of the following parameters in order to be prescribed natalizumab: (a) at least one disabling relapse with residual disabilities; residual disability is defined as incomplete recovery at 1 month from a relapse [15, 16]; relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection that lasted for at least 24 h and were accompanied by new neurologic signs found by the examining neurologist; (b) disease progression evident by an increase of at least 1.5 points on Expanded Disability Status Scale (EDSS) score [17], or (c) an increase in magnetic resonance imaging (MRI) activity evident by either new gadolinium-enhancing (Gad+) or new T2 lesions. Pretreatment annualized rate of relapse (ARR) was defined as the number of relapses that occurred in the year prior to natalizumab initiation, while on-treatment ARR was calculated as the number of relapses per duration of therapy.

Patients' demographics (age, gender), clinical characteristics (course of the disease, disease duration, relapse rate, EDSS score) and treatment parameters (prior DMTs usage, number of natalizumab infusions, adverse events related to natalizumab) were collected. Patients visited the clinic every 3 months for neurological assessment, blood chemistry and hematologic tests, and evaluation of adverse events. Patients were also seen by the treating neurologist at unscheduled visits if there were any new neurologic symptoms suggestive of relapse or if they had experienced side effects. Brain MRI and selected cervical/thoracic spine scans had been performed at baseline and every 6 months after treatment. The study received the approval of the local Ethics Committee and all the patients had signed appropriate informed consent.

The primary outcome was the proportion of relapse-free patients at the last follow-up. Secondary outcomes were the change in mean ARR, EDSS and the proportion of patients with MRI activity at the last follow-up visit. Baseline EDSS might play an important role in response to natalizumab institution based on several studies. Patients with high baseline EDSS might still have benefit in one study [18], whereas another study showed that improvement was independent of baseline EDSS [19]. Hence, patients with EDSS <3 and those with EDSS ≥3 were analyzed with respect to the proportion of relapse-free patients to assess the clinical response to natalizumab. Patients with primary progressive MS, secondary progressive MS or patients with incomplete data were excluded.

All analyses were performed using SPSS 19 for Windows. Simple descriptive statistical tests (mean and standard deviation) were used to describe the numerical values of the sample. The significance of the differences of mean ARR and EDSS scores before and after treatment were compared by using the paired-sample Student's t test while χ^2 tests were used for nonparametric variables (MRI activity and proportion of relapse-free patients); p value <0.05 was regarded as significant.

Results

Of the 44 patients with MS, 27 (61.4%) and 17 (38.6%) were females and males, respectively. The mean age of the studied cohort was 29.05 ± 7.25 years while the mean disease duration was 5.71 ± 3.37 years as shown in table 1. Thirty-eight (86.4%) of the patients had received prior DMTs (IFN beta-1b s.c., n = 14, 36.8%; IFN beta-1a s.c., n = 13, 34.2%, and IFN beta-1a i.m., n = 11, 29%) with a mean treatment duration of 38.1 ± 8.9 months. The mean number of natalizumab infusions was 18.14 ± 9.47 (median 15, range 10–51). Natalizumab was found to be effective upon assessment of both primary and secondary outcomes at the last follow-up visit (table 2). A significant increase in the proportion of relapse-free patients after treatment was observed compared to that in the year prior to natalizumab initiation (90.91 vs. 11.36%, p < 0.0001). There was no statistical difference in the proportion of

Table 1. Demographic and baseline disease characteristics of the studied cohort

Variable	
Age, years	29.05±7.25
Sex	
Male	17 (28.64)
Female	27 (61.36)
Inclusion criteria	
Patients with relapses	42 (94.45)
Patients with progression	2 (5.55)
Duration of disease, years	5.71±3.37
Patients with prior DMTs	38 (86.4)
Natalizumab infusions, n	18.14±9.47
EDSS	4.76±1.38
ARR	1.32±0.74
MRI activity	42 (95.5)
Gadolinium enhancement	20 (45.5)
New T2 lesions	42 (95.5)

Values are number (%), or mean ± SD. DMTs: IFN beta-1b s.c., IFN beta-1a s.c. and IFN beta-1a i.m.

Table 2. Primary and secondary outcomes

Outcomes	Baseline	Last follow-up visit	p value
Primary outcomes			
Proportion of relapse-free patients	5 (11.36)	40 (90.91)	<0.0001
Secondary outcomes			
ARR	1.32±0.74	0.09±0.29	<0.0001
EDSS	4.76±1.38	3.15±1.5	<0.0001
MRI activity	42 (95.5)	8 (18.2)	<0.0001
Gad+ lesions	20 (45.5)	5 (11.4)	<0.0001
New T2 lesions	42 (95.5)	7 (15.9)	<0.0001

Values are number (%), or means ± SD.

relapse-free patients, when patients were dichotomized on the basis of EDSS of 3 or less prior to the initiation of treatment ($p = 0.67$). The mean ARR was significantly reduced, after the observational period (1.32 ± 0.74 vs. 0.09 ± 0.29, $p < 0.0001$). Also, there was a significant reduction in mean EDSS scores after the observational period (4.76 ± 1.38 vs. 3.15 ± 1.5, $p < 0.0001$); 72.3% (n = 32) of patients had an improvement by at least 1 EDSS step. MRI activity was significantly improved at the last visit compared to baseline (95.5 vs. 18.2%, $p < 0.0001$). This was evident by a reduction of the proportion of patients with Gad+ lesions (45.5 vs. 11.4%, $p < 0.0001$) and the proportion of patients with new T2 lesions (95.5 vs. 15.9%, $p < 0.0001$) after the observational period (table 2). Overall, 81.8% (n = 36) of patients were disease-free based on the rate of relapses, disability measures and MRI parameters.

Few adverse events such as headache, thinning or loss of hair, nausea or vomiting, and fatigue were observed; 2 patients had mild infusion reactions while none experienced hypersensitivity reaction, and 1 patient had elevated liver transaminases (<5× normal). This was transient and returned to normal within 3 months. Patients who had relapses were tested for neutralizing antibodies against natalizumab and none was tested positive.

Of the 44 patients, 6 (13.6%) discontinued treatment after a mean time of 22 ± 9.44 months (median 27, range 12–39); 5 (11.4%) stopped it due to positive JC virus and 1 (2.2%) due to pregnancy. Of the 32 patients screened for JC virus, 11 (34.4%) were positive. Three patients elected not to be on any DMTs and they accepted close clinical and radiological vigilance whereas fingolimod was initiated in 2 patients. However, there were no reported cases with progressive multifocal leukoencephalopathy in our cohort.

Discussion

Most patients improved during the treatment phase from both clinical and radiological perspectives. Our results confirmed previous studies of randomized controlled phase II and phase III studies [4, 5] that had shown that natalizumab is effective in reducing ARR and disease progression as measured by means of EDSS. Observational studies performed in similar patient populations in different European countries revealed similar findings [20–22].

At baseline, there was high disease activity among our patients despite the use of other DMTs in the majority. These were patients with highly active disease who could benefit from an early escalation therapy to more efficacious DMTs. The definition of highly active disease is debatable. In a post hoc analysis of the AFFIRM data, a subgroup of highly active patients was defined as patients with ≥2 relapses in the year prior to inclusion in the study and ≥1 Gad+ lesion [23]. In our study, we included patients with at least one disabling relapse and new Gad+ lesions.

Postmarketing studies such as ours are important to confirm what were established in clinical trials and also to monitor any safety concerns. A Swiss multicenter study

assessed 85 RRMS who had been treated with natalizumab for at least 12 months. The mean treatment duration was 18.4 months and 88.2% of patients were on prior DMTs. The authors found that 79% of the patients were relapse-free during the observation period, 92.9% were progression-free after 12 months and 91.7% had reduction in Gad+ lesions [21]. Putzki et al. [22] reported a prospective observation study on 31 RRMS patients who failed first-line DMTs according to a predefined protocol. The ARR was reduced from 2.1 to 0.2 one year after switching and the EDSS decreased by 0.7. There were 94% fewer Gad+ lesions with natalizumab.

A high relapse rate prior to the initiation of natalizumab remains the single parameter most influencing the decisions of most neurologists to switch to natalizumab. Furthermore, baseline disability measures assessed by EDSS may also play a role in the physician's decision. Prosperini et al. [18] indicated that a better response to natalizumab was more likely found in patients with ≤2 relapses in the year prior to treatment initiation and in those with baseline EDSS score ≤2.5. However, real-life data from a Swiss cohort reported sustained efficacy of natalizumab treatment in RRMS irrespective of disability at baseline [19]. However, in our study, the effect of treatment was independent of baseline EDSS probably because the EDSS cutoff in our study was arbitrary. Several epidemiological studies of the natural history of MS tried to assess the EDSS scores at which the disease might progress faster if reached [24, 25]. Pittock et al. [26] concluded that once an EDSS score of 3 was reached, progression of disability was more likely and more rapid. We included patients with higher EDSS and they could have been in the late phase of RRMS and hence might have benefited from natalizumab. Our results were similar to that of a multicenter Spanish study [27] in which 825 patients had a significant decrease in the number of relapses during the observation period (at least 12 months) among patients with different EDSS scores. In the study, an 87.9 and 93.2% reduction in ARR in patients with EDSS of 0–1.5 and >6, respectively, was reported. The authors suggested that the efficacy of natalizumab could extend to patients with higher EDSS score (>6) if they had an increase in their disease activity [27].

Assessment of disability progression could be affected by the duration of natalizumab therapy. In a retrospective study, Lanzillo et al. [8] indicated that in the 2nd year of therapy, natalizumab continued to be more effective in terms of disease activity than IFN beta-1a s.c., especially when assessing contrast-enhancing lesions. Our results showed that natalizumab increased the proportion of disease-free patients after the first year of therapy. A prospective observational study comparing two groups of patients who failed first-line DMTs showed that patients who were escalated to natalizumab were more likely to be free of disease activity after 24 months when compared to patients who switched between first-line DMTs [7]. A post hoc analysis of data from the AFFIRM study indicated that the effect of natalizumab during the second year was most notable on radiological and composite measures (clinical and radiological). The authors suggested that, not only was natalizumab effective during early treatment, but also its efficacy might increase over time [28].

The discontinuation rate of natalizumab in our study was 13.6%, which was similar to that of a large Spanish cohort (14.1%) [27]. The reasons for discontinuation were somewhat different. The discontinuation of therapy in our study was related to pregnancy and positive JC virus screen, while in the Spanish cohort, lack of efficacy, tolerability, patient decision, neutralizing antibodies, and hypersensitivity were the main reasons. However, the discontinuation rate in our study was slightly higher than in most of the other observational studies [20, 21]. This could be explained by the differences of the number of studied patients and study durations. The percentage of seropositive patients to anti-JC virus antibody was lower than what is reported in Western countries [29, 30]. Several factors including our small sample size, a relatively younger cohort and possibly a geographical difference in the JC virus infection rate might have contributed to the differences. The development of a JC virus screening test and the availability of alternative potential escalation therapies such as fingolimod influenced the decision of both the treating physicians and patients as whether or not to continue on natalizumab treatment, especially when 2 years of natalizumab treatment elapsed.

Our study had several limitations. First, it was an observational study, which lacked randomization. One confounding factor was the possibility of a differential detection of outcomes, which could be overcome by using the patients as their own controls in their pretreatment period. Another possible confounder in the interpretation of observational studies with no control arm was that the treatment effect might be partly explained by regression to the mean. Thus, patients were likely to start natalizumab treatment during moments of high disease activity and this activity would subside to a certain extent anyway, regardless of treatment. Second, a selection bias might have played a role since natalizum-

ab was the only approved therapy for active relapsing MS at the time of institution of treatment. The proportion of patients who might have been treated with natalizumab decreased after the availability of fingolimod in Kuwait in June 2011. The bias was minimized by the fact that most of the studied patients (~80%) received natalizumab for at least 12 months. Lastly, our study had a small number of patients with short duration on natalizumab due to the recent establishment of the Kuwait MS Registry and the conservative approach of most neurologists in prescribing such a potent therapy with a serious side effect such as progressive multifocal leukoencephalopathy.

Conclusion

Natalizumab for RRMS significantly reduced clinical relapses and the progression of disability along with suppression of the activity of disease as evidenced by MRI. During the observational period, natalizumab was safe and tolerable.

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