Multiple Sclerosis and Related Disorders 24 (2018) 113–116

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

# Efficacy and safety of natalizumab extended interval dosing

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ARTICLE INFO

*Keywords:*
Natalizumab
Extended
Dosing interval
Efficacy
Multiple sclerosis

ABSTRACT

*Objective:* It is postulated that extending the dosing interval of natalizumab (NTZ) from 4 to 5–8 weeks might decrease the risk of progressive multifocal leukoencephalopathy (PML). The aim of this study was to assess the effect of extended interval dosing (EID) on the therapeutic efficacy of natalizumab.

*Methods:* We reviewed 85 patients treated at two MS centers in the Middle East with natalizumab for at least 6 months using EID. Patients were shifted after an initial treatment period at standard interval dosing (SID) to an EID ranging from 5–8 weeks.

*Results:* The mean treatment duration on SID and EID was 15.4 ± 11.9 and 11.8 ± 7.0 months, respectively. By the end of SID and EID treatment 95.3% and 93.9% of patients were free of relapses ($P = 0.41$) with an annualized relapse rate (ARR) of 0.0006 and 0.001 respectively ($P = 0.42$). The mean EDSS at the end of SID and EID periods was 2.56 ± 1.62 and 2.59 ± 1.61 respectively ($P = 0.84$). A total of 97.6% and 94.7% of patients had no enhancing lesions on MRI during the SID and EID periods respectively ($P = 0.18$). There were no cases of PML and the rate of infections was lower during the EID period.

*Conclusion:* In patients treated with natalizumab, shifting from SID to EID has no negative effect on efficacy as evidenced by relapse rate, disability progression and MRI activity.

## Introduction

Natalizumab (NTZ) is a monoclonal antibody that binds to the adhesion molecule α4-integrin on the surface of mononuclear cells, reducing their central nervous system (CNS) trafficking (Rudick et al., 2013). PML, caused by reactivation of JC virus (JCV) has been the biggest barrier to use of natalizumab (Linda et al., 2009), which otherwise is a highly effective and relatively safe agent for relapsing-remitting MS (Polman et al., 2006, Butzkueven et al., 2014, Miller et al., 2003). In patients with positive JCV serology, treatment duration longer than 2 years, and prior exposure to immunosuppressants and/or high antibody index, the risk of PML may be as high as 1% (Plavina et al., 2014, Koendgen, 2016). PML is believed to result from diminution of immune surveillance that allows JC virus infected mononuclear cells to move from the bone marrow into the brain (Frohman et al., 2014, Major et al., 2013). The drug's saturation of α4-integrin, a key factor in its mechanism of action, does not fall below 50% until 82 days post-dosing (Khatri et al., 2009, Tan et al., 2011). Recent data support the concept that a longer dosing interval could preserve natalizumab efficacy, since partial saturation in the range of 70–80% might be enough to prevent relapses and new MRI lesions (Zhovtis and Ryerson, 2016). On the other hand, partial saturation may allow enough immune surveillance in the nervous system to maintain JC virus suppression and therefore reduce the risk of PML.

## Methods

This was a retrospective review study of prospectively followed cohorts of MS patients in two specialized MS Centers at the American University of Beirut Medical Center and Tehran University of Medical Sciences. Both cohorts were part of a patient registry approved by the IRB of the respective universities. We reviewed the charts of all patients treated with NTZ using an extended interval dosing (EID) regimen for at least 3 months, defined as an interval dosing ≥5 weeks. All patients were initially treated with standard interval dosing (SID) every 4 weeks before switching to EID. The following parameters were recorded: age, gender, disease duration, treatment duration, previous therapies, reason for switching to natalizumab, MS phenotype, clinical relapses,

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https://doi.org/10.1016/j.msard.2018.06.015
Received 16 April 2018; Received in revised form 28 May 2018; Accepted 19 June 2018
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EDSS and serum JCV status. Clinical relapses were defined as new neurological symptoms lasting more than 24 hours, which were judged by the treating neurologist to represent new MS activity. Annualized relapse rates (ARR) were calculated based on the number of relapses divided by the length of follow-up, measured in years. Brain MRI scans were obtained as part of routine practice every 6–12 months and new T2 and/or gadolinium enhancing (Gd+) lesions were assessed compared to a baseline scan performed before initiation of natalizumab, or upon switching from SID to EID regimen.New MRI activity was defined as new or enlarging T2 and/or Gd+ lesions.

Statistical analysis was performed to determine if switching from SID to EID affected the efficacy of natalizumab as evidenced by relapse rate, EDSS and MRI activity.The Statistical Package for Social Sciences (SPSS), version 24, was used for the data entry, management, and analyses. Descriptive statistics were summarized by presenting the number and percentage for categorical variables and mean and standard deviation for continuous variables. The association between SID and EID in the same patient and other categorical variables was carried out by using the Mac Nemar or Marginal Homogeneity test, as appropriate. Paired *t*-testor Wilcoxon test were used for the association with continuous variables, as appropriate. *P*-value $< 0.05$ was used to indicate statistical significance.

## Results

A total of 85 patients received an EID regimen of natalizumab for at least 3 months, 55 of which were from Lebanon and 30 from Iran. The dosing interval in the EID regimen ranged from 5 to 8 weeks. The baseline demographic and clinical characteristics are shown in Table 1. The majority of patients were females (77.6%) with a mean age of 33.8 ± 10.9 years, and mean disease duration of 6.2 ± 6.2 years. Most of them were initially switched to natalizumab due to persistent disease activity (93.3%) as reflected by a mean ARR of 1.31 ± 1.25 in the previous 2 years and a baseline EDSS of 3.27 ± 1.68. Upon starting natalizumab, 94.1% and 63.5% of patients had new MRI activity or Gd + lesions respectively. The most common prior therapy were interferons (54.1%), followed by fingolimod (27.1%), and 11.8% of patients were treatment naïve. Less than 5% of patients had progressive MS, and 45.2% were JCV positive including 42.9% with an antibody index >0.9.

**Table 1**
Baseline characteristics ($n = 85$).

| | |
|---|---|
| Gender (%) | Male 19 (22.4)<br>Female 66 (77.6) |
| Age (years) (mean ± SD) | 33.76 ± 10.93 |
| MS Duration (years) (mean ± SD) | 6.22 ± 6.22 |
| MS phenotype (%) | RRMS 77 (95.3)<br>SPMS 4 (4.7) |
| ARR (mean ± SD) | 1.31 ± 1.25 |
| Baseline EDSS (mean ± SD) | 3.27 ± 1.68 |
| Baseline JCV status (%) | Positive 38 (45.2)<br>Negative 46 (54.8) |
| JCV Index (%) | <0.9 40 (57.1)<br>≥0.9 30 (42.9) |
| Previous therapy (%) | IFN 46 (54.1)<br>Fingolimod 23 (27.1)<br>Dimethyl Fumarate 1 (1.2)<br>Mycophenolate 1 (1.2)<br>Teriflunomide 1 (1.2)<br>Treatment Naïve 10 (11.8)<br>Other 3 (3.5) |
| Overall Treatment Duration (months) (mean ± SD) | 26.08 ± 13.34 |
| Reason for switching to Natalizumab (%) | Disease activity 70 (93.3)<br>Adverse events 5 (6.7) |
| Patients with new MRI activity (%) | 80 (94.1) |
| Patients with Gd+ lesions (%) | 54 (63.5) |

SD: standard deviation; MS: multiple sclerosis; ARR: annualized relapse rate; EDSS: expanded disability status scale; JCV: JC virus; INF: interferon; MRI: magnetic resonance imaging; Gd: gadolinium.

All 85 patients were initially treated with SID for a mean duration of 15.4 ± 11.9 months then switched to EID for a mean duration of 11.8 ± 7.0 months. Clinical disease activity was very low during both SID and EID periods (Table 3). The pre-treatment ARR of 1.31 ± 1.25 dropped to 0.0006 ± 0.003 during SID and 0.001 ± 0.006 during EID ($P = 0.42$), with 95.3% and 93.9% of patients free of relapses on SID and EID respectively ($P = 0.41$). Radiological activity was also significantly reduced on both regimens. Overall, 81.2% and 92.0% of patients had no evidence of new MRI activity on SID and EID respectively ($P = 0.05$), while 97.6% and 94.7% had no Gd+ lesions on SID and EID respectively ($P = 0.18$). It is of note that new MRI activity during SID was assessed by comparison to the first MRI performed upon initiation of natalizumab, which might explain the slightly higher activity seen during the SID period. The mean EDSS improved upon initiation of natalizumab and remained stable throughout the SID and EID periods: 2.56 ± 1.62 and 2.59 ± 1.61 respectively (Table 2).

In a subgroup analysis of the 55 Lebanese patients, adverse events were less frequent on the EID compared to the SID regimen (51% and 31% respectively) (Table 3). This was driven mainly by a lower rate of infections (42% and 20% on SID and EID respectively). No PML cases were seen during the total period of observation. Specifically, fatigue was not reported more commonly in patients on EID.

## Discussion

The rationale for monthly dosing of NTZ was based on pharmacokinetic studies showing that α4-integrinreceptor saturation remains ≥80% four weeks after a single 300 mg intravenous infusion (Rudick and Sandrock, 2004). However, such a high level of receptor saturation might not be needed to maintain the same degree of clinical efficacy (Punet-Ortiz et al., 2018). Maximal receptor saturation is defined as 70–80% occupancy while receptor desaturation is defined as <50% occupancy. Studies have shown that α4-integrin receptor saturation is maintained >50% in almost all patients with NTZ serum levels >1 μg/ml (Khatri et al., 2009). With monthly dosing, trough serum concentrations of NTZ were >2 μg/ml in all patients and >10 μg/ml in 94% of patients without neutralizing antibodies. Interestingly, higher serum levels did not correlate with better clinical outcomes (Kempen, 2017). Serum levels >1 μg/ml can actually be maintained for up to 8 weeks following a single 300 mg infusion of NTZ (Sheremata et al., 1999). Accordingly, the hypothesis was that longer dosing intervals up to 8 weeks might decrease α4-integrin receptor saturation without affecting the drug's clinical efficacy while allowing for a certain degree of immunosurveillance within the CNS that might prevent PML.

The aim of this study was to show that shifting patients from SID to EID had no effect on NTZ efficacy as evidenced by relapses, MRI activity and disability progression. The ARR decreased significantly upon initiating NTZ and was unchanged during SID and EID periods. The proportion of relapse-free patients was also similar during both periods. The mean EDSS of our cohort improved upon starting NTZ and was stable at the end of the SID and EID periods, reflecting similar effect of both regimens on disability progression. All patients had routine MRIs every 6–12 months. Both regimens had similar effect on MRI inflammatory activity as shown by similar near complete suppression of Gd+ lesions. New MRI activity, defined as new/enlarging T2 and/or Gd+ lesions was actually slightly higher in the SID group (18.8% vs 8.0% of patients) although it did not reach statistical significance. This is probably due to the fact that the first MRI performed 6–12 months after NTZ initiation was compared to the baseline MRI obtained at the start of therapy. Since NTZ takes around 3 months to suppress clinical and radiological disease activity, and in view of high baseline MRI activity in our patients (94.1% of patients had new MRI activity before initiating NTZ), new lesions could have formed during the first few

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