International Immunopharmacology 46 (2017) 105–111

Contents lists available at ScienceDirect

International Immunopharmacology

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

Long-term effectiveness and safety of natalizumab in a Portuguese population

I Correia [a,*], S Batista [a], O Galego [b], IB Marques [a], J Jesus-Ribeiro [a], AI Martins [a], C Nunes [a], MC Macário [a], L Cunha [a], L Sousa [a]

[a] Department of Neurology, Centro Hospitalar e Universitário de Coimbra, Portugal
[b] Department of Neuroradiology, Centro Hospitalar e Universitário de Coimbra, Portugal

ARTICLE INFO

Article history:
Received 5 January 2017
Received in revised form 2 March 2017
Accepted 4 March 2017
Available online 7 March 2017

Keywords:
Multiple sclerosis
Relapsing-remitting
Natalizumab
Monoclonal antibodies
Treatment outcome

ABSTRACT

Objectives: Natalizumab long-term effectiveness data in real-world relapsing-remitting multiple sclerosis (RRMS) is needed. Our objective is to report the long-term effectiveness and safety of natalizumab in a cohort of RRMS patients.
Methods: This is a retrospective study of natalizumab treatment for two years or longer in RRMS. Annualized relapse rate, Expanded Disability Status Scale (EDSS), brain magnetic resonance imaging T2 lesion volume, JC virus antibody status, previous treatments and adverse events were analysed.
Results: Seventy-one patients were included with a mean treatment duration of 44.86 ± 17.39 months. Over the treatment duration there was a significant decrease in annualized relapse rate (88.37%) and EDSS (28.57%); no evidence of clinical disease activity in 73.24% and 61.97% after one and two-years respectively; and brain magnetic resonance imaging T2 lesion volume remained stable. Forty patients suspended natalizumab, in 85% due to high risk of developing progressive multifocal leukoencephalopathy (PML). The major complication was PML (n = 3).
Conclusions: Natalizumab showed effectiveness in the long-term follow up period of our cohort, with reduction of ARR, EDSS, and MRI lesion load stabilization. PML was the major complication.

1. Introduction

Natalizumab is a humanized monoclonal antibody against alpha 4-integrin which interferes with the binding of leukocytes to VCAM-1 on the luminal surface of blood vessels, impairing the migration of leukocytes from peripheral blood into other tissues, particularly the brain in the case of multiple sclerosis [1]. Following monthly intravenous infusions of natalizumab (300 mg), a steady state is achieved after 36 weeks, with a calculated mean half-life of 16 ± 4 days [2].

The short-term efficacy of natalizumab in relapsing-remitting multiple sclerosis (RRMS) was demonstrated in two large, randomized, double-blind, placebo-controlled, multicentre, phase III trials: AFFIRM (Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis) [3] and SENTINEL (Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis) [4]. In AFFIRM, natalizumab reduced the risk of sustained progression of disability by 42% over two years and of clinical relapse at one year by 68%, and led to an 83% reduction in the accumulation of new or enlarging T2 hyperintense lesions in brain magnetic resonance imaging (MRI) over two years [3]. In SENTINEL, the combination therapy with interferon beta-1a resulted in a 24% reduction in the relative risk of sustained disability progression and a lower annualized rate of relapse over a two-year period with fewer new or enlarging T2 lesions on brain MRI [4].

There are also two large, long-term, open-label observational studies based on the previous trials' populations, which were designed to assess long-term efficacy: STRATA (Safety of Tysabri Re-dosing and Treatment), the results of which have already been published, showing stability in Expanded Disability Status Scale (EDSS) scores and consistently low relapse rates over 5 years of natalizumab treatment [5]; and the Tysabri (natalizumab) Observational Program (TOP), which is currently ongoing although some results have been published, showing a low relapse rate and stabilised disability levels with natalizumab [6].

Real-world use of natalizumab in RRMS has been described in several studies, which has contributed to a better understanding of natalizumab effectiveness regarding relapse rate, disability progression and safety [7–22]. Overall, natalizumab was consistently effective in these studies. However, the majority of studies have several limitations including a short follow-up time, and a lack of information regarding

* Corresponding author at: Av. Bissaya Barreto - Praceta Prof. Mota Pinto, 3000-075 Coimbra, Portugal.
E-mail address: mcorreia.ines@gmail.com (I. Correia).

http://dx.doi.org/10.1016/j.intimp.2017.03.006
1567-5769/

MRI results and the period after natalizumab suspension. Moreover, samples were small in some studies.

The most common adverse events associated with natalizumab, occurring with a frequency of 1/100 to 1/10 patients, are urinary tract infections, nasopharyngitis, headache, dizziness, vomiting, nausea, arthralgia, rigors, pyrexia and fatigue. Uncommon adverse events, occurring with a frequency of 1/1000 to 1/100 patients, are hypersensitivity and progressive multifocal leukoencephalopathy (PML) [2]. PML is a rare, disabling and potentially fatal infection of the central nervous system, caused by reactivation of the John Cunningham virus (JCV). In post-marketing settings worldwide, approximately 161,300 patients have received natalizumab until September 30, 2016 and 695 confirmed cases of PML have been reported until December 1, 2016 [23].

Our centre is a tertiary referral hospital for multiple sclerosis and we therefore follow patients with very aggressive disease, previously followed in other hospitals, who need a more specialized approach and more effective treatments. Real-world long-term data is still needed, in particular regarding these patients, which motivated us to perform this study. Furthermore, long-term lesion volume in brain MRI has not been addressed before. Lastly, the follow-up of patients after withdrawal of natalizumab has been the subject of controversy regarding the rebound of disease activity and thus it would be important to further explore this topic in our population.

2. Materials and methods

2.1. Participants

This was a retrospective study. The start date for inclusion was August 1, 2007 and the last date for data introduction was April 30, 2015.

The inclusion criteria were: patients followed in the Neurology Department of our Portuguese University Hospital with the diagnosis of RRMS, according to the McDonald Criteria of 2010 [24]; treatment with natalizumab for more than two years; and age above 18 years. Exclusion criteria were the diagnosis of progressive multiple sclerosis or incomplete medical records.

This study was approved by the local ethics committee.

2.2. Clinical assessment

A relapse was defined as patient-reported symptoms or objectively observed signs, current or historical, typical of an acute inflammatory demyelinating event in the central nervous system, lasting at least 24 h, in the absence of fever or infection [24].

Confirmed EDSS progression was defined as an increase, sustained for six months, of 0.5 points or more in patients with a baseline EDSS score above 5.5; 1.0 points or more in patients with a baseline EDSS score between 1.0 and 5.5; and 1.5 points or more in patients with a baseline EDSS score of 0.0 [3,4]. Confirmed EDSS improvement was defined as a decrease of at least 1.0 point in the EDSS score sustained for six months [25].

A rebound of disease activity was defined as an individual relapse rate after cessation of natalizumab higher than the relapse rate previous to this treatment [26].

It was assumed that there was no evidence of clinical activity in those patients who presented no relapses or disability progression during the considered follow-up time.

Adverse events were reported when there were serious infections, neoplasms, or other medical complications.

Patients were evaluated at months 3, 6 and 12 in the first year and thereafter generally every six-months or before if clinically indicated.

The following data were obtained for all patients: gender, age at MS diagnosis, age at natalizumab start, disease duration, previous disease modifying therapy (DMT), previous annualized relapse rate (ARR), which was defined as the number of confirmed relapses during the 12-month period prior to starting natalizumab, ARR with natalizumab, EDSS preceding natalizumab treatment (baseline) and EDSS at the last observation on natalizumab. In the patients who stopped treatment, the ARR and EDSS after one year of treatment withdrawal were evaluated.

2.3. MRI acquisition and analysis

Data from 1.5 Tesla MRI were obtained and analysed by an experienced neuroradiologist. Axial FLAIR acquisitions were preferred for supratentorial lesions and axial T2-weighted for infratentorial lesions delineation. Quantitative assessment of T2 hyperintense lesion volume (T2LV) was performed by manually contouring the white matter lesions using the 3D Slicer software (v4.3.1, freely available at http://www.slicer.org). New gadolinium enhancing lesions were not evaluated for this purpose and therefore MRI data was not used to evaluate disease activity. Although all patients underwent at least one brain MRI per year, not all the exams were done in our hospital and therefore the studies were not available for all patients. Thus, only cases with a brain MRI performed within 6 months of treatment initiation were included for this analysis, and these results were compared with the MRI at natalizumab withdrawal or with the last MRI available in patients who continued on treatment. Patients who developed PML were excluded from this analysis since a T2LV increase related to the infection would be expected. Regarding MRI data analysis, categorical subgroups were defined based on the variation of T2 lesion volume from baseline to the last MRI performed: decreased (a reduction higher than 0.50 cm^3); stable (a variation of <0.50 cm^3); increased (an increase higher than 0.50 cm^3) [27].

2.4. Statistical analysis

Demographic characteristics were presented as means and standard deviations for continuous variables, and as frequencies and percentages for categorical variables. The ARR, a continuous variable, was described as the mean and standard deviation and the EDSS, a numerical non-continuous variable, as the median and interquartile range (IQR). Safety outcomes were reported descriptively.

In our sample all the variables have a non-normal distribution, except for the EDSS before natalizumab commencement; so nonparametric tests were used. The Wilcoxon Signed Ranks Test was used to compare related continuous and related ordinal samples, and the Mann-Whitney Test is used to compare different groups of patients. Survival analysis through Kaplan-Meier survival plots was used to determine the proportion of relapse-free patients by duration of treatment, and the time from first natalizumab infusion to confirmed EDSS improvement. p values (2-tailed) <0.05 were considered statistically significant; in the graphs 95% confidence intervals (CI) were used.

3. Results

3.1. Demographic characteristics of patients

Among the MS population regularly followed in our outpatient department (n = 1014 patients), 222 patients were treated with natalizumab, of which 71 fulfilled the inclusion criteria and did not have any exclusion criteria. Patient baseline characteristics are summarized in Table 1. 71.83% of patients were female, mean age at RRMS diagnosis was 29.72 ± 9.11 years and mean disease duration at treatment start was 7.20 ± 6.12 years. The mean treatment duration with natalizumab was 44.86 months (minimum of 24 months, maximum of 96 months, ± 17.39 months) and the distribution of patients according to the number of months of continued treatment can be consulted in Table 1.

The mean number of treatments before natalizumab was 1.83 ± 1.18 DMTs, with 38.03% of the patients (n = 27) previously treated with only one DMT, 29.58% (n = 21) with two DMTs, 11.27% (n = 8)