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Predictors of freedom from disease activity in natalizumab treated-patients with multiple sclerosis

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ABSTRACT

Purpose: To identify baseline predictors of the response to natalizumab in patients with relapsing–remitting multiple sclerosis (RRMS).
Methods: We prospectively collected clinical and magnetic resonance imaging (MRI) data of RRMS patients treated with natalizumab and followed-up for 24 months. They were categorized according to different outcomes of response to natalizumab: (i) "full" responders, i.e. those having no relapses, no sustained disability worsening on Expanded Disability Status Scale (EDSS), and no MRI activity; (ii) "partial" responders, i.e. those having MRI activity, but not relapses and/or EDSS worsening; and (iii) "poor" responder, i.e. those experiencing relapses and/or EDSS worsening.
Results: We analysed data of 210 RR-MS patients (147 F, 63 M); at the end of the 24-month study period, 120 (57.1%), 36 (17.1%), and 54 (25.8%) patients were defined as "full", "partial" or "poor" responders, respectively. Thirty-two (89%) patients classified as "partial" responders experienced MRI activity at the 6-month scan; the majority of them had >2 contrast-enhancing lesions at baseline MRI scan or >2 relapses in the year prior to starting therapy. A "full" response to natalizumab was found more likely in patients with ≤2 relapses in the year prior to treatment start (OR = 3.68; p = 0.002), and in those with an EDSS score ≤2.5 at baseline (OR = 3.60; p < 0.001). Accordingly, patients with >2 relapses in the year prior to treatment start, or those with an EDSS score ≥3.0 at baseline were more likely to be classified as "poor responders". These figures were replicated even after excluding 20 patients who developed anti-natalizumab antibodies.
Conclusion: Our results suggest that natalizumab may lead to a complete remission of MS if started in patients with less aggressive disease (i.e. few relapses and mild disability), thus suggesting its possible role as first switching option, or even first-line therapy, at least in JCV-negative patients. We also support the recommendation against an immediate discontinuation of despite the occurrence of MRI activity in the first few months of treatment, since the freedom from clinical disease activity could be still achieved.

1. Introduction

Natalizumab (Tysabri®, Biogen Idec, Inc., Cambridge, MA, USA, and Elan Pharmaceuticals, Inc., San Francisco, CA, USA) is the first monoclonal antibody approved as a monotherapy with a special restricted distribution programme for the treatment of relapsing–remitting (RR) multiple sclerosis (MS). It significantly decreases the migratory capacity of peripheral blood mononuclear cells through inflammatory endothelium, via binding the α4-β1 integrins, the main homing molecules involved in lymphocyte migration to inflammatory sites in the central nervous system (CNS) [1].

Natalizumab has proven a highly effective treatment for patients with RRMS [2,3]. More than one third of natalizumab-treated patients reached a complete remission of the disease, i.e. the freedom from clinical and radiological disease activity, as seen on magnetic resonance imaging (MRI) [4]. Post-marketing experiences provided better or at least similar results even in MS populations with a more severe disease than in phase III trials [5–10]. Head-to-head comparison studies clearly show the superiority of natalizumab with respect to other disease-modifying therapies (DMTs) [11,12].

Nonetheless, about 2/3 of patients in the AFFIRM trial experienced relapses, disability worsening, and/or MRI activity at the end of the 2-year study period [4]. More recently, a post-hoc analysis combining data from SENTINEL and AFFIRM trial suggested that the occurrence of MRI activity during treatment did not necessarily preclude continued significant clinical efficacy of natalizumab over two years [13].

Although another post-hoc analysis from the phase III trials on natalizumab reported a better outcome, in terms of reduction in relapse

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rate, in patients having a "highly active" (HA) disease, i.e. ≥2 relapses in the previous 12 months and ≥1 contrast enhancing lesions (CELs) [14], no data are available to identify any clinical or MRI factors, as evaluated prior to starting the therapy, useful in predicting those natalizumab-treated patients reaching the complete remission of the disease (i.e. the freedom from disease activity) [15].

Our purpose was to determine, in a post-marketing setting, whether baseline clinical and MRI variables are valuable tools for discriminating patients experiencing clinical disease activity from those having an optimal response (i.e. the freedom from any disease activity), or a clinical benefit even in the presence of persistent MRI activity over a 24-month period of natalizumab treatment.

2. Methods

2.1. Participants

Patients affected by RR-MS according to revised McDonald criteria [16], and starting natalizumab at the MS Centre of S. Andrea Hospital in Rome according to the Italian regulatory criteria [17], were consecutively enlisted for this independent, single-centre, post-marketing, prospective study. The authorized prescription of natalizumab in Italy was restricted to (i) patients non-responders to Interferon Beta (IFNB) or Glatiramer Acetate (GA) carried out for an adequate period of time (A criterion), or (ii) those having a rapidly worsening disease course, regardless of previous treatment (B criterion).

Patients were regularly followed-up before the start of the natalizumab treatment; clinical and MRI data were prospectively collected and stored into an electronic database (after obtaining an informed consent by each patient). The local Ethical committee board provides exemption of approval for post-marketing, observational, prospective studies.

Only patients having a regular follow-up for at least 24 months were included in the present study.

Demographic and clinical information were collected at baseline visit (i.e. at natalizumab start), including gender, disease duration, number of exacerbations in the previous year, Expanded Disability Status Scale (EDSS) score [18], data on previous treatments, presence of contrast enhancing lesions (CELs) at MRI scan performed in the month before the natalizumab start, and determination of HA disease (i.e. ≥2 relapses in the previous 12 months and ≥1 CELs) [14].

Clinical relapses and changes in EDSS score during treatment, as well as any other medical event occurred as a result of natalizumab treatment, were recorded. A relapse was defined as the appearance or reappearance of one or more symptoms attributable to MS, accompanied by objective deterioration on neurological examination lasting at least 24 h, in the absence of fever and preceded by neurological stability for at least 30 days [16].

Also, we collected MRI data after 6, 12, and 24 months (±4-week window) of natalizumab treatment, focusing on the presence of CELs on post-contrast T1-weighted scans and the appearance of new hyperintense lesions on T2-weighted sequences (when compared to the previous scan). Unscheduled MRI scans were also performed, if necessary.

To ensure a more reliable comparison between each scan, images were acquired in the same outpatient centre using a superconducting 1.5 T magnet (GE Excite), according to published guidelines [19]. Reproducible slice positioning was maintained throughout the follow-up using the same anatomical landmarks for each patient. All MRI scans were interpreted by experienced radiologists unaware of clinical data.

Furthermore, all patients who experienced clinical and/or MRI activity, or infusion reactions, were tested for the development of anti-natalizumab antibodies [20].

2.2. Outcome definition

At the end of the 24-month follow-up period we calculated the proportion of patients experiencing the following measures of disease activity: (i) one or more clinical relapses; (ii) a sustained disability worsening, defined as an increase of ≥1 EDSS-point (if previous EDSS score was <5.5) or 0.5 point (if previous EDSS score was ≥5.5) confirmed in two consecutive visits separated by a 6-month interval; and (iii) MRI activity, defined as the presence of CELs, and/or new or enlarging T2-hyperintense lesions (when compared to the baseline scan).

On the basis of these measures of disease activity, we defined three different outcomes of response to natalizumab:

- "full" response, i.e. the complete remission of the disease, i.e. no relapses, no sustained disability worsening, and no MRI activity [14];
- "partial" response, i.e. the occurrence of MRI activity, but not clinical relapses and/or sustained disability worsening;
- "poor" response, i.e. the occurrence of clinical relapses and/or sustained disability worsening.

2.3. Statistical analysis

All values are expressed as mean (SD), median (range), or proportion, as appropriate.

As baseline (i.e. at natalizumab start) characteristics we considered: gender (female or male), age, disease duration, number of relapses in the previous 12 months (1, 2, 3 or more), EDSS score, number of CELs, determination of HA disease (absence or presence), criterion for enrolment according to Italian regulatory agency (A or B), number of DMTs previously taken (0, 1, 2, 3 or more), and prior exposure to immunosuppressant agents (yes or not).

Differences between groups were tested using the Chi-Square test with Yate's continuity correction and Mann–Whitney *U* test, for dichotomous and continuous variables, respectively.

The EDSS changes (ΔEDSS) over the 24-month study period were assessed by the Wilcoxon rank sum test within each outcome groups ("full", "partial" or "poor" response to natalizumab).

A classification and regression tree-based analysis [21] was performed to search the best classification of patients by the response to natalizumab (i.e. the dependent variable) over all potential predictors (i.e. the independent variables) and all possible cut-points. The order of the variables and the specific cut-points were detected using an exhaustive Chi-squared Automatic Interaction Detection (CHAID) algorithm that, at each node, selects those predictors having the strongest interaction with the dependent variable, after examining each possible split.

Moreover, odds ratios (OR), their corresponding 95% confidence intervals (CIs), and p-values were computed using a logistic regression analyses (forward stepwise selection) to identify the baseline predictors for having a "full" response to natalizumab treatment. The aforementioned baseline patients' characteristics were added in the model as potential predictors; interaction terms were also tested, where appropriate. In each subsequent step, the regression equations comprised those predictors reaching specific thresholds of F- and p-values (for predictor inclusion: $F \geq 1$ and $p \leq 0.05$; for exclusion: $F < 1$ and $p > 0.05$). Finally, the logistic regression models were re-built after removing patients who developed anti-natalizumab antibodies, in order to minimize the influence of potential confounding factors related to the anti-natalizumab antibody development, rather than the response to therapy.

All p-values less than 0.05 in either direction were considered as significant. Analyses were carried out using a PC version of Statistical Package for Social Sciences 16.0 (SPSS, Chicago, IL, USA).