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Eligibility Criteria to Natalizumab Therapy in Patients with Relapsing-remitting Multiple Sclerosis: A Real-life Study in an Italian Population-based Cohort

Franco Granella[1], Eleonora Baldi[2], Sara Montepietra[3], Caterina Senesi[1], Luisa Motti[3], Maria Rosaria Tola[2] and Paolo Immovilli[4]*

[1]Department of Neurosciences, Multiple Sclerosis Centre, University of Parma, Italy
[2]Department of Neuroscience and Rehabilitation, Neurology Unit, University Hospital, Ferrara, Italy
[3]Neuromotor Department, Multiple Sclerosis Centre, Santa Maria Hospital-IRCCS, Reggio Emilia, Italy
[4]Neurology Unit, G. da Saliceto Hospital, Piacenza, Italy

Abstract

Background: Many patients with relapsing-remitting MS (RRMS) show a suboptimal response to first-line disease-modifying drugs. In these patients treatment with natalizumab is highly effective, however its use has been limited due to safety concerns.

Objective: To evaluate the consistency between the eligibility to natalizumab according to Italian Drug Agency (AIFA), European Medicines Agency (EMA) and Food and Drug Administration (FDA) criteria, and its use in clinical practice.

Methods: Medical records of 402 patients from four Italian MS Centres were reviewed to identify patients eligible to natalizumab according to AIFA, EMA, and FDA criteria and verify how many of them were currently treated or had been previously treated in practice.

Results: Of 316 RRMS patients, 13.3% were currently or had been previously treated with natalizumab, while additional 7.0%, 14.2%, and 27.2% were not receiving the drug although they were eligible according to AIFA, EMA, and FDA criteria, respectively. Compared to patients treated with natalizumab, subject who were eligible but remained untreated were older and with shorter education.

Conclusion: In a cohort of RRMS patients, 20.3%, 27.5%, and 40.5% were eligible to natalizumab according to AIFA, EMA, and FDA, respectively, although only part of them were actually treated.

Keywords: Eligibility criteria; Multiple sclerosis; Natalizumab; Prescription practices

Introduction

First-line immunomodulatory agents, i.e., interferons-beta (IFNs-β) and Glatiramer Acetate (GA), demonstrated to be effective in the treatment of relapsing-remitting multiple sclerosis (RRMS) together with a favourable safety profile [1-4]. In the individual pivotal trials, all IFNs-β (IFN-β 1a IM, IFN-β 1a SC, and IFN-β 1b) and GA reduced the annualized relapse rate (ARR) by approximately one third and decreased the number and/or the volume of radiological lesions compared to relative placebo controls [1-4]. However, these therapies are not always able to fully control disease activity and, in the real-life setting, a considerable fraction of patients still shows the occurrence of clinical and/or radiological signs of the disease – a suboptimal response – despite treatment [5-7]. As of today no evidence-based guideline has been established on how to identify and manage patients with suboptimal response to first line therapies; however, there is large consensus on the benefits of early escalating these patients to a more effective treatment as they fulfil the eligibility criteria before irreversible disability has been reached [5-11].

Natalizumab is the first humanized monoclonal antibody belonging to the class of selective inhibitors of adhesion-molecules approved for the treatment of RRMS patients with inadequate response to immunomodulators or with rapidly evolving disease [12,13]. Natalizumab binds the α4 subunit of α4β1 integrin on human activated T and B cells and other circulating leukocytes (with the exception of neutrophils) and inhibits the migration of these cells from peripheral blood into the Central Nervous System through the Brain-Blood Barrier, thus reducing the severity of local inflammatory response [14,15]. In the AFFIRM phase III study natalizumab demonstrated to be highly effective on clinical and radiological measures of MS activity [16-18]. In this large, randomized, multi-center, placebo-controlled, 2-year trial, natalizumab significantly reduced the annualized rate of clinical relapses (-68%) and the risk of disability sustained progression (-42% and -54% confirmed at 12 and 24 weeks, respectively) and delayed the progression to the EDSS "milestones" of 4 (-67%) and 6 (-70%), compared to placebo in patients with RRMS over two years [17-19]. A post-hoc analysis of the AFFIRM study also demonstrated that a significantly greater percentage of patients receiving natalizumab (37% vs. 7% in the placebo control group) was free of combined clinical and radiological disease activity over 2 years [19]. In the SENTINEL trial, natalizumab induced a 55% reduction in ARR and a 24% reduction in the risk of sustained disability progression as an add-on treatment to IFN-β 1a, compared to IFN-β 1a alone [20].

However, the association between the use of natalizumab and the risk of a severe opportunistic infection of the Central Nervous System, i.e. Progressive Multifocal Leukoencephalopathy (PML), particularly in those patients having one or more of the identified risk factors[21-23],

***Corresponding author:** Paolo Immovilli, Neurology Unit, G. da Saliceto Hospital, Piacenza, Italy, Tel: +390521704117; E-mail: franco.granella@unipr.it

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led the Regulatory Agencies, including the American Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Italian Drug Agency (AIFA), to issue restricted therapeutic indications to identify eligible patients (Table 1) [24-26]. In particular, when the use of natalizumab was approved in Italy in 2006, AIFA issued even more restrictive criteria for reimbursement in Italy compared therapeutic indications approved in EU by EMA [26]. As of today the use of natalizumab in the eligible population of RRMS patients in the setting of clinical practice in Italy was never evaluated and, therefore, still represents an unmet question.

The aim of this study was to evaluate the percentages of subjects eligible to treatment with natalizumab according to AIFA, EMA, and FDA criteria effective at the time of the analysis, in an Italian real-life cohort and to estimate how many of these patients were or had already been treated with the anti-α4 monoclonal antibody in practice.

Patients and Methods

This study was conducted in four Multiple Sclerosis Centres (located in Parma, Reggio Emilia, Ferrara, and Piacenza) of Emilia-Romagna Region, in Northern Italy. Medical records from all patients (n=402) followed in the participating Centres between June and September 2010 were obtained and reviewed in order to identify subjects eligible to the study. Patients were included if they met the following criteria: i) they had at least one visit during the year prior to the inclusion in the study, and ii) had complete medical records. All patients were required to sign an informed consent before enrolment. The study was conducted according to the Helsinki Declaration and the protocol was approved by the Ethical Committees of the individual Centres.

A specifically-designed 31-item form (see Supplementary File) was used to collect data from the medical records of enrolled patients and to evaluate their eligibility to natalizumab according to AIFA, EMA, and FDA criteria (as effective at the time of the analysis; Table 1). The first 13 items were related to demographic data and disease characteristics, while the following 18 items were only addressed to patients with RRMS defined according to Lublin's classification [27]. The last three of these questions were specific for patients who had ever received natalizumab and were aimed at evaluating whether i) natalizumab was still administered or had been discontinued; ii) which AIFA criterion did the patient fulfil when natalizumab treatment was started (i.e., criterion A or B, Table 1); and iii) the reason leading to drug discontinuation in patients who were not on treatment any longer.

Collected data were analysed with descriptive statistics. Comparisons between groups were performed with chi-square test and Student's t test, as appropriate. A p value <0.05 was considered statistically significant. To compare patients ever treated with natalizumab to those eligible but still untreated, a multivariate analysis (backward logistic regression) was performed, taking into account the following variables: Centre of inclusion, age, gender, education, age at onset, disability (measured on Extended Disability Status Scale, EDSS) at onset and at the time of last visit, number of relapses and of disabling relapses during last year.

Results

A total of 402 patients were included in the study (264 females, 65.7%, and 137 males, 34.3%; mean age: 41.1±10.84 years, range: 18-73 years). Among the 402 patients evaluated, 316 (78.6%) had a diagnosis of RRMS (211 females, 66.8%, and 105 males, 33.2%; mean age: 38.4±9.42 years, range: 18-68 years) and entered the subsequent evaluation for the eligibility to and use of natalizumab (Figure 1).

Disease activity in RRMS patients

More than a half of RRMS patients (n=174, 55.1%) had had no clinical relapses during the year prior to evaluation, while 142 patients were clinically active with 97 (30.7%) having 1 relapse and 45 (14.2%) having 2 or more relapses. A not negligible minority of patients (n=69, 21.8%) experienced disabling relapses with incomplete recovery as defined as 6-month confirmed post-relapse score progression on EDSS.

Regarding the radiological evaluation, the great majority of patients (n=238, 75.3%) had ≥9 T2 hyperintense lesions (see AIFA and EMA criteria, Table 1), while 69 patients (21.8%) showed the presence of gadolinium-enhancing lesions at the last available scan.

Use of disease-modifying treatments in RRMS patients

Among the RRMS patients included in the study, 14 (4.4%) had never been treated with disease-modifying therapies (DMTs), while other 11 (3.5%) had been treated before with DMTs but had then

1a. Therapeutic indications of natalizumab according to Food and Drug Administration [24].
As monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. Natalizumab is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy.
1b. Therapeutic indications of natalizumab according to European Medicines Agency (EMA)[25][a].
Natalizumab is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following patient groups: - Adult patients aged 18 years and over with high disease activity despite treatment with a beta-interferon. These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial Magnetic Resonance Image (MRI) or at least 1 Gadolinium-enhancing lesion. A "non responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year. or - Adult patients aged 18 years and over with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.
1c. Reimbursement criteria for natalizumab according to Italian Drug Agency (AIFA)[26].
- RRMS patients who failed to respond to a full and adequate course of the actually approved RRMS therapies. Patients should have had: at least 12 months of disease modifying treatment (shorter treatment period allowed if disease activity is clearly evident after a shorter time); at least 2 relapses in the previous year while on therapy or 1 relapse in the previous year while on therapy, with a residual EDSS ≥2 and a cranial MRI with at least 9 T2 lesions or 1 Gd+ enhancing lesion in comparison with a previous exam not older than 1 year; *or* *- RRMS patients with serious and rapidly evolving disease (patients without any disease modifying treatment also included). Patients should have had: at least 2 disabling relapses in the previous year with incomplete recovery and a residual EDSS ≥2 and new T2 lesions (number and volume) as compared to a previous MRI (not older than 12 months) or new Gd+ lesions as compared to a previous MRI (not older than 12 months).*

Table 1: Eligibility criteria for natalizumab treatment according to US (FDA, 1a), EU (EMA, 1b), and Italian (AIFA, 1c) drug Regulatory Agencies.

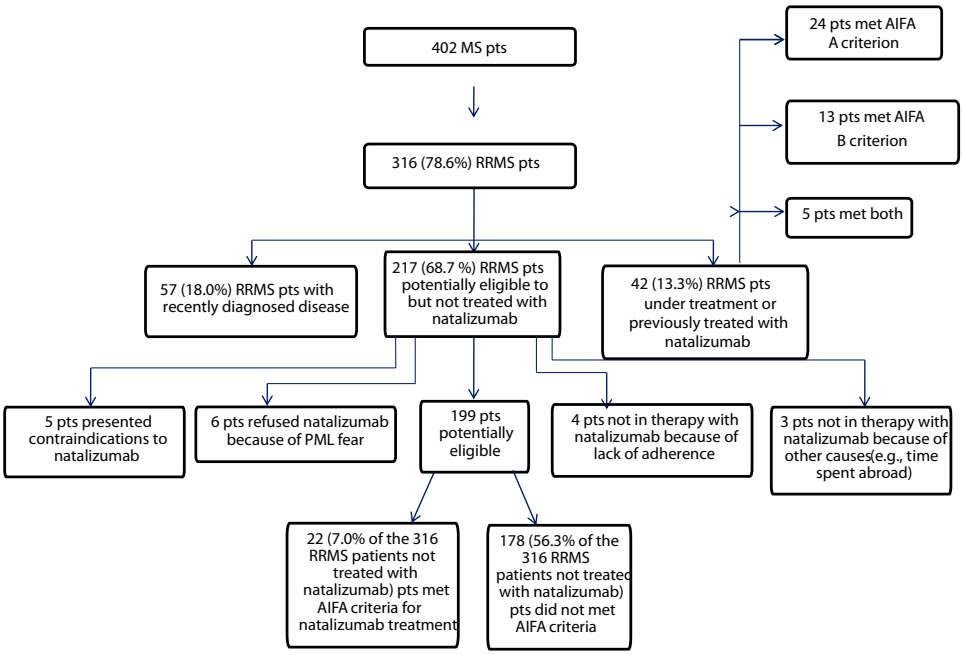

Figure 1: Flow-chart of the population studied.

discontinued treatment. The remaining 291 patients (92.1%) were currently on treatment with immunomodulatory (n=271, 85.8%) or immunosuppressant (n=20, 6.3%) drugs at study entry, 66 of which (27.2%) by less than one year. Fifty-three patients (16.8%) had temporarily discontinued an immunomodulatory treatment before the analysis because of an adverse event, while 59 (18.7%) had expressed the wish to discontinue the current therapy due to poor tolerability.

Eligibility to natalizumab treatment

Of the 316 RRMS patients, 42 (13.3% of all RRMS patients) were under treatment (n=32) or had been previously treated (n=10) with natalizumab (Figure 1). AIFA criteria A and B were fulfilled in 24 and 13 of the 42 cases, respectively, whereas 5 patients simultaneously fulfilled both criteria.

In 10 of these 42 patients treatment had been discontinued due to the following reasons: lack of efficacy (n=2), allergic reaction (n=3), increase of liver enzymes (n=2), presence of neutralizing antibodies (n=1) or patient's decision (n=2).

We also evaluated whether other patients were eligible to treatment among the remaining 274 who had never received natalizumab at the time of the inclusion. Fifty-seven (20.8%) had been recently diagnosed with MS and therefore were not eligible to natalizumab either because they had not experienced a full course of immunomodulatory drugs (see AIFA and EMA criteria, Table 1) or because MRI data did not fulfil eligibility criteria (Figure 1). Of the remaining 217 patients (79.2%, Figure 1), 5 patients presented contraindications to natalizumab, 6 refused to consider the possibility to be treated with natalizumab (mostly because of the fear of PML), 4 were excluded from the treatment because they did not guarantee a sufficient adherence, and 3 were excluded for other reasons (long time to be spent abroad in 2 cases). Twenty-two (7.0% of 316 RRMS patients) of the 199 remaining patients fulfilled AIFA criteria (A and B in 19 and 3 cases, respectively) but were not treated with natalizumab (Figure 1). Additional 45 (14.2% of 316 RRMS patients) and 86 patients (27.2%) were eligible to therapy according to EMA and FDA indications, respectively.

Characteristics of natalizumab-treated patients vs. natalizumab-untreated patients

Patients treated with natalizumab (NTPs; n=42) were younger than patients who were not treated with the monoclonal antibody (NUPs; n=274) (32.6±7.38 vs. 39.3±9.40 years, p<0.0001) and had an earlier onset of MS (25.4±7.48 vs. 31.0±8.45 years, p<0.0001). As expected, NTPs had more active and more severe disease, from either clinical or neuroradiological point of view (Table 2).

Characteristics of natalizumab-treated patients vs. natalizumab-eligible untreated patients

Compared to patients eligible to but not treated with natalizumab (NEPs; n=22), NTPs (n=42) were younger (32.6□7.38 years vs. 41.9 10.56 years, p<0.0001), had an earlier onset of MS (25.4±7.48 years vs. 29.9□8.27 years, p=0.03) and had received a longer education (71.4% vs. 45.5% with high school or higher degree, p=0.04). Interestingly, clinical and radiological measures, including the number of relapses in the previous year and the severity of disability (EDSS score), of NEPs at the time of the analysis were not different from those of NTPs when natalizumab administration was started (Table 3). At a multivariate analysis, the only significantly different parameters between the two groups were Centre of inclusion (p=0.001) and age (higher in NEPs, p=0.01).

Discussion

Treatment with disease-modifying immunomodulatory drugs changed the natural history of RRMS, improving the outcomes in most of the patients [28]. However, there is a substantial percentage of patients who either do not respond optimally to first line drugs or have an aggressive disease from the onset [5-7]. The introduction of natalizumab, a very effective and well tolerated drug, represented a breakthrough change for these patients [16-20]. Safety concerns,

	NTPs (n = 42)[a]	NUPs (n = 274)[a]	p
Gender (% of females)	61.9	67.5	n.s.
Age (years; mean ± SD)	32.6 ± 7.38	39.3 ± 9.40	<0.0001
Education (% of patients with high school or higher degree)	71.4	67.4	n.s.
Age at MS onset (years; mean ± SD)	25.4 ± 7.48	31.0 ± 8.45	<0.0001
EDSS at onset (mean ± SD)	2.0 ± 1.04	2.0 ± 0.79	n.s.
Current EDSS (mean ± SD)	2.9 ± 1.43[b]	1.8 ± 1.0	<0.0001
Number of relapses in the previous year (mean ± SD)	1.3 ± 1.07[c]	0.5 ± 0.71	<0.0001
Number of disabling relapses in previous year (mean ± SD)	0.9 ± 0.82[c]	0.2 ± 0.42	<0.0001
MRI parameters (according to AIFA and EMA criteria, Table 1):			
- At least 9 T2-hyperintense lesions (%)	92.9	72.6	0.02
- At least 1 gadolinium-enhancing lesion (%)	35.7[c]	19.7	n.s.
- New or enlarged T2 lesions as compared to a			
previous MRI performed not more than 12 months before (%)	45.2[c]	24.5	0.002
- New gadolinium-enhancing lesions as compared to a previous MRI performed not more than 12 months before (%)	33.3[c]	15.0	0.004
- Significant increase in T2 lesion load as compared to a previous recent MRI (%)	35.7[c]	11.7	<0.0001

Table 2: Demographic variables and disease characteristics in RRMS patients currently or previously treated (NTPs) and not treated with natalizumab (NUPs).

	NTPs (n = 42)[a]	NEPs (n = 22)[b]	p
Gender (% of females)	61.9	68.2	n.s.
Age (years; mean ± SD)	32.6 ± 7.38	41.9 ± 10.56	<0.0001
Education (high school or degree%)	71.4	45.5	0.04
Age at MS onset (years; mean ± SD)	25.4 ± 7.48	29.9 ± 8.27	0.03
EDSS at onset (mean ± SD)	2.0 ± 1.04	2.1 ± 0.56	n.s.
Current EDSS (mean ± SD)	2.9 ± 1.43[c]	3.1 ± 1.1	n.s.
Number of relapses in previous year (mean ± SD)	1.3 ± 1.07[d]	1.6 ± 0.60	n.s.
Number of disabling relapses in previous year (mean ± SD)	0.9 ± 0.82[d]	1.1 ± 0.53	n.s.
MRI parameters (according to AIFA and EMA criteria, Table 1):			
- At least 9 T2-hyperintense lesions (%)	92.9	95.5	n.s.
- At least 1 Gadolinium-enhancing lesion (%)	35.7[d]	18.2	n.s.
- New or enlarged T2 lesions as compared to a previous MRI performed not more than 12 months before (%)	45.2[d]	45.5	n.s.
- New gadolinium-enhancing lesions as compared to a previous MRI performed not more than 12 months before (%)	33.3[d]	16.7	n.s.
- Significant increase in T2 lesion load as compared to a previous recent MRI (%)	35.7[d]	27.3	n.s.

Table 3: Demographic variables and disease characteristics in RRMS patients currently or previously treated (NTPs) and not treated with natalizumab although eligible to it (NEPs).

however, induced the Regulatory Agencies to issue restricted indications for natalizumab and also its use in clinical practice has been limited [24-26].

As of today no evidence-based guideline has been established on how to identify patients with suboptimal response to first line therapies who may benefit from an escalation to a more effective treatment as natalizumab [5-8]. Thus, approved therapeutic indications represent the more appropriate criteria to select the patients to be considered for a prompt switch to natalizumab. In addition to address a relevant clinical need, having an estimate of the RRMS patients being eligible to escalate to natalizumab could provide an useful theoretical benchmark to evaluate conditions of under- or overtreatment and a guidance when planning resource allocation for healthcare management.

Despite the limitations of our research, including the use of a small sample from few Centres belonging to the same (and quite homogeneous) area, the evaluation of eligibility to natalizumab but not to the other now available second-line drug, i.e., fingolimod, that had not been approved yet at the time of this analysis, and, last but not least, the evaluation of eligibility according to criteria that have been modified once the analysis had been already performed and the manuscript was in preparation (Table 1), this represents the first study specifically designed to simultaneously evaluate the prevalence of RRMS patients eligible to a second line therapy according to the criteria approved by different national and international Regulatory Agencies in a real-life cohort. A partial estimate comes from a large multicentre retrospective study in German MS Centers (the TYPIC study) aimed at characterizing disease course during immunomodulatory treatment and factors associated with physicians' considerations regarding a change of treatments [6]. In this large sample of approximately 8,000 patients receiving immunomodulatory treatments, 24% fulfilled EMA criteria for therapy escalation to natalizumab [7]. In the cohort evaluated in our study, 20.3%, 27.5% and 40.5% of RRMS patients were eligible to natalizumab treatment according to AIFA, EMA, and FDA criteria, respectively, considering those currently treated and those having the clinical and radiological characteristics to appropriately start the drug although still not treated at the time of the analysis (Figure 1). Thus the results of our study are consistent to those obtained from the abovementioned TYPIC study performed in a cohort of MS patients from another Country [6]; the smaller percentage of patients eligible to natalizumab according to AIFA criteria is due to the more restrictive criteria adopted by the Italian Drug Agency compared to EMA indications approved in EU [26].

Among the factors influencing the use of natalizumab, we found that in our cohort younger age, younger age at MS onset and higher education were correlated to higher use of the drug, as well as younger age was a feature associated to therapy escalation to natalizumab in TYPIC study [6]. Furthermore, in a post-hoc analysis of pivotal studies AFFIRM and SENTINEL, an age greater than 40 years was a predictive factor of more limited efficacy [29]. More difficult to explain appears the effect of education, although one may speculate that higher education may favour a more profound awareness of disease-associated risks and understanding of treatment benefit/risk profile and a request for a highly efficacious therapy, as natalizumab, in a condition of unsatisfactory response to first-line drugs. However, this still remains a pure speculation and is yet to be demonstrated.

In our cohort natalizumab was underused: about a third of patients eligible according to local AIFA criteria (and about half of patients according to EMA) were not treated despite they had clinical and radiological characteristics that were not different from those at therapy initiation in patients being or having been treated with the monoclonal antibody and could have potentially equally benefit from treatment. It seems therefore important to closely follow the patients in order to appropriately identify those who may benefit from a prompt drug escalation to a second line therapy as natalizumab.

Currently, the availability of a serological test for the detection [23,30,31] and potentially the quantitative measurement [32] of antibodies against JC virus, the etiological agent of PML, to be considered together with the other risk factors, namely previous use of immunosuppressant drugs and treatment duration [23], allows a more accurate and individualized stratification of patients for PML risk and benefit/risk estimate and helps physicians and patients in considering personalized treatment and monitoring approaches [33,34].

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