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The Italian Pharmacovigilance Program: An Observational Study of Adverse Effects of Natalizumab in Multiple Sclerosis Therapy

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Background: This study shows the results of a regional pharmacovigilance program on Natalizumab therapy in relapsing-remitting multiple sclerosis (RR-MS) patients after 3 years of experience.

Material/Methods: The primary objectives of this study were to estimate the incidence of expected and unexpected adverse effects correlated to Natalizumab therapy in a cohort of 88 RR-MS patients from Sicily, Italy, and to investigate the procedures adopted by the physicians to minimize the risk of developing severe adverse reactions correlated to Natalizumab therapy. Secondary objectives of this study were to evaluate the effectiveness of Natalizumab therapy for a careful examination of the risk/benefit ratio and to assess the actions undertaken in case of adverse reactions.

Results: Among 88 RR-MS patients, 55.68% did not report any type of adverse reaction, 35.22% showed expected adverse reactions (58.70% slight, 22.58% moderate, and 19.35% severe), and 9.10% showed unexpected adverse effects (62.50% slight, 25.00% moderate, and 12.50% severe). Approximately 4.54% of the patients treated with Natalizumab interrupted the therapy. Overall, among all patients, 56.62% showed ameliorated condition, 32.53% had stable disease condition, and 10.85% worsened.

Conclusions: We provide a short overview of evidence, which may be useful to better characterize the efficacy and potential adverse effects correlated to Natalizumab therapy.

MeSH Keywords: Antibodies, Monoclonal, Humanized • Drug-Related Side Effects and Adverse Reactions • Multiple Sclerosis, Relapsing-Remitting • Pharmacovigilance

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Background

Natalizumab (Tysabri®, Biogen Idec, and Elan Pharmaceuticals) is an humanized monoclonal antibody belonging to a new class of selective adhesion molecule inhibitors [1]. Natalizumab binds to the α4 subunit of α4β1 and α4β7 integrins expressed in leukocytes and prevents the interaction with its complementary receptor VCAM-1 (vascular cell adhesion molecule-1) on endothelial cells and other ligands within the central nervous system (CNS), such as fibronectin and osteopontin [2,3]. Disruption of these molecular interactions avoids the migration of leukocytes across the blood-brain barrier into the brain parenchyma and reduces inflammation [4]. According to the European Medicines Agency (EMA), Natalizumab was approved in 2006 for the treatment of relapsing-remitting multiple sclerosis (RR-MS) patients with high disease activity despite treatment with glatiramer acetate or beta interferon [5]. Several phase III clinical trials have established that Natalizumab is able to reduce disease activity as measured by the Expanded Disability Status Scale (EDSS), and to decrease the rate of relapses and the number of brain lesions detected by magnetic resonance imaging, as well as preventing disability progression [6–8]. At the cellular level, it is well recognized that Natalizumab provides significant protection from relapses in RR-MS patients by preventing migration of T cells into the CNS. In addition, it has been recently reported that Natalizumab treatment increases circulating B cells expressing the chemokine receptor CXCR3, suggesting a potential role of this receptor in controlling B cell migration in RR-MS patients [9]. Furthermore, some reports suggest that there may be a positive influence of Natalizumab on cognition, depression, fatigue, and quality of life in MS patients [10–13]. Nevertheless, some RR-MS patients experience a clinical relapse or worsening of the EDSS during Natalizumab therapy, probably due to the disrupted balance of T cells in patients undergoing Natalizumab treatment [14].

Natalizumab, administered 300 mg intravenously once every 4 weeks [1], is commonly well tolerated. However, the treatment is associated with a rare but severe increased risk of developing progressive multifocal leukoencephalopathy (PML) [15,16]. PML is a debilitating and often fatal neurological condition resulting from infection of oligodendrocytes caused by JC-virus (JCV) [17]. Indeed, it has been noticed that long-term treatment (over 24 months of therapy) with Natalizumab may cause PML, predominantly in patients with prior exposure to immunosuppressive agents [18]. For this reason, Natalizumab was withdrawn from the market shortly after its approval, for a re-evaluation of the benefit/risk profile. Moreover, extensive pharmacovigilance measures and a risk management program were imposed [19]. Post-marketing observational studies and passive surveillance have shown that Natalizumab therapy is associated with some adverse effects, including liver damage, pharyngitis, urinary tract infection, urticaria, cephalgia, dizziness, nausea, arthralgia, fever, and rigidity, which occur with a probability of more than 1/100 as reported in a summary of product characteristics [20]. Therefore, it has become necessary to monitor all patients who undergo Natalizumab therapy throughout the treatment, especially for the occurrence of serious expected and unexpected adverse reactions. In 2006, the Italian Drug Agency (AIFA) and the medical community established a country-wide surveillance program on Natalizumab therapy in MS patients in Italy to obtain information about the utilization and safety of Natalizumab. This study shows the results of a regional pharmacovigilance program (supported by AIFA), which was aimed to estimate the incidence of adverse reactions in a cohort of 88 RR-MS patients from Sicily (Italy), treated with Natalizumab and observed for 3 years.

Material and Methods

Patients

The study population comprised 88 RR-MS patients (63 women and 25 men; range, 21–74 years; Figure 1) who have undergone at least 1 Natalizumab treatment. All patients treated with Natalizumab were enrolled between January 2012 and February 2015. Forty-four patients were enrolled at the IRCCS Center Neurolesi "Bonino-Pulejo" Messina and 44 patients were enrolled at the Foundation IRCCS Istituto San Raffaele "G. Giglio "Cefalù", Palermo. All patients were retrospectively identified by reviewing medical records from centers involved in the study. According to our local jurisdiction, approval for this study is not required because it was supported by funds from the pharmacovigilance regional project. Nevertheless, the privacy of all patients was guaranteed.

For all RR-MS patients, the personal (age and sex) and clinical data were collected retrospectively from medical records. Specifically, the date of diagnosis of RR-MS (disease duration), the presence of any concurrent disease with Natalizumab therapy, and previous therapy for MS were recorded. In addition, disease severity indicators were collected: 1) number of clinical relapses occurring before treatment with Natalizumab and the number of relapses that occurred up to the last available follow-up in patients treated with Natalizumab for at least 6 months; and 2) the score of the last EDSS before starting the treatment with Natalizumab and that of the last available follow-up. Moreover, as reported in a 2016 paper [21], JCV seroconversion and index values may be influenced by treatment with Natalizumab. Therefore, it is important to monitor the JCV serology of patients and to incorporate additional risk factors into the PML risk stratification [21]. Consequently, our patients were screened for previous JCV infection and observed to evaluate changes in JCV seropositivity over the entire period of treatment. Descriptive statistics for the entire cohort of

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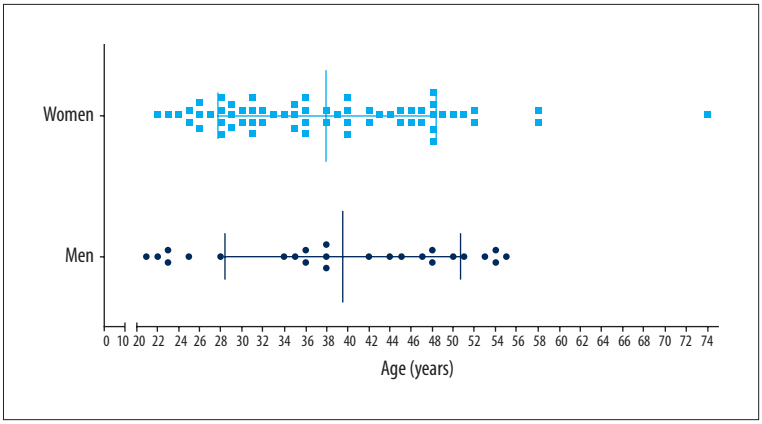

Figure 1. Correlation age/sex of RR-MS patients.

Table 1. Baseline characteristics of all enrolled patients.

	Total	Range 1–2.5	Range 3–4.5	Range ≥5
EDSS Score Pre-Natalizumab				
Median	3	2	3.5	6
N of patients (%)	83	37 (44.4)	23 (27.8)	23 (27.8)
EDSS Score Post-Natalizumab				
Median	3	1.5	3.5	6
N of patients (%)	83	40 (48.2)	25 (30.1)	18 (21.7)
JCV-seropositive Pre-Natalizumab				
N of patients (%)	41	21 (51.2)	11 (26.9)	9 (21.9)
JCV-seropositive Post-Natalizumab				
N of patients (%)	64	36 (56.2)	18 (28.2)	10 (15.6)
Male, N (%)	25 (30.1)	11 (29.7)	7 (30.4)	7 (30.4)
Female, N (%)	58 (69.9)	26 (70.3)	16 (69.6)	16 (69.6)
Age (years)				
Range	21–74	21–58	22–74	22–52
Mean ±SD	38.4 ± 10.5	8.3 ± 8.2	14.9 ± 11	14.1 ± 8
Duration of disease (years)				
Range	3–43	4–28	4–43	3–26
Mean ±SD	11.9±7.3	33.0±4.5	45.5±10.3	39.8±5.2

patients are provided in Table 1 and general features of each individual patient are shown in Table 2.

Results

Clinical characteristics of the patients

The study involved a cohort of 88 RR-MS patients (Sicily, Italy) treated 5–75 times with Natalizumab (1 infusion/month) at enrollment.

Objective evaluation was performed by using EDSS scores. Due to the unavailability of EDSS scores in 5 patients, we excluded these patients from the analysis. Consequently, we evaluated the EDSS in 83 patients. Of these, 37 patients showed a range of EDSS pre-Natalizumab between 1.0 and 2.5 (median 2); 23 patients between 3.0 and 4.5 (median 3.5); and 23 patients more than or equal to 5.0 (median 6.0).

Moreover, 16 patients had comorbidities, mostly involving thyroid function, such as autoimmune Hashimoto thyroiditis (N=5) and hypothyroidism (N=3). Patients with thalassemia

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Table 2. Overview of the 88 enrolled RR-MS patients.

ID	Age (years)	Age at disease onset (years)	Duration disease (years)	Sex	Concomitant diseases	N. doses of Natalizumab	Previous therapy	N. Relapse Pre-Natalizumab	N. R elapse Post-Natalizumab	EDSS Pre-Natalizumb	EDSS Post-Natalizumb
1	25	25	NA	F	No	6	NA	NA	NA	1.5	1.5
2	45	43	15	F	No	26	Yes	2	0	5.0	5.0
3	40	27	17	F	No	24	Yes	6	2	6.0	5.5
4	51	47	NA	M	No	8	Yes	NA	0	NA	NA
5	36	31	16	F	No	51	Yes	1	4	6.0	5.0
6	29	27	NA	F	No	15	Yes	2	0	2.0	1.5
7	28	26	12	F	No	22	Yes	1	0	6.0	5.0
8	28	24	5	F	Hashimoto thyroiditis	39	Yes	4	0	1.0	1.0
9	40	37	NA	F	No	24	Yes	2	0	1.5	1.0
10	22	21	3	M	No	7	Yes	1	0	NA	NA
11	31	30	12	F	No	12	Yes	2	0	6.5	4.0
12	23	18	6	F	No	53	Yes	1	0	5.5	4.5
13	40	38	12	F	No	5	Yes	NA	NA	6.0	3.5
14	39	36	15	F	No	38	Yes	1	0	3.0	1.0
15	47	42	16	M	No	54	Yes	2	0	6.0	5.5
16	47	42	16	F	No	50	Yes	2	0	4.0	4.0
17	48	47	8	M	No	16	Yes	1	0	3.5	3.0
18	38	34	15	F	No	37	Yes	2	NA	6.0	5.5
19	38	36	10	F	No	23	Yes	1	1	6.0	3.5
20	22	21	NA	F	No	10	NA	NA	NA	3.0	2.5
21	44	40	17	M	No	47	Yes	2	2	6.0	4.5
22	28	24	13	M	No	27	Yes	6	0	2.5	2.0
23	55	54	8	M	No	19	Yes	3	0	4.0	3.0
24	52	49	13	F	No	33	Yes	1	0	5.5	3.5
25	36	32	11	F	No	40	Yes	7	0	4.5	4.0
26	26	21	NA	F	No	21	Yes	9	NA	NA	NA
27	42	37	17	M	No	46	Yes	2	1	3.0	3.0
28	43	36	16	F	No	75	Yes	1	2	6.0	5.0
29	30	27	15	F	No	17	Yes	3	1	6.5	6.0
30	48	44	8	F	Hypothyroidism	47	Yes	2	0	4.0	4.0
31	36	32	16	F	No	43	Yes	7	1	6.0	6.0
32	48	45	NA	F	No	9	Yes	6	0	7.5	7.0
33	42	37	16	F	No	54	Yes	5	3	3.0	3.0
34	33	32	4	F	No	9	Yes	3	0	3.0	2.5
35	44	38	14	F	No	38	Yes	12	2	NA	NA
36	51	46	18	F	No	25	Yes	5	0	6.0	5.5
37	40	38	15	F	No	20	Yes	3	0	6.5	6.0
38	52	47	21	F	No	46	Yes	NA	NA	NA	NA
39	31	29	9	F	Thalassemia	23	Yes	4	0	2.0	2.0
40	28	26	12	F	No	17	Yes	5	0	2.5	2.5
41	23	16	9	M	No	81	Yes	6	0	2.0	1.5
42	34	31	10	F	No	34	Yes	5	0	1.5	1.0
43	34	28	11	M	Psoriasis	51	Yes	5	0	2.0	2.0
44	45	37	23	F	No	89	Yes	7	0	4.5	4.0
45	32	31	6	F	No	18	Yes	5	0	2.0	1.0
46	48	46	28	M	No	23	Yes	4	0	2.5	2.5
47	74	67	43	F	Hypertension	75	Yes	5	0	4.0	3.5

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Table 2 continued. Overview of the 88 enrolled RR-MS patients.

ID	Age (years)	Age at disease onset (years)	Duration disease (years)	Sex	Concomitant diseases	N. doses of Natalizumab	Previous therapy	N. Relapse Pre-Natalizumab	N. R elapse Post-Natalizumab	EDSS Pre-Natalizumb	EDSS Post-Natalizumb
48	29	26	3	F	Hashimoto Thyroiditis	29	Yes	2	0	2.5	2.0
49	30	28	8	F	No	19	Yes	3	0	2.0	1.5
50	23	17	7	M	No	61	No	3	0	2.0	1.0
51	38	34	7	M	No	42	Yes	2	0	2.0	1.5
52	32	31	4	F	Diabetes type I	9	Yes	2	0	1.0	1.0
53	54	52	5	M	No	23	Yes	2	0	3.5	2.5
54	35	33	7	F	No	17	No	1	0	6.0	6.0
55	25	20	10	F	No	62	Yes	2	0	2.0	1.5
56	31	27	7	F	No	37	Yes	2	0	2.5	1.5
57	48	45	7	F	No	35	Yes	1	0	2.5	1.5
58	38	37	12	M	No	13	Yes	5	0	1.5	2.0
59	53	52	18	M	No	3	Yes	2	0	5.5	4.5
60	26	19	10	F	No	81	Yes	2	0	1.5	1.0
61	24	22	4	F	No	20	Yes	1	0	2.0	2.0
62	21	19	7	M	No	11	Yes	4	0	1.0	0.0
63	35	28	21	F	No	84	Yes	3	1	4.5	4.0
64	36	34	4	M	No	17	Yes	1	1	2.0	2.0
65	36	32	9	F	No	33	Yes	2	0	1.5	1.0
66	49	45	19	F	No	46	Yes	4	0	6.5	6.0
67	42	41	8	F	Hypertension	2	Yes	1	0	1.5	1.5
68	28	26	5	F	Hashimoto Thyroiditis	27	Yes	1	0	1.5	1.0
69	58	56	12	F	Hashimoto thyroiditis hypercho-lesterolemia	17	Yes	3	0	1.5	2.5
70	36	32	6	M	No	46	Yes	2	1	1.5	1.5
71	58	55	35	F	Depression	35	Yes	5	0	3.5	3.5
72	27	24	4	F	No	29	No	2	0	2.0	2.0
73	31	30	7	F	No	17	Yes	2	0	2.0	1.5
74	35	33	3	M	No	20	No	1	0	6.0	6.0
75	50	49	4	M	No	14	No	1	0	3.0	3.0
76	26	24	3	F	No	20	Yes	1	0	2.0	1.5
77	46	44	8	F	No	17	Yes	2	0	2.5	3.0
78	50	44	16	F	Hypertension Hypothyroidism	65	Yes	4	0	4.5	4.5
79	54	47	22	M	No	2	Yes	5	1	4.5	6.5
80	25	20	6	M	No	41	Yes	4	0	3.0	3.5
81	45	37	13	M	Hypercho-lesterolemia	70	Yes	4	0	2.0	2.0
82	48	41	9	F	No	45	No	3	0	3.5	3.5
83	46	40	8	F	No	74	Yes	2	1	3.0	6.0
84	47	42	6	F	No	42	Yes	2	1	3.0	3.5
85	38	33	26	M	No	89	Yes	6	2	5.5	7.0
86	48	41	27	F	Hashimoto Thyroiditis	73	Yes	3	1	4.0	3.5
87	35	30	6	F	Hypothyroidism	62	Yes	3	0	1.5	1.5
88	29	27	7	F	No	17	Yes	2	0	1.0	1.0

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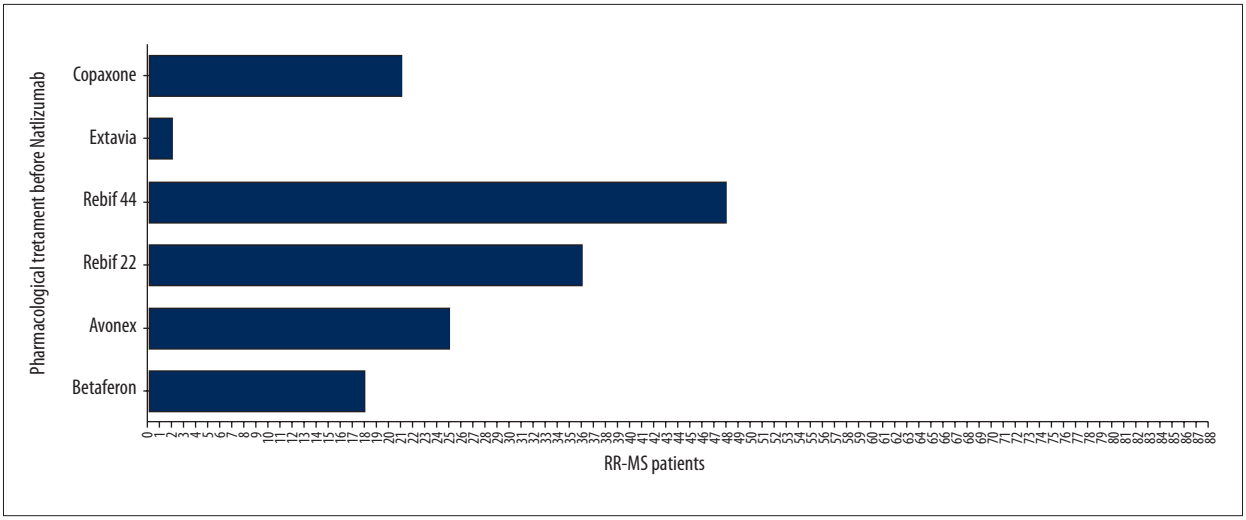

Figure 2. Pharmacological therapies before Natalizumab infusions.

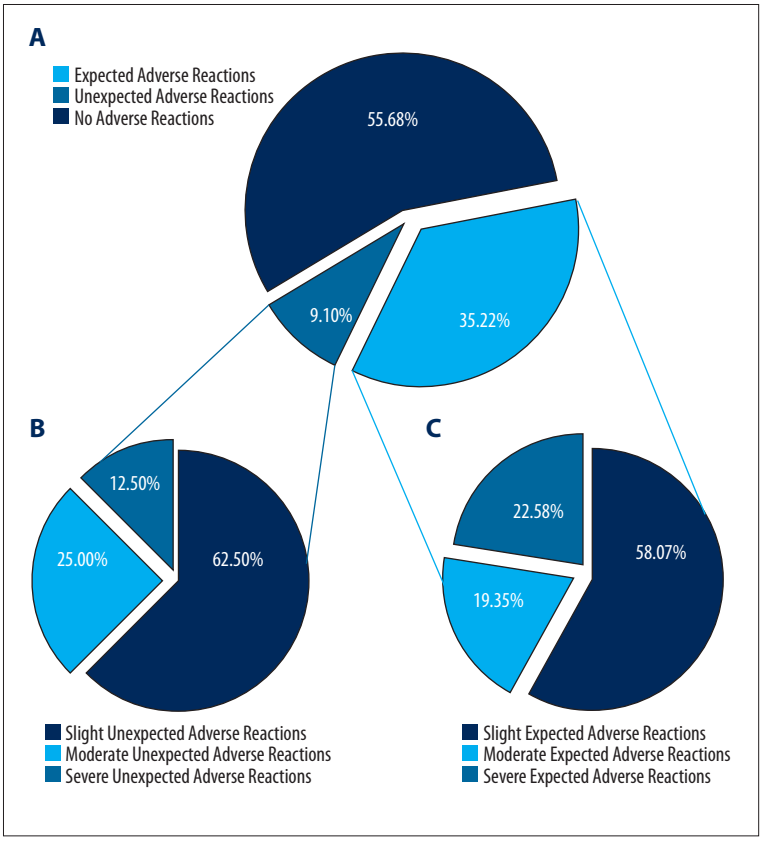

Figure 3. (**A**) Percentage of expected and unexpected adverse reactions. (**B**) Degree of severity of unexpected adverse reactions (slight, moderate, and severe). (**C**) Degree of severity of expected adverse reactions (slight, moderate, and severe).

(N=1), hypertension (N=3), psoriasis (N=1), depression (N=1), diabetes type I (N=1), and hypercholesterolemia (N=2) were also recorded. In these cases, an appropriate concurrent therapy was prescribed.

Among the 88 RR-MS patients, 45 received Natalizumab infusions for more than 24 months. It is well known that in JCV-positive patients, the risk of developing PML is relatively low during the first 2 years of treatment and increases thereafter. However, Natalizumab therapy may be continued after thorough information is given to the patient and with careful evaluation for PML symptoms.

Therefore, all 88 patients receiving Natalizumab were screened for previous JCV infection. The risk of PML in JCV-negative patients is low (<0.09/1000) and is probably associated with

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recent conversion or a false-negative test result. Our data show that 46.60% of RR-MS patients were JCV seropositive before the beginning of Natalizumab treatment and 53.40% were JCV seronegative. Afterwards, patients were subjected to anti-JCV antibody evaluation every 6 months. After 36 months of Natalizumab therapy, 72.34% were JCV-positive.

Anamnesis showed that most patients did not respond to other drug therapies validated for the treatment of MS, including glatiramer acetate, interferon β-1a, and interferon β-1b. The patients showed a number of therapy changes due to the failure of previous treatments, ranging from a minimum of 1 to a maximum of 3. Further evaluations also revealed that prior to treatment with Natalizumab, 48 patients had undergone treatment with Rebif 44, 36 with Rebif 22, 25 with Avonex, 18 with Betaferon, 21 with Copaxone, and 2 with Extavia (Figure 2). Only 6 had not undergone any previous immunomodulating therapies, showing a rapidly evolving clinical course.

Adverse effects correlated with Natalizumab therapy

We evaluated the incidence of expected and unexpected adverse events correlated to Natalizumab therapy in the enrolled RR-MS patients. According to the World Health Organization (WHO), an expected adverse event is any adverse reaction whose nature and intensity have been previously recorded and documented for the study product (e.g., Investigator's Brochure for an unapproved investigational medicinal product). An adverse event is considered unexpected if it is not consistent with applicable product information or characteristics of the drug. Additionally, in relation to the degree of intensity, adverse reactions are classified into: "severe" when marked limitation in activity occurs, assistance and medical intervention/therapy is required, and hospitalization is possible; "moderate" when mild-to-moderate limitation in activity occurs, assistance may be needed, or minimal medical intervention/therapy is required; and "slight" when discomfort is transient or mild (<48 h and no medical intervention/therapy is required). Our evaluations showed that 55.68% of RR-MS patients did not report any type of adverse reaction, whereas 35.22% of patients showed expected adverse events correlated with Natalizumab therapy and 9.10% displayed unexpected adverse reactions (Figure 3A). In particular, we found unexpected adverse reactions with slight (62.50%), moderate (25.00%), and severe (12.50%) degree (Figure 3B). Also, 58.07% of patients exhibited expected adverse reactions with slight (19.35%), moderate (19.35%), and severe (22.58%) seriousness (Figure 3C). Adverse events expected and not expected in RR-MS patients are displayed in Table 3.

Efficacy of Natalizumab therapy

The efficacy of Natalizumab treatment has been proven by looking into the annualized relapse rate (ARR) before and after treatment with Natalizumab (Figure 4, Table 4). Patients with only pre-ARR or post-ARR were excluded from this analysis. Consequently, we evaluated 81 patients. Our data showed that 7 patients had a value of post-ARR Natalizumab ≥ pre-ARR Natalizumab.

Additionally, in these patients, 56.62% improved, 32.53% had stable disease condition, and 10.85% worsened. Moreover, we observed a decrease tendency of the EDSS score from 3.48 to 3.15 (0.33) in RR-MS patients treated with Natalizumab. We also evaluated the progression of disease by dividing the patients according to EDSS obtained to follow-up of the Natalizumab therapy. In patients with a low value of EDSS (between 1.0 and 2.5), we found that 49.00% showed amelioration, 55.55% showed stable disease condition, and 22.22% showed worsened condition. In patients with medium value of EDSS (between 3.0 and 4.5), 27.60% improved, 27.63% were stable, and 44.44% showed worsened condition. In patients with an EDSS value equal to or greater than 5.0, 23.40% showed improved condition, 14.82% showed stable condition, and 33.34% had aggravated condition.

Discussion

MS is one of the world's most common neurological diseases, and in many countries it is the primary cause of non-traumatic neurological disability in young adults, affecting approximately 2.3 million people worldwide, with a higher incidence in women than in men (2: 1 ratio) [22]. In Italy, it is estimated that at least 68 000 patients and about 1800 new cases every year are diagnosed with MS. Specifically; in our region, about 6000 people have MS (*http://www.epicentro.iss.it*). Currently, there are no disease-modifying treatments for the progressive phase, only for symptomatic palliative care [23]. The conventionally used medications for the treatment of acute inflammatory relapses in MS, including immunosuppressive agents and corticosteroids, did not show convincing evidence of slowing or preventing disease evolution in secondary progressive or primary progressive MS patients. In addition, these treatments are associated with many adverse effects that prevent long-term use [24].

Generally, injectable medications, including interferons and glatiramer acetate, or oral treatment with dimethyl fumarate and teriflunomide are chosen as a starting therapy among the first-line preparations for *de novo* RR-MS [23]. In the case of breakthrough disease on first-line therapy, or rapidly evolving severe RR-MS, second-line therapy with Natalizumab, Fingolimod, or Alemtuzumab is preferred based on careful risk/benefit stratification [23,25–27].

Although Natalizumab is generally well tolerated, the treatment is associated with the occurrence of certain expected adverse

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Table 3. Adverse events expected and unexpected in RR-MS patients.

ID	Adverse event	Duration of adverse event (days)	Adverse event severity	Expected event	Continuation/ Discontinuation	Outcome
1	PML	NA	Severe	Yes	Definitive discontinuation	No changes
2	Urinary infection	90	Moderate	Yes	Temporary discontinuation	Resolution
3	Urinary infection	NA	Moderate	Yes	Continuation	Resolution
4	Urinary infection	60	Moderate	Yes	Continuation	Resolution
5	Urinary infection	26	Slight	Yes	Continuation	Resolution
6	Urinary infection	NA	Slight	Yes	Continuation	Resolution
7	Urinary infection	90	Severe	Yes	Temporary discontinuation	Resolution
8	Pharyngitis,	7	Slight	Yes	Continuation	Resolution
9	Pharyngitis	NA	Slight	Yes	Continuation	Resolution
10	Stomatitis	17	Slight	No	Continuation	Resolution
11	Glossitis	30	Slight	No	Continuation	Resolution
12	Pneumonia	30	Severe	No	Definitive discontinuation	No changes
13	Pharyngodinia	NA	Slight	Yes	Continuation	Resolution
14	Mycotic infections (Candida albicans)	NA	Moderate	Yes	Continuation	Resolution
15	Mycotic infections (Candida albicans)	30	Severe	Yes	Continuation	Resolution
16	Viral infection (Herpes simplex)	7	Slight	Yes	Continuation	Resolution
17	Viral infection (Herpes zoster)	60	Moderate	Yes	Continuation	Resolution
18	Viral infection (Herpes zoster)	20	Severe	Yes	Temporary discontinuation	Improvement
19	Cutaneous infection (uncertain origin)	NA	Severe	Yes	Temporary discontinuation	Resolution
20	Abnormal liver function	NA	Moderate	Yes	Temporary discontinuation	No changes
21	Increased level of gamma-glutamyltransferase	30	Moderate	No	Temporary discontinuation	Resolution
22	Allergic reaction with generalized purpura	1	Severe	Yes	Definitive discontinuation	Resolution
23	Dermatitis and allergic reactions	3	Slight	Yes	Continuation	Resolution
24	Dermatitis and allergic reactions	1	Slight	Yes	Continuation	Resolution
25	Dermatitis and allergic reactions	2	Slight	Yes	Temporary discontinuation	Resolution
26	Dermatitis and allergic reactions	4	Slight	Yes	Continuation	Resolution
27	Nausea and vomit	1	Slight	Yes	Continuation	Resolution

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Table 3 continued. Adverse events expected and unexpected in RR-MS patients.

ID	Adverse event	Duration of adverse event (days)	Adverse event severity	Expected event	Continuation/ Discontinuation	Outcome
28	Nausea and vomit	NA	Slight	Yes	Continuation	Resolution
29	Headache	NA	Slight	Yes	Continuation	Resolution
30	Headache	NA	Slight	Yes	Continuation	Resolution
31	Gastralgia	30	Slight	Yes	Continuation	Resolution
32	Gastralgia	10	Slight	Yes	Continuation	Resolution
33	Dizziness	NA	Slight	Yes	Continuation	Resolution
34	Tachycardia	NA	Slight	No	Continuation	Resolution
35	Generalized urticaria		Severe	Yes	Definitive discontinuation	Resolution
36	Fever	120	Slight	Yes	Continuation	Resolution
37	Dry cough	90	Slight	No	Continuation	Resolution
38	Dryness of mouth	NA	Slight	No	Continuation	Resolution
39	Blurred vision associated with anxiety crisis	1	Moderate	No	Temporary discontinuation	Resolution

effects, classified as: common adverse effects (with a probability of more than 1/10), such as infections of urinary tract, urticaria, headaches, dizziness, nausea, vomiting, fever, fatigue, joint pain, cold chills, sore throat, and nasal congestion; uncommon adverse effects (1/100) include PML and severe allergy (hypersensitivity); and rare adverse effects (1/1000), such as hypersensitivity reactions (anaphylaxis), opportunistic and atypical infections, and severe anemia.

Our evaluations, performed on a cohort of 88 RR-MS patients in Sicily, Italy, treated with Natalizumab, showed that the majority of RR-MS patients (55.68%) did not report any type of adverse reaction; 35.22% of patients showed expected adverse events correlated to Natalizumab therapy; and 9.10% reported unexpected adverse reactions (Figure 3A). Particularly, we found unexpected adverse reactions with 62.50% of slight degree, 25.00% moderate, and 12.50% severe (Figure 3B). Also, 58.07% of patients exhibited expected adverse reactions of slight severity, 19.35% moderate, and 22.58% severe (Figure 3C). Moreover, only 1 case of PML occurred, as expected, considering the number of patients exposed to Natalizumab and the duration of therapy course. Most of these adverse effects were minor and were similar to those reported in previous studies. Specifically, bacterial infections of the urinary tract (N=6), respiratory tract, and oral cavity, including pharyngitis (N=2), pharyngodynia (N=1), stomatitis (N=1), glossitis (N=1), and pneumonia (N=1), and mycotic infections by *Candida albicans* (N=2) and viral infections (1 patient affected by Herpes simplex and 2 patients affected by Herpes zoster) have been recorded. Only 1 patient developed a cutaneous infection of uncertain cause. Overall, these reactions were treated symptomatically and did not lead to drug discontinuation. However, in the case of severe adverse reactions, including an infection of the urinary tract caused by *Proteus mirabilis*, and infection caused by Herpes zoster. In the case of a cutaneous bacterial infection of uncertain cause, the therapy was provisionally interrupted, leading to the resolution of adverse events. Strangely, in 2 cases, we observed abnormal liver function and an increased level of gamma-glutamyltransferase. Although cases of hepatic dysfunction have been already reported [28], alteration of gamma-glutamyltransferase has not been found. For these patients, the treatment was interrupted until they recovered completely from adverse events. In addition, a severe allergic reaction with generalized purpura was found in 1 patient, for whom the therapy was permanently discontinued. Dermatitis and minor allergic reactions were observed in 4 patients. The adverse effects temporarily associated with Natalizumab infusion include nausea and vomiting (N=2), headache (N=2), gastralgia (N=2), dizziness (N=1), tachycardia (N=1), generalized urticarial (N=1), fever (N=1), dry cough (N=1), dry mouth N= (1), and blurred vision associated with anxiety crisis (N=1).

Summarizing, 4.54% of the RR-MS patients definitively discontinued Natalizumab therapy, 9.10% temporarily discontinued the therapy; whereas 86.36% continued the therapy, showing a total resolution of adverse events.

Overall, the efficacy of Natalizumab treatment has been proven by assessing the annualized relapse rate (ARR) pre- and

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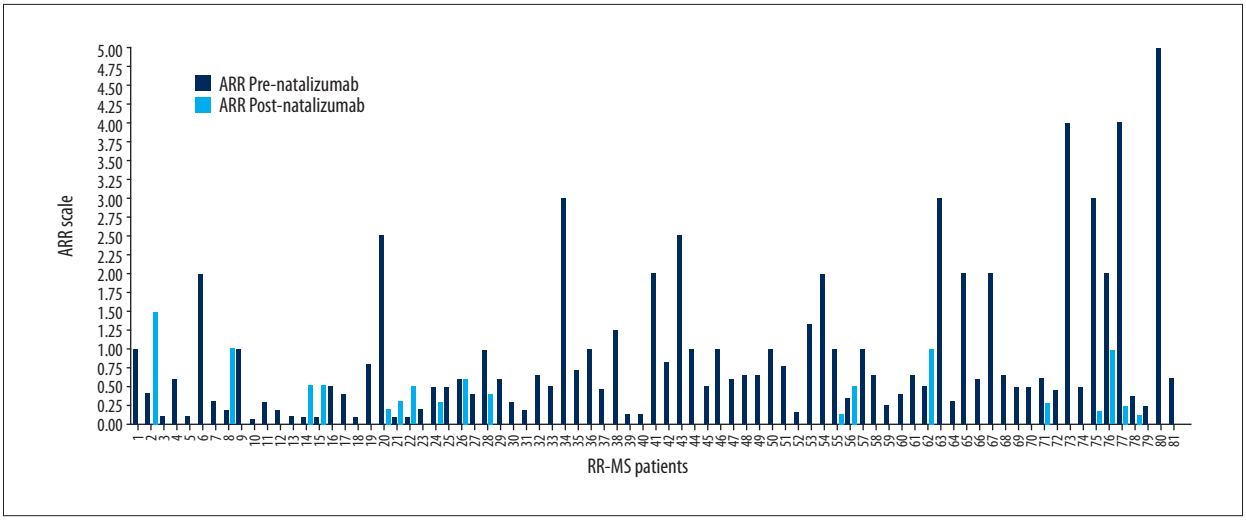

Figure 4. Evaluation of the annualized relapse rate (ARR) at pre- and post-treatment with Natalizumab.

Table 4. Annualized relapse rate (ARR) at pre- and post-treatment with Natalizumab.

	ARR Pre-Natalizumab	ARR Post-Natalizumab
ARR		
Median	0.6	0
Range	0–5	0–5
N of patients	81	81
Male, N (%)	28 (34.57)	28 (34.57)
Female, N (%)	53 (65.43)	53 (65.43)
Duration of disease (years)		
Range	3–43	3–43
Mean ±SD	10.4±7.9	10.4±7.9

post-treatment with Natalizumab (Figure 4). According to our data, only 8.64% of RR-MS patients had a value of post-ARR Natalizumab ≥ Natalizumab pre-ARR. As it is recognized that Natalizumab may fail to control disease in patients positive for neuromyelitis optica (NMO) [29], our patients were also evaluated for NMO diagnosis. We found that all patients were negative for water channel aquaporin 4, a specific biomarker used to identify patients with NMO [30].

In addition, among all the examined patients, 56.62% had ameliorated disease, 32.53% had stable disease, and 10.85% worsened. Overall, in RR-MS patients treated with Natalizumab, we observed a decrease of the EDSS score, from 3.48 to 3.15 (0.33). We evaluated the progression of disease by dividing the patients according to EDSS obtained to follow-up of the Natalizumab therapy. In patients with low values of EDSS (between 1.0 and 2.5), we found that 49.00% improved, 55.55% were stable, and 22.22% worsened. In patients with medium value of EDSS (between 3.0 and 4.5), 27.60% ameliorated, 27.63% were stable, and 44.44% worsened. In patients with a EDSS value equal to or greater than 5.0, we found that 23.40% ameliorated, 14.82% were stable, and 33.34% worsened. Our data suggest the efficacy of Natalizumab therapy, mainly in patients with low values of EDSS.

Conclusions

Our results show that most of the adverse effects in RR-MS patients treated with Natalizumab were expected adverse reactions with slight severity. One case of PML was recorded in our study, in agreement with the percentages already demonstrated in other clinical trials. Other unexpected adverse events with slight relevance were also reported. Indeed, only 4.54%

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of RR-MS patients definitively discontinued Natalizumab therapy. In addition, the majority of RR-MS patients treated with Natalizumab had stable or ameliorated disease. We aimed to provide a short but important overview of evidence to better characterize the efficacy and potential adverse effects associated with Natalizumab therapy. We hope that our results encourage the scientific community to increase the number of post-marketing observational studies and pharmacovigilance programs, such as the one established in our region by AIFA, on Natalizumab therapy in chronic diseases such as MS.

Conflict of interest

The authors declare no competing financial interests.

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