Multiple Sclerosis and Related Disorders 44 (2020) 102311

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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

Original article

# Prevention of rebound effect after natalizumab withdrawal in multiple sclerosis. Study of two high-dose methylprednisolone schedules

Luna Fuentes-Rumí[a,b,*], Rocío Hernández-Clares[a,b,c], Ester Carreón-Guarnizo[a,b,c], Gabriel Valero-López[a,b,c], Francisca Iniesta-Martinez[b,c], Jose Maria Cabrera-Maqueda[a], Adelaida León-Hernández[d], Joaquín Zamarro-Parra[d], Ana Morales-Ortiz[a], José E Meca-Lallana[a,b,c]

[a] Department of Neurology, Hospital Clínico Universitario Virgen de la Arrixaca, IMIB-Arrixaca, Carretera Madrid-Cartagena S/N ES, 30120, Murcia, Spain
[b] Clinical Neuroimmunology Unit and Multiple Sclerosis CSUR, Department of Neurology, Hospital Clínico Universitario Virgen de la Arrixaca, IMIB-Arrixaca, Murcia, Spain
[c] Clinical Neuroimmunology and Multiple Sclerosis, Universidad Católica San Antonio de Murcia (UCAM), Murcia, Spain
[d] Department of Diagnostic Imaging, Neuroradiology Unit, Hospital Clínico Universitario Virgen de la Arrixaca, IMIB-Arrixaca, Murcia, Spain

ARTICLE INFO

*Keywords:*
Multiple sclerosis
Natalizumab
Rebound
Relapse
Methylprednisolone
Washout period

ABSTRACT

*Background:* Natalizumab (NTZ) is a disease-modifying treatment (DMT) in multiple sclerosis (MS) whose discontinuation can produce a "rebound effect", consisting of severe clinical deterioration and/or evidence of disease reactivation on magnetic resonance imaging (MRI).
*Objective:* To analyze the efficacy of two treatment schedules with intravenous methylprednisolone (IVMP) administered during the washout period of natalizumab (i.e., before starting another DMT) in preventing the rebound phenomenon.
*Methods:* Five-year retrospective study of NTZ withdrawals after at least 24 uninterrupted doses. Two IVMP schedules were tested. In schedule 1 (3-month washout), 1, 2, and 3 g of IVMP were administered on the first, second, and third month respectively. In schedule 2 (2-month washout), 1 and 2 g of IVMP were administered on the first and second month respectively. A new DMT was started 10 days after the end of each schedule. Rebound was defined as at least one clinical relapse plus rebound activity on MRI (>5 gadolinium-enhanced lesions and a number of new/T2-enhanced and/or gadolinium-enhanced lesions greater than before initiation of NTZ) during washout or at 6 months after new DMT initiation (6M-DMT). Clinical and MRI evaluations were performed at 3, 6, 12, and 24 months after initiation of the new DMT.
*Results:* Fifty patients (68% women) were included, with a mean (SD) age of 37.76 (10.88) years and pre-NTZ annualized relapse rate (ARR) of 1.78 (1.04). During NTZ therapy, mean Expanded Disability Status Scale (EDSS) score was 3.7 (1.73) and ARR was 0.23 (0.39). The ARR (mean of both schedules) was 0.1 (0.71) during washout and 0.32 (0.84) at 6M-DMT. Rebound was observed in 10% of cases ($n = 5$), with no significant clinical or radiological differences ($p > 0.05$) between the two IVMP schedules. Rebound was observed in younger patients and was associated with new MRI lesions and higher ARR at 3M-DMT and 6M-DMT respectively, with no difference in EDSS after 2 years of follow-up. Neither the ARR before NTZ initiation nor the choice of new DMT after NTZ discontinuation was associated with development of rebound effect.
*Conclusions:* Both IVMP schedules were well tolerated during NTZ washout and rebound was observed in only 10% of cases. In our experience, administration of IVMP during NTZ washout could reduce the possibility of a rebound effect.

* Corresponding author.
*E-mail address:* lunafr24@gmail.com (L. Fuentes-Rumí).

https://doi.org/10.1016/j.msard.2020.102311
Received 21 April 2020; Received in revised form 3 June 2020; Accepted 16 June 2020
Available online 20 June 2020

## 1. Introduction

Natalizumab (NTZ)[1] is a monoclonal antibody widely used as a disease-modifying treatment (DMT) in relapsing-remitting multiple sclerosis (RRMS). NTZ acts by blocking lymphocyte alpha-4 integrin and preventing the migration of activated lymphocytes into the central nervous system (CNS) (Wingerchuk and Weinshenker, 2016). Both the results of clinical trials and real-world experience have shown that NTZ is highly effective in reducing the annualized relapse rate (ARR), reducing the risk of disability progression, and improving radiological parameters on magnetic resonance imaging (MRI) (Delbue et al., 2017; Clerico et al., 2017). However, NTZ therapy carries a risk of progressive multifocal leukoencephalopathy (PML) in patients who have been exposed to the JC virus (JCV). When the risk is high (more than 2 years of treatment with high anti-JCV antibody titres or a history of previous exposure to immunosuppressive treatment), therapeutic management must be customized and a change of DMT must be considered in order to maintain an optimal risk-benefit ratio (Wingerchuk and Carter, 2014).

Since 2008, studies have shown that, in the months following cessation of NTZ therapy, there is an increase in the number of relapses and a substantial increase in inflammatory activity on MRI, with a variable incidence across different cohorts but usually peaking 4 to 6 months after discontinuation (Vellinga et al., 2008; Kerbrat et al., 2011). This phenomenon is believed to be due to rapid immune reconstitution in the CNS after NTZ withdrawal, due to the reestablishment of lymphocyte migration through the blood-brain barrier, thus reactivating—sometimes in an exaggerated manner—the inflammatory cascade within the CNS (Miravalle et al., 2011).

Subsequently, various observational studies and post-marketing clinical surveillance of NTZ have analyzed in greater depth this excessive increase in inflammatory activity which sometimes occurs after the drug has been discontinued, and which has been termed the “rebound effect” (Prosperini et al., 2019). However, there have been important differences in defining “rebound” across studies. It has been defined by such diverse criteria as increased number of relapses, development of new gadolinium-enhancing lesions on MRI, occurrence of more severe relapses with increased EDSS score, or combinations thereof (Capobianco et al., 2015; Vidal-Jordana et al., 2015; Sempere et al., 2013). This imprecision and heterogeneity in definition has led to disparate results between different studies in terms of the incidence and consequences of rebound, which has made these findings difficult to interpret and precluded any definitive conclusions. Regardless of definition, however, the onset of rebound implies serious clinical and/or radiological reactivation of MS, with a high risk of serious neurological sequelae (O'Connor et al., 2011).

Within this context, the objective of our study is to analyze the efficacy of two intravenous methylprednisolone (IVMP) treatment schedules administered during the washout period of natalizumab—i.e., before starting another DMT—in preventing rebound.

[1] List of abbreviations: AFFIRM, nAtalizumab safety and eFFIcacy in Relapsing-remitting Multiple sclerosis; ARR, annualized relapse rate; CNS, central nervous system; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; FLAIR, fluid-attenuated inversion recovery; Gd, gadolinium; GLANCE, GLatiramer Acetate and Natalizumab Combination Evaluation; IVMP, intravenous methylprednisolone; JCV, JC virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; NTZ, natalizumab; PML, progressive multifocal leukoencephalopathy; RESTORE, Randomized Treatment Interruption of Natalizumab; RRMS, relapsing–remitting multiple sclerosis; SD, standard deviation; SENTINEL, Safety and Efficacy of NaTalizumab in combination with INterferon beta-1a in patients with rELapsing-remitting multiple sclerosis; SPSS, Statistical Package for the Social Sciences; TYSEDMUS, TYSabri chapter of the European Database for Multiple Sclerosis registry.

## 2. Materials and methods

We conducted an observational, retrospective, single-center study at a multiple sclerosis referral center. Data were collected on all patients with RRMS who were treated with NTZ for 2 or more years (at least 24 uninterrupted doses) from January 2012 to January 2017 and whose NTZ treatment was discontinued permanently either because of ineffectiveness or because of safety issues (PML risk).

### 2.1. Washout schedules

After discontinuing NTZ and before starting a new DMT, a washout period was imposed as recommended in the Summary of Product Characteristics. During this period, pulse IVMP treatment was administered, as pre-established in the local NTZ management protocol. Patients were included in one of two schedules following time selection criteria: during 2012–2013, patients who discontinued NTZ followed a three-month-washout period; in 2014, this period was shortened to two months, according to usual clinical practice, trying to minimize the rebound phenomenon.

- Schedule 1 (used in the years 2012–2013): 3-monthwashout period. 1, 2, and 3 g of IVMP administered on the first, second, and third month, respectively.
- Schedule 2 (used in the years 2014–2016): 2-monthwashout period. 1 and 2 g of IVMP administered on the first and second month, respectively.

In both schedules, the new DMT was started 10days after the last IVMP session (Fig. 1).

### 2.2. Variables

Epidemiological parameters, clinical variables, and evidence of inflammatory activity on MRI were collected in the year prior to the start of NTZ and during NTZ therapy. Monthly clinical follow-up visits were held during the washout period and at 3, 6, 12, and 24 months after initiation of the new DMT; the post-washout visits also included control MRI. All relapses were recorded. The EDSS score was calculated and presence of any adverse effects was noted at all visits.

MRIs were acquired on a 1.5-T scanner (GE Healthcare, United Kingdom). Evaluations consisted of T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and proton density–weighted sequences before and after administration of paramagnetic gadolinium (Gd) contrast agent. Changes in T2-hyperintense lesion volume, new and enlarging T2-hyperintense lesion counts, and Gd-enhancing T1-hyperintense lesion counts were evaluated. “MRI activity” was defined as the presence of new T2-enhanced and/or Gd-enhancing lesions. The presence of a high degree of inflammatory activity on MRI, defined as the presence of more than 5 Gd-enhancing lesions and a greater number of new/T2-enhanced and/or Gd-enhancing lesions than before initiation of NTZ therapy (Gueguen et al., 2014), was termed “radiological rebound”. The MRI findings were confirmed by a neurologist and a neuroradiologist.

For the purposes of this study, rebound was defined as the onset of at least one clinical relapse plus presence of “radiological rebound” at any time during washout and during the first 6 months with the new DMT (6M-DMT). The presence of a clinical relapse without “radiological rebound” or, conversely, the presence of “radiological rebound” alone without a concomitant clinical relapse was not considered rebound.

Patients were divided into two groups by presence or absence of rebound after NTZ discontinuation, and between-group differences were analyzed. Subsequently, we also analyzed whether there were any differences between the two IVMP treatment schedules during washout.

This study was conducted in accordance with the World Medical

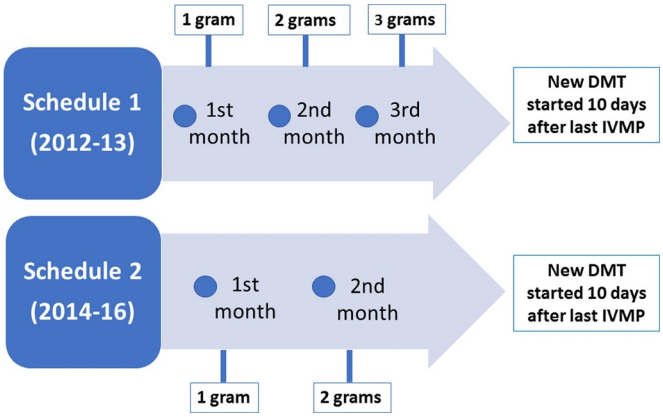


**Fig. 1.** IVMP treatment schedules during the washout period.

Association Declaration of Helsinki, all its amendments, and applicable national regulations. Ethics approval was obtained, and all patients gave written informed consent for participation.

### 2.3. Statistical analysis

Quantitative variables were expressed as mean (standard deviation); quantitative variables were expressed as proportions. Parameters were compared using either a chi-square test or Student's *t*-test, as appropriate. All analyses were carried out in SPSS Version 22.0.

## 3. Results

A total of 50 patients stopped NTZ treatment during the study period, 78% for safety reasons. During washout, schedule 1 was followed by 19 patients and schedule 2 by 31 patients. The most frequently used DMT after NTZ discontinuation was fingolimod (78%, $n = 39$). The mean ARR was 1.78 (1.04) in the year before NTZ initiation; 0.23 (0.39) during NTZ therapy; and 0.10 (0.71) during washout (mean of both schedules). Six months after the end of the washout period, i.e., after 6 months of the new DMT (6M-DMT), the mean ARR was 0.32 (0.84), while 6 months thereafter (12M-DMT), it was 0.17 (0.56). Fig. 2 shows a plot of ARR evolution.

The mean EDSS score was 3.70 (1.73) points before the washout and varied very little thereafter: 3.61 (1.66) at 3 months after new DMT initiation (3M-DMT), 3.61 (1.71) at 6M-DMT, 3.63 (1.76) at 12M-DMT, and 3.89 (1.91) at the end of 2-year follow-up (24M-DMT).

The presence of MRI activity (new/T2-enhanced and/or Gd-enhancing lesions) after initiation of the new DMT occurred in 9 patients (17.6%) at 3 months, in 5 (10%) at 6 months, and in 7 (13.7%) at 12 months, dropping to 5 (9.8%) at 24 months.

Rebound (defined at least one clinical relapse plus radiological rebound activity) was observed in 5 patients (10%) across the two IVMP schedules. No relevant adverse effects occurred during IVMP treatment. The characteristics of patients who experienced rebound are shown in Table 1. Three of the five patients who rebounded had a higher EDSS score 12 months after washout than before NTZ discontinuation (Table 1).

### 3.1. Analysis based on rebound

Variables were analyzed according to the presence of rebound. Baseline characteristics are shown in Table 2.

Patients who experienced rebound were significantly younger than those who did not (mean age at washout, 31.8 [1.79] years, $p = 0.000$), with no difference in disease duration, ARR before NTZ initiation, or ARR during NTZ treatment. There was also no association between the presence of rebound after NTZ discontinuation and the new DMT or the

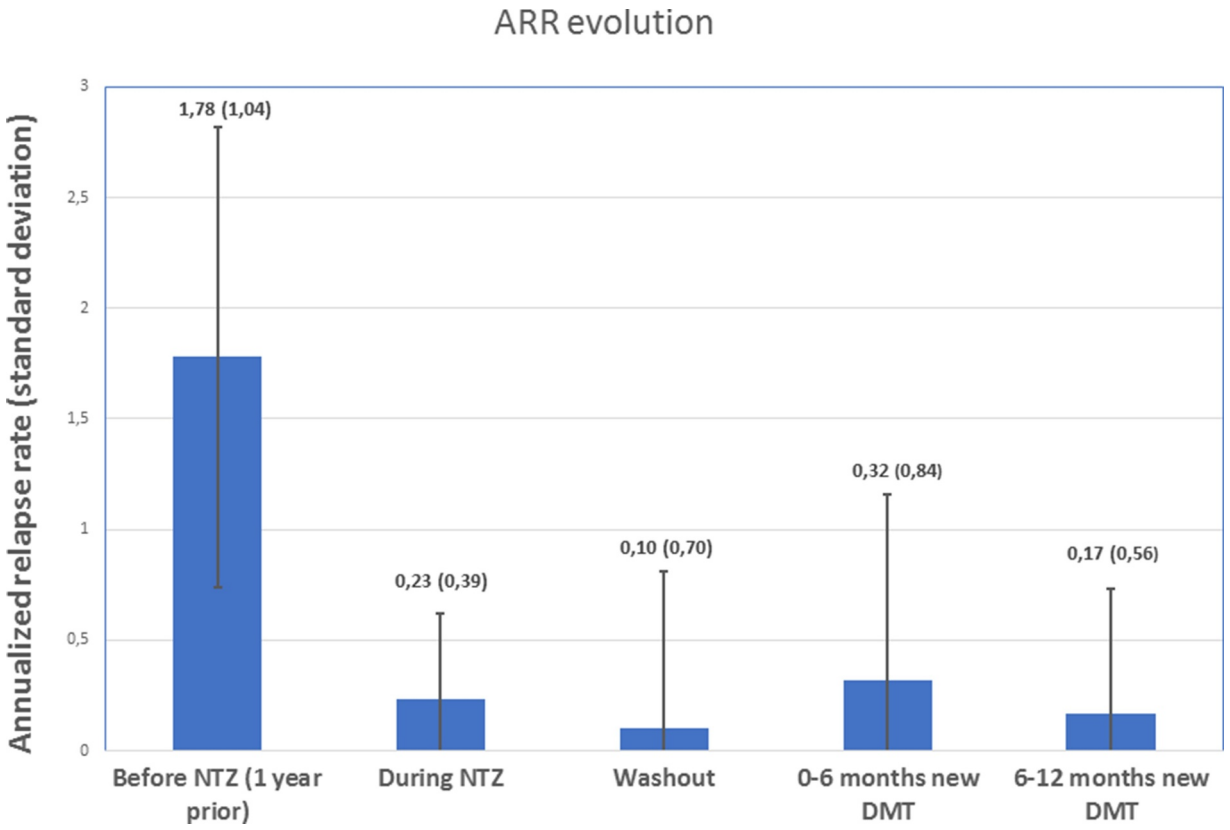


**Fig. 2.** Evolution of ARR during different periods of natalizumab therapy (mean of both schedules). A rebound in ARR is observed after the washout period, but it is never higher than baseline.

**Table 1**
Clinical and radiological characteristics of patients who experienced rebound.

| Patient | Gender | Before NTZ | | During NTZ | | | | New DMT | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ARR 1 year prior | Duration of disease (months) | Age at initiation | No. doses | ARR | Reason for switching | EDSS before washout | Age at switch | Washout (months) | New treatment | No. relapses 6 months | MRI rebound activity in 0–6 months | EDSS 12 months |
| 1 | F | 1 | 132 | 28 | 48 | 0 | Safety | 3.5 | 32 | 2 | Fingolimod | 2 | Yes | 4 |
| 2 | M | 1 | 72 | 28 | 25 | 0 | Safety | 4 | 30 | 2 | Fingolimod | 1 | Yes | 4 |
| 3 | F | 2 | 24 | 31 | 27 | 0.88 | Safety | 4 | 33 | 2 | Fingolimod | 1 | Yes | 4 |
| 4 | F | 4 | 18 | 23 | 68 | 0 | Safety | 2 | 30 | 3 | Fingolimod | 1 | Yes | 3.5 |
| 5 | F | 1 | 144 | 30 | 52 | 0 | Safety | 1 | 34 | 2 | Alemtuzumab | 1 | Yes | 1.5 |

number of relapses during the washout period. The ARR at 6 months with the new DMT (6M-DMT) was significantly higher in the group that experienced rebound (2.4 [1.41] vs. 0.13 [0.51], $p = 0.000$), and was higher than in the year preceding NTZ initiation (which is consistent with the established definition of rebound in the literature). The ARR at 2 years with the new DMT trended higher in the group that experienced rebound, though without reaching statistical significance (2.00 [1.54] vs. 0.21 [0.34], $p = 0.060$). Likewise, the group experiencing rebound developed MRI activity at 3M-DMT in a significantly higher proportion ($p = 0.000$) than the group without rebound. A trend toward persistent radiological activity remained at 12M-DMT, although it did not reach statistical significance. There were no significant differences in EDSS scores in the 2-yearfollow-up period.

### 3.2. Analysis by washout schedule

We conducted a separate analysis according to the IVMP schedule followed after discontinuation of NTZ. No statistically significant differences were found between the two washout schedules in terms of ARR or risk of developing rebound. Fewer patients who followed the 3-month washout schedule (schedule 1) developed radiological activity at 6 months compared to those who followed the 2-month washout schedule (0 vs. 5 [16.1%], $p = 0.020$), with no difference in radiological activity found at 3, 12, or 24 months and no impact on EDSS score. Comparative data are shown in Table 3 and Fig. 3.

## 4. Discussion

There is much controversy and variability surrounding definitions of the rebound phenomenon in the literature, which has made the actual incidence of this effect difficult to estimate in patients discontinuing NTZ therapy (Clerico et al., 2017). In some studies, an increase in exclusively clinical or radiological activity after withdrawal of NTZ is considered a “rebound” (Capobianco et al., 2015); others analyze both aspects, but without taking into account disease activity before NTZ initiation (Sempere et al., 2013).

In a post-hoc analysis of three clinical trials of natalizumab (AFFIRM, SENTINEL, and GLANCE) (O'Connor et al., 2011), which together enrolled more than 1800 patients, an increase in disease activity was observed after withdrawal of NTZ, both in number of relapses and in number of contrast-enhanced lesions; however, this increase was not significantly different from that observed in patients receiving placebo, which led to the conclusion that there was no statistical evidence of rebound. Subsequently, in the TYSEDMUS study cohort, 37.1% of patients experienced relapses after withdrawal of NTZ, but as the ARR after NTZ discontinuation did not exceed the ARR observed before NTZ initiation, the authors did consider this evidence of a rebound phenomenon (Papeix et al., 2016). Similar data were obtained in other observational studies, such as those of Jokubaitis et al. (2014) and Melis et al. (2014), in which there was evidence of increased inflammatory activity following NTZ withdrawal but without reaching the degree observed prior to NTZ initiation.

Gueguen et al. (2014) reported a 39% incidence of rebound, defined as a combination of clinical relapse and an unusual increase in inflammatory activity on MRI (>5 Gd-enhancing lesions and a higher number of lesions after NTZ withdrawal than before NTZ initiation). In another series, 38.3% of patients were found to exhibit either clinical or radiological activity higher than that observed prior to NTZ initiation, but this was only considered rebound when the clinical deterioration was significant (2-point increase in EDSS), which occurred in 19% of patients (Vidal-Jordana et al., 2015. In a Danish study, rebound phenomenon—defined by the authors as an ARR after NTZ withdrawal higher than the pre-NTZ rate—occurred in 22.1% of cases (Sorensen et al., 2014).

Analysis of our series, which used the same definition of rebound proposed by Gueguen et al. (2014) and included two IVMP treatment schedules during NTZ washout, shows a low incidence of rebound effect (only 10%) compared to other observational studies. We consider this definition to be optimal because it includes both variables (clinical and

**Table 2**
Baseline and follow-up characteristics of the sample, stratified by rebound.

| | | No Rebound ($n = 45$) | Rebound ($n = 5$) | p-value |
|---|---|---|---|---|
| **Age at NTZ initiation in years, mean (SD)** | | 38.84 (10.90) | 28 (3.08) | **0.000** |
| **Female sex, n (%)** | | 30 (66.7) | 4 (80) | 0.544 |
| **Disease duration before NTZ in months, mean (SD)** | | 101.24 (78.95) | 78 (58.79) | 0.527 |
| **No. of NTZ doses, mean (SD)** | | 32.73 (17.45) | 44 (18.07) | 0.178 |
| **ARR before NTZ, mean (SD)** | | 1.78 (1.02) | 1.80(1.30) | 0.964 |
| **ARR during NTZ, mean (SD)** | | 0.23 (0.38) | 0.20 (0.45) | 0.871 |
| **Reason for switch, n (%)** | **Safety** | 34 (75.6) | 5 (100) | 0.211 |
| | **Ineffectiveness** | 11 (24.4) | 0 (0) | |
| **EDSS before washout, mean (SD)** | | 3.8 (1.75) | 2.90(1.26) | 0.223 |
| **Age at switch in years, mean (SD)** | | 41.73 (10.91) | 31.80(1.79) | **0.000** |
| **Washout period, months** | **2** | 27 (60) | 4 (80) | 0.382 |
| | **3** | 18 (40) | 1 (20) | |
| **ARR during washout, mean (SD)** | | 0.11 (0.75) | 0.00 (0.00) | 0.743 |
| **New DMT, n (%)** | Fingolimod | 35 (77.8) | 4 (80) | 0.745 |
| | Glatiramer acetate | 2 (4.4) | | |
| | Teriflunomide | 2 (4.4) | | |
| | Alemtuzumab | 2 (4.4) | 1 (20) | |
| | IFN-b1a | 2 (4.4) | | |
| | Others | 2 (4.4) | | |
| **ARR 0–6, mean (SD)** | | 0.13 (0.51) | 2.40(1.41) | **0.000** |
| **ARR 6–12, mean (SD)** | | 0.09 (0.42) | 1.00(1.16) | 0.213 |
| **ARR at 2 years, mean (SD)** | | 0.21 (0.34) | 2.00(1.54) | 0.060 |
| **EDSS at 3 months, mean (SD)** | | 3.66 (1.74) | 3.20 (0.45) | 0.178 |
| **EDSS at 6 months, mean (SD)** | | 3.63 (1.78) | 3.40 (0.96) | 0.775 |
| **EDSS at 12 months, mean (SD)** | | 3.66 (1.81) | 3.40(1.19) | 0.661 |
| **EDSS at 24 months, mean (SD)** | | 3.91 (1.93) | 3.50 (2.12) | 0.772 |
| **MRI activity at 3 months, n (%)** | | 4 (8.9) | 5 (100) | **0.000** |
| **MRI activity at 6 months, n (%)** | | 4 (8.9) | 1 (20) | 0.718 |
| **MRI activity at 12 months, n (%)** | | 5 (11.1) | 2 (40) | 0.055 |
| **MRI activity at 24 months, n (%)** | | 4 (8.9) | 1 (20) | 0.156 |

**Table 3**
Baseline and follow-up characteristics of the sample, stratified by IVMP schedule followed.

| | | SCHEDULE 1 3 MONTHS, *n* = 19 | SCHEDULE 2 2 MONTHS, *n* = 31 | p-value |
|---|---|---|---|---|
| **Age at NTZ initiation in years, mean (SD)** | | 41.47 (13.29) | 35.48 (8.56) | 0.091 |
| **Female sex, n (%)** | | 12 (63.2) | 22 (71) | 0.566 |
| **Disease duration before NTZ in months, mean (SD)** | | 117.32 (92.62) | 87.65(64.74) | 0.231 |
| **No. of NTZ doses, mean (SD)** | | 32.32 (15.91) | 34.81 (18.84) | 0.633 |
| **ARR before NTZ, mean (SD)** | | 1.79 (1.18) | 1.77 (0.96) | 0.960 |
| **ARR during NTZ, mean (SD)** | | 0.16 (0.27) | 0.27 (0.44) | 0.307 |
| **Reason for switch, n (%)** | **Safety** | 14 (73.7) | 25 (80.6) | 0.564 |
| | **Ineffectiveness** | 5 (26.3) | 6 (19.4) | |
| **EDSS before washout, mean (SD)** | | 4.11 (1.79) | 3.45 (1.67) | 0.197 |
| **Age at switch in years, mean (SD)** | | 44.42 (12.75) | 38.48 (8.86) | 0.058 |
| **ARR during washout, mean (SD)** | | 0.00 (0.00) | 0.16 (0.89) | 0.439 |
| **New DMT, n (%)** | Fingolimod | 15 (78.9) | 24 (77.4) | 0.254 |
| | Glatiramer acetate | 0 | 2 (6.5) | |
| | Teriflunomide | 2 (10.5) | 0 (0) | |
| | Alemtuzumab | 0 | 3 (9.7) | |
| | IFN-b1a | 1 (5.3) | 1 (3.2) | |
| | Others | 1 (5.3) | 1 (3.2) | |
| **ARR 0–6, mean (SD)** | | 0.32 (0.75) | 0.32 (0.91) | 0.978 |
| **ARR 6–12, mean (SD)** | | 0.22 (0.65) | 0.13 (0.51) | 0.599 |
| **ARR at 2 years, mean (SD)** | | 0.43 (0.74) | 0.36 (0.79) | 0.768 |
| **EDSS at 3 months, mean (SD)** | | 3.92 (1.73) | 3.42 (1.61) | 0.305 |
| **EDSS at 6 months, mean (SD)** | | 3.92 (1.64) | 3.42 (1.75) | 0.318 |
| **EDSS at 12 months, mean (SD)** | | 3.86 (1.72) | 3.48 (1.80) | 0.478 |
| **EDSS at 24 months, mean (SD)** | | 4.20 (1.90) | 3.71 (1.94) | 0.439 |
| **MRI activity at 3 months, n (%)** | | 2 (10.5) | 7 (22.6) | 0.125 |
| **MRI activity at 6 months, n (%)** | | 0 (0) | 5 (16.1) | **0.020** |
| **MRI activity at 12 months, n (%)** | | 3 (15.8) | 4 (12.9) | 0.735 |
| **MRI activity at 24 months, n (%)** | | 1 (5.3) | 4 (12.9) | 0.492 |
| **Rebound after NTZ withdrawal, n (%)** | | 1 (5.3) | 4 (12.9) | 0.382 |

radiological) to account for an unusually high increase in disease-related inflammatory activity, compared to that observed prior to NTZ initiation.

Predictive factors for rebound have also been described, although with substantial variability across studies. One of the most consistently identified factors is more aggressive disease(higher ARR) before the start of NTZ therapy (Gueguen et al., 2014; Papeix et al., 2016; Fox et al., 2014). In our study, rebound was not associated with a higher ARR in the year prior to NTZ initiation, although the administration of IVMP during washout may have influenced this result.

When considering the duration of the washout period, it is important to take into account the pharmacokinetics of NTZ. The half-life of NTZ is 11 days, so its elimination from the bloodstream after five half-lives is expected to occur 2 months after the last dose, although saturation of alpha-4-integrin by NTZ drops dramatically 4 weeks after administration of the last usual dose (Plavina et al., 2017). In several studies, a longer washout duration (especially exceeding 2 or 3 months) has been associated with rebound; hence, most studies recommend that washout should not exceed 2 months (Jokubaitis et al., 2014; Giovannoni and Naismith, 2014). In our study, we found no clinical difference between 2 and 3 months of washout, although patients who completed a 3-month washout exhibited a lower degree of radiological activity at 6 months of treatment with their new DMT. This might be influenced by exposure to twice the methylprednisolone dose during washout schedule 1 versus schedule 2. Other predictors described with less consistency have been a higher EDSS score before NTZ initiation, a higher ARR during NTZ therapy, or duration of NTZ exposure (Vidal-Jordana et al., 2015; Sorensen et al., 2014). In the TYSEDMUS registry (Papeix et al., 2016), a significant association was found between younger age and occurrence of rebound. In our study, the association of rebound with younger age at both onset and discontinuation of NTZ therapy could be explained by the predominance of inflammatory phenomena in younger versus older patients (Giovannoni and Naismith, 2014).

Different studies have analyzed whether the switch from NTZ to specific DMTs could reduce the incidence of rebound effect, with contradictory findings. Several studies have shown that interferon (IFN) beta-1a or glatiramer acetate, if started shortly after NTZ discontinuation, could reduce the risk of disease reactivation (Rossi et al., 2013),

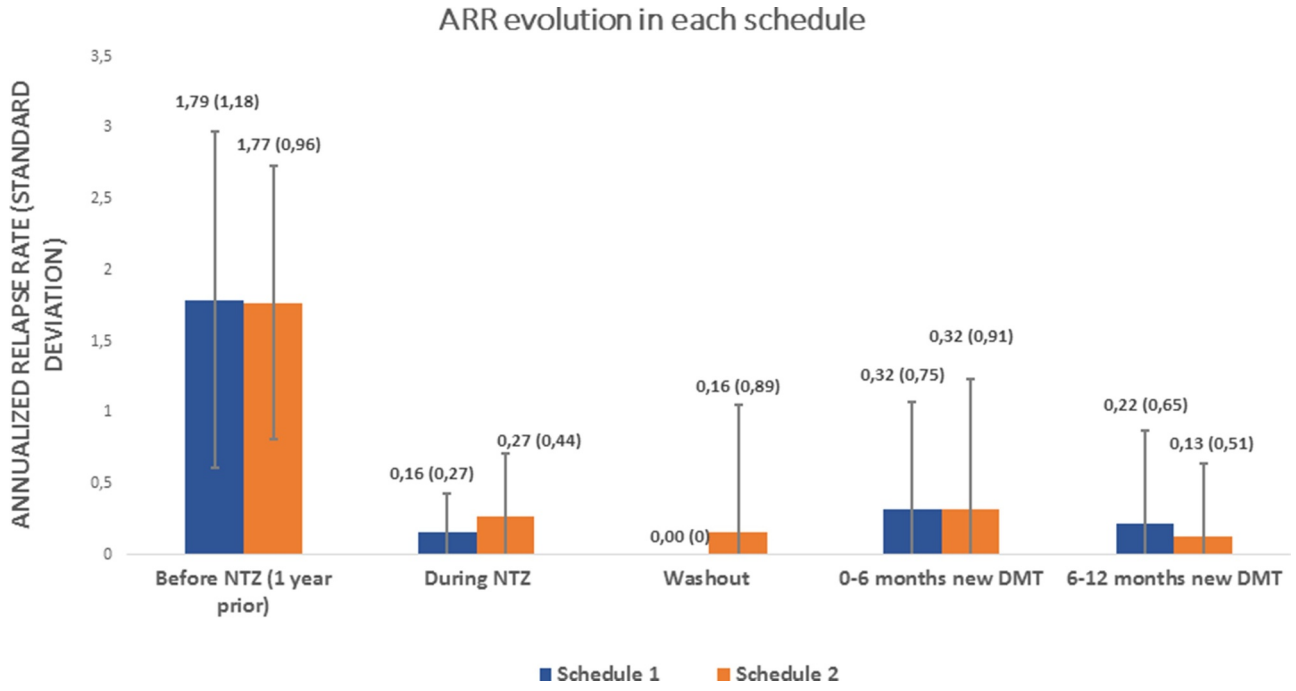


**Fig. 3.** Comparative evolution of ARR during different periods of natalizumab therapy (mean of each different schedule).

although this was not confirmed in a subsequent study by O'Connor et al. (2011), nor in the RESTORE trial (Fox et al., 2014). Other studies have compared first-line versus second-line treatment options and found no differences between them (Sangalli et al., 2014). In contrast, one study (Iaffaldano et al., 2015) found a lower incidence of relapse after NTZ discontinuation in patients who switched to fingolimod compared to those who switched to IFN or glatiramer. The optimal treatment to reduce incidence of rebound after withdrawal of NTZ has not been established, but it has been shown that initiating any DMT is clearly better than no treatment at all (Sangalli et al., 2014). In our study, most patients were switched to fingolimod ($n$ = 39, 78%), but we found no difference in rebound incidence across different DMTs. Further studies are warranted to analyze the potential effect of different DMTs after discontinuation of NTZ.

Several studies have examined the effect of pulse IVMP treatment on rebound, with equally mixed results. Evangelopoulos et al. (2016) showed that treatment with megadose methylprednisolone administered monthly for a 6-monthwashout period was associated with reduced incidence of clinical and radiological activity compared to no treatment. In another study, administration of IVMP during washout was not a predictor of rebound prevention, but IVMP treatment was administered for only 3 months during a very long washout (mean, 6.82 months), and, in most cases, NTZ was switched to an injectable immunomodulator (Vidal-Jordana et al., 2015). In our study, the combined effect of IVMP, a short washout period, and switching from NTZ to a highly effective immunosuppressant may have influenced our low overall rebound incidence.

In our study, we empirically administered pulse IVMP treatment during two different washout durations (3 and 2 months), established by changes in clinical practice over time, with no differences between them in terms of preventing rebound or MS relapse. Although we have not compared this therapeutic strategy with others, the incidence of rebound effect in our population was lower than that described elsewhere in the literature, which may be attributable to the use of IVMP during the washout period. Additional studies, preferably using randomized controlled designs, are warranted to confirm this hypothesis.

## 5. Conclusions

In this observational, retrospective study of 50 patients who discontinued natalizumab, in which two different IVMP treatment schedules were used during the washout period, we found a combined incidence of rebound of 10%, which is lower than expected according to the results obtained in other studies. The rebound effect occurred in younger patients, although more data would be needed to confirm age as a risk factor, and was not associated with a higher ARR in the pre-NTZ initiation year, nor with any new DMT initiated after NTZ. Treatment with IVMP during a short washout period might be associated with a lower incidence of rebound.

## Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## CRediT authorship contribution statement

**Luna Fuentes-Rumí:** Methodology, Formal analysis, Writing - original draft, Visualization. **Rocío Hernández-Clares:** Validation, Investigation. **Ester Carreón-Guarnizo:** Investigation. **Gabriel Valero-López:** Investigation. **Francisca Iniesta-Martinez:** Software, Data curation. **Jose Maria Cabrera-Maqueda:** Investigation. **Adelaida León-Hernández:** Investigation. **Joaquín Zamarro-Parra:** Investigation. **Ana Morales-Ortiz:** Supervision. **José E Meca-Lallana:** Conceptualization, Resources, Writing - review & editing, Supervision.

## Declaration of Competing Interests

José E Meca-Lallana has received gants and consulting or speaking fees from Almirall, Biogen, Celgene, Genzyme, Merck, Novartis, Roche and Teva. The rest of authors disclose neither conflict of interest.

## References

Wingerchuk, D.M., Weinshenker, B.G., 2016. Disease modifying therapies for relapsing multiple sclerosis. BMJ 354, i3518 Aug 22.
Delbue, S., Comar, M., Ferrante, P, 2017. Natalizumab treatment of multiple sclerosis: new insights. Immunotherapy 9 (2), 157–171.
Clerico, M., Artusi, C.A., Liberto, A.D., Rolla, S., Bardina, V., Barbero, P., et al., 2017. Natalizumab in multiple sclerosis: long-term management. Int. J. Mol. Sci. 18 (5) Apr 29.
Wingerchuk, D.M., Carter, J.L, 2014. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. Mayo Clin. Proc. 89 (2), 225–240 Feb.
Vellinga, M.M., Castelijns, J.A., Barkhof, F., Uitdehaag, B.M.J., Polman, C.H, 2008. Postwithdrawal rebound increase in T2 lesional activity in natalizumab-treated MS patients. Neurology 70 (13 Pt 2), 1150–1151 Mar 25.
Kerbrat, A., Le Page, E., Leray, E., Anani, T., Coustans, M., Desormeaux, C., et al., 2011. Natalizumab and drug holiday in clinical practice: an observational study in very active relapsing remitting multiple sclerosis patients. J. Neurol. Sci. 308 (1–2), 98–102 Sep 15.
Miravalle, A., Jensen, R., Kinkel, R.P, 2011. Immune reconstitution inflammatory syndrome in patients with multiple sclerosis following cessation of natalizumab therapy. Arch. Neurol. 68 (2), 186–191 Feb.
Prosperini, L., Kinkel, R.P., Miravalle, A.A., Iaffaldano, P., Fantaccini, S, 2019. Post-natalizumab disease reactivation in multiple sclerosis: systematic review and meta-analysis. Ther. Adv. Neurol. Disord. 12, 1756286419837809.
Capobianco, M., di Sapio, A., Malentacchi, M., Malucchi, S., Matta, M., Sperli, F., et al., 2015. No impact of current therapeutic strategies on disease reactivation after natalizumab discontinuation: a comparative analysis of different approaches during the first year of natalizumab discontinuation. Eur. J. Neurol. 22 (3), 585–587 Mar.
Vidal-Jordana, A., Tintoré, M., Tur, C., Pérez-Miralles, F., Auger, C., Río, J., et al., 2015. Significant clinical worsening after natalizumab withdrawal: predictive factors. Mult.Scler. Houndmills Basingstoke Engl. 21 (6), 780–785 May.
Sempere, A.P., Martín-Medina, P., Berenguer-Ruiz, L., Pérez-Carmona, N., Sanchez-Perez, R., Polache-Vengud, J., et al., 2013. Switching from natalizumab to fingolimod: an observational study. Acta Neurol. Scand. 128 (2), e6–10 Aug.
O'Connor, P.W., Goodman, A., Kappos, L., Lublin, F.D., Miller, D.H., Polman, C., et al., 2011. Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis. Neurology 76 (22), 1858–1865 May 31.
Gueguen, A., Roux, P., Deschamps, R., Moulignier, A., Bensa, C., Savatovsky, J., et al., 2014. Abnormal inflammatory activity returns after natalizumab cessation in multiple sclerosis. J. Neurol. Neurosurg. Psychiatry 85 (9), 1038–1040 Sep.
Papeix, C., Vukusic, S., Casey, R., Debard, N., Stankoff, B., Mrejen, S., et al., 2016. Risk of relapse after natalizumab withdrawal. Neurol. Neuroimmunol. Neuroinflamm. 3 (6) [Internet]Oct 28Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5087255/.
Jokubaitis, V.G., Li, V., Kalincik, T., Izquierdo, G., Hodgkinson, S., Alroughani, R., et al., 2014. Fingolimod after natalizumab and the risk of short-term relapse. Neurology 82 (14), 1204–1211 Apr 8.
Melis, M., Cocco, E., Frau, J., Lorefice, L., Fenu, G., Coghe, G., et al., 2014. Post-natalizumab clinical and radiological findings in a cohort of multiple sclerosis patients: 12-month follow-up. Neurol. Sci. 35 (3), 401–408 Mar.
Sorensen, P.S., Koch-Henriksen, N., Petersen, T., Ravnborg, M., Oturai, A., Sellebjerg, F, 2014. Recurrence or rebound of clinical relapses after discontinuation of natalizumab therapy in highly active MS patients. J. Neurol. 261 (6), 1170–1177 Jun.
Fox, R.J., Cree, B.A.C., De Sèze, J., Gold, R., Hartung, H.-.P., Jeffery, D., et al., 2014. MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study. Neurology 82 (17), 1491–1498 Apr 29.
Plavina, T., Muralidharan, K.K., Kuesters, G., Mikol, D., Evans, K., Subramanyam, M., et al., 2017. Reversibility of the effects of natalizumab on peripheral immune cell dynamics in MS patients. Neurology 89 (15), 1584–1593 Oct 10.
Giovannoni, G., Naismith, R.T., 2014a. Natalizumab to fingolimod washout in patients at risk of PML: when good intentions yield bad outcomes. Neurology 82 (14), 1196–1197 Apr 8.
Giovannoni, G., Naismith, R.T., 2014b. Natalizumab to fingolimod washout in patients at risk of PML: when good intentions yield bad outcomes. Neurology 82 (14),

1196–1197 Apr 8.
Rossi, S., Motta, C., Studer, V., De Chiara, V., Barbieri, F., Monteleone, F., et al., 2013. Effect of glatiramer acetate on disease reactivation in MS patients discontinuing natalizumab. Eur. J. Neurol. 20 (1), 87–94 Jan.
Sangalli, F., Moiola, L., Ferrè, L., Radaelli, M., Barcella, V., Rodegher, M., et al., 2014. Long-term management of natalizumab discontinuation in a large monocentric cohort of multiple sclerosis patients. Mult. Scler. Relat. Disord. 3 (4), 520–526 Jul.
Iaffaldano, P., Lucisano, G., Pozzilli, C., Brescia Morra, V., Ghezzi, A., Millefiorini, E., et al., 2015. Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis. Brain J. Neurol. 138 (Pt 11), 3275–3286 Nov.
Evangelopoulos, M.E., Koutoulidis, V., Andreadou, E., Evangelopoulos, D.S., Kilidireas, C, 2016. Pulsed corticosteroid treatment in MS patients stabilizes disease activity following natalizumab withdrawal prior to switching to fingolimod. Int. J. Neurosci. 126 (12), 1097–1102 Dec.