Treatment Options to Reduce Disease Activity After Natalizumab: Paradoxical Effects of Corticosteroids

Silvia Rossi, Caterina Motta, Valeria Studer, Laura Boffa, Valentina De Chiara, Maura Castelli, Francesca Barbieri, Fabio Buttari, Fabrizia Monteleone, Giorgio Germani, Giulia Macchiarulo, Sagit Weiss & Diego Centonze

Clinica Neurologica, Dipartimento di Medicina dei Sistemi, Università Tor Vergata, & Centro Europeo per la Ricerca sul Cervello (CERC)/Fondazione Santa Lucia, Rome, Italy

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Correspondence

D. Centonze, Clinica Neurologica, Dipartimento di Medicina dei Sistemi, Università Tor Vergata, Via Montpellier 1, 00133 Rome, Italy.
Tel.: +39-06-7259-6010;
Fax: +39-06-7259-6006;
E-mail: centonze@uniroma2.it
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SUMMARY

Aim: Natalizumab (NTZ) discontinuation leads to multiple sclerosis (MS) recurrence, but represents the only known strategy to limit the risk of progressive multifocal leukoencephalopathy (PML) in JCV seropositive patients. Here, we compared the clinical and imaging features of three groups of patients who discontinued NTZ treatment. **Methods:** We treated 25 patients with subcutaneous INF β -1b (INF group), 40 patients with glatiramer acetate (GA group), and 40 patients with GA plus pulse steroid (GA+CS group). **Results:** Six of 25 patients (24%) of the INF group were relapse-free 6 months after NTZ suspension. In GA group, a significant higher proportion of patients (26 of 40 patients, 65%) were relapse-free ($P < 0.05$). Far from improving the clinical effects of GA in post-NTZ setting, combination of GA+CS was associated with lower relapse-free rate than GA alone (40% vs. 65%, $P = 0.04$). Also on MRI parameters, combination of GA+CS was associated with worse outcome than GA alone, as 22 of 26 subjects (84.6%) had MRI evidence of disease activity 6 months after NTZ discontinuation. **Conclusion:** Corticosteroids should not be used in combination with GA to prevent post-NTZ disease recurrence.

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). The pathobiology of MS includes inflammatory and neurodegenerative mechanisms that affect both white and gray matter. The inflammatory demyelinating component seems to be predominant in the initial relapsing-remitting (RR) phase of the disease, whereas the progressive disease appears to be characterized by neuronal degeneration and extensive axonal damage.

Current medical treatment mainly influences disease progression via immunomodulatory or immunosuppressive actions. First-line disease-modifying therapies include three different preparations of interferon-beta (INF β) and glatiramer acetate (GA), which reduce relapse rates with well-tolerated side effects and a very good long-term safety profile. In fact, these immunomodulators shift immune responses from pro-inflammatory autoimmune conditions (mediated by TH-1 cytokines released from autoreactive T cells) toward a more beneficial antiinflammatory environment (mediated through TH-2 cytokines secreted by regulatory T cells), without suppressing immunological properties [1]. Among second-line treatments, natalizumab (NTZ) is a humanized monoclonal antibody that binds the alpha 4 subunit of the very late

antigen-4 integrin present on leukocytes, which prevents the egress of these cells outside of the bloodstream. It is a highly effective therapy for reducing disease activity in RR MS, but its use is limited by the risk of progressive multifocal leukoencephalopathy (PML), a demyelinating disease of the CNS occurring in the setting of severe immunosuppression, and caused by the reactivation of the polyomavirus JC virus (JCV) [2]. The emergence of PML in this setting has moved PML from being a rare disease mostly seen in HIV-infected individuals to become an important cause of complications in patients receiving immunomodulatory treatments, which suppress the host cellular immune response.

NTZ induces broader changes in the T-cell immune repertoire beyond lymphocyte migration, thus leading to an altered immune surveillance of the CNS, which may contribute to the increased risk of PML [3]. The risk of PML in JC seropositive MS patients increases with NTZ exposure [2]. Thus, treatment discontinuation still appears the only option to prevent PML in these patients. It is unclear, however, how MS reactivation or rebound can be minimized after NTZ. NTZ suspension, in fact, has been associated with a significant disease return within 6 months, often presenting with severe clinical and radiological manifestations, especially in patients with high disease activity the year before initiating the treatment [4].

Immunomodulation with INF β or GA is commonly offered to patients willing to suspend NTZ to minimize the risk of PML and to prevent, in parallel, post-NTZ MS recurrence. As shown in several independent studies, neither INF β nor GA provides full disease control when prescribed after NTZ [5–11], causing clinicians to explore other treatment algorithms to enhance their effects. In this respect, pulse steroids have long been used not only for the treatment of acute MS relapses, but also to prevent MS disease reactivation, for example in the postpartum period [12] or in combination with immunomodulants [13,14]. In these paradigms, pulse steroids have generally been found of some efficacy. Whether and how corticosteroids impact on disease reappearance and severity in MS patients who discontinue NTZ is not clearly established.

Methods

We followed since 2009 a group of 105 patients willing to discontinue NTZ to limit their risk of PML. About 40% of the patients were tested after the approval of the anti-JCV antibody test to recognize NTZ-treated patients at risk of PML and appeared to be seropositive for the JCV. These patients were converted to INF β -1b (Betaferon, alternate days by subcutaneous injections, INF group) or to GA (Copaxone, daily subcutaneous injections, GA group) as their NTZ therapy was initiated following treatment failure with GA or interferon-beta, respectively.

INF or GA treatment was started 4 weeks after the last infusion of NTZ. Having achieved with the first 40 patients treated with GA a promising but still suboptimal disease control [10], we then decided to add pulse steroids (intravenous 1000 mg methylprednisolone every month for three consecutive months) in the following patients. For the purpose of evaluating the efficacy of this scheme as a post-NTZ discontinuation treatment, we observed subjects for 6 months or until a clinical relapse leading to study consent withdrawn occurred.

All subjects had active forms of relapsing-remitting MS. In fact, 92% of the INF group, 85% of the INF and GA group, and 86% of the GA+CS group had 2 or more relapses the year before NTZ initiation, while on treatment with GA or high-dose IFN β . Subjects were treated with NTZ for at least 12 months. All patients have been fully responsive to NTZ (no occurrence of clinical relapses nor detection of active scans at magnetic resonance imaging (MRI) for the entire duration of the treatment). None of the patients was treated with corticosteroids or any other immunoactive drugs during NTZ therapy.

Patients' demographic, clinical, and treatment information are shown in Table 1. The study complied with the principles of the Declaration of Helsinki and was approved by the Ethical Committee of the Policlinico Università Tor Vergata in Rome. All the subjects gave their written informed consent to the study.

Study procedures

Subjects were observed after NTZ for 6 months (P0–P6) or until a clinical relapse leading to study consent withdrawn occurred.

Expanded Disability Status Scale (EDSS), a 10-point disease severity score derived from nine ratings for individual neurological domains [15–17], was used to assess disability every 3 months

Table 1 Demographic and clinical characteristics of MS subjects

	Total	INF	GA	GA+CS
Number	105	25	40	40
Gender (M/F)	44/61	9/16	16/24	19/21
Age (years)	36.1 $\pm$ 9.0	34.6 $\pm$ 8.8	37.3 $\pm$ 9.1	36.5 $\pm$ 9.2
Disease duration (years)	10.1 $\pm$ 5.8	10.9 $\pm$ 6.0	9.1 $\pm$ 5.5	10.3 $\pm$ 5.8
Baseline EDSS	2.6 $\pm$ 0.8	2.6 $\pm$ 0.9	2.8 $\pm$ 0.9	2.5 $\pm$ 0.9
ARR before NTZ	2.4 $\pm$ 0.8	2.5 $\pm$ 0.9	2.3 $\pm$ 0.9	2.3 $\pm$ 0.8

INF, interferon; GA, glatiramer acetate; GA+CS, glatiramer acetate plus corticosteroids; M, male; F, female; EDSS, Expanded Disability Status Scale; ARR, annualized relapse rate; NTZ, natalizumab.

in all patients. Patients with suspected exacerbations were instructed to return to the clinic to be evaluated. Relapses were confirmed when an increase in at least 1 point in one functional system (FS) was recorded. Assessment of disability and confirmation of relapses were performed by a neurologist who was unaware of the patients' clinical details and laboratory data.

MRI acquisition and analysis

Cerebral and/or spinal MRI scans were performed 6 months prior to and just before the first infusion of NTZ (T0). They were also performed every 6 months during NTZ treatment (T6/T12) and at P0 and P6 in the three groups of patients [10,11]. MRI scans (1.5 Tesla) consisted of dual-echo proton density, FLAIR, T2-weighted spin-echo images (T2-WI), and precontrast and postcontrast (pre- and postgadolinium (Gd) 0.2 ml/kg e.v. infusion) T1-weighted spin-echo images (T1-WI).

All images were acquired in the axial orientation with 3-mm-thick contiguous slices. A new Gd-enhancing (Gd+) lesion was defined as a typical area of hyperintense signal on postcontrast T1-WI. A new/enlarging lesion on T2-WI was defined as a rounded or oval lesion arising from an area previously considered as normal-appearing brain tissue and/or showing an identifiable increase in size from a previously stable-appearing lesion.

The mean number of new combined active lesions (CALs), as the number of enhancing lesions plus the number of new or newly enlarging nonenhancing lesions, was also determined. An active scan was defined as showing any new, enlarging or recurrent lesion(s) on postcontrast T1- and T2-WI. Rebound was defined as an increase in disease activity following NTZ dosage interruption (at least 4 T1 Gd+ lesions more than in pre-NTZ scans). Analyses were performed by a neuroradiologist who was unaware of the patients' clinical details and laboratory data.

Statistical analysis

If not otherwise indicated, data are given as mean $\pm$ standard deviation (SD). Differences between two groups were analyzed using Student's *t*-test or Mann–Whitney test or Fisher exact test, as appropriate. Multiple comparisons were performed by ANOVA followed by Tukey's HSD in case of parametric data or by Kruskal–Wallis test followed by Mann–Whitney test in case of nonparametric data. Nonparametric statistics were used if distribution of

data deviated from normality. Shapiro–Wilk test was used to assess normal distribution. The association between CS administration and clinical/radiological outcomes was assessed using multivariate binary logistic regression models. Odds ratios (ORs) along with the corresponding 95% confident intervals (95% CIs) were provided. Survival curves were analyzed using log-rank (Mantel–Cox) test. Patients who did not reach the endpoint were considered as censored data. The level of significance was designated as $P < 0.05$ (two-tailed tests).

Results

Effects of NTZ to INF, GA, or GA+CS switch on clinical relapses

Sixty-eight confirmed relapses occurred during the study (19 in INF, 19 in GA, and 30 in GA+CS group). Only 6 of 25 patients (24%) of the INF group were relapse-free 6 months after NTZ suspension. In the GA group, conversely, a significant higher proportion of patients (26 of 40 patients, 65%) were relapse-free in the same time window ($P < 0.05$). Surprisingly, far from further improving the clinical effects of GA in the post-NTZ setting, combination of GA+CS was associated with a lower relapse-free rate than GA alone (40% vs. 65%, $P = 0.04$; Figure 1A). Accordingly, the probability to relapse, adjusted for the number of relapses in

the year before NTZ, baseline EDSS score, and age, was related to CS administration, being higher in GA+CS than GA group (Figure 1A).

EDSS values at the peak of the relapses increased by 1.23 ± 0.7 points from 2.21 ± 0.7 in the INF group, by 0.95 ± 0.5 points from 2.03 ± 0.5 in the GA group and by 1.37 ± 0.9 points from 2.15 ± 0.8 in the GA+CS group ($P = 0.16$). The median time from NTZ discontinuation to clinical relapse was 85 days (range 40–170) in the INF group, 85 days (range 40–180) in the GA group and 57.5 days (range 30–140) in the GA+CS group. Mean time to relapse was 83.7 ± 34.2 months in the INF group, 91.1 ± 40.1 days in the GA group and 64.6 ± 27.6 days in the GA+CS group, again confirming a negative influence of CS treatment on GA effects in the post-NTZ period ($P = 0.04$, $F = 3.32$; Figure 1B).

The time to relapse was significantly different in comparison with the occurrence of relapses prior to initiation of NTZ only for the GA group (GA: $P = 0.003$; GA-CS: $P > 0.1$; INF: $P > 0.1$; Figure 1C).

Effects of NTZ to INF, GA, or GA+CS switch on MRI parameters

Of the 8 patients who underwent MRI at P6 in the INF group, 4 (50%) had MRI evidence of disease activity (Figure 2A). In the

Figure 1 Effect of postnatalizumab switch treatments on clinical relapses. (A) The graphs show the number of relapsed subjects occurred during the study in the three switch treatment groups (INF, GA, and GA+CS). Logistic regression confirmed the increased probability of relapse associated to CS administration, as shown on the right. OR and 95% CI are provided. (B) The time to relapse was lower in GA+CS group. (C) The relapse-free rate and the time to relapse during the protocol were significantly lower than before natalizumab only in GA group. * $P < 0.05$.

Figure 2 Effect of postnatalizumab switch treatments on MRI parameters. **(A)** The graph shows the number of subjects with MRI disease reactivation after natalizumab discontinuation. Logistic regression confirmed the increased probability of active MRI associated with CS administration, as shown on the right. OR and 95% CI are provided. **(B)** The histogram shows that in the active scans of GA group, the mean number of T1 Gd+ lesions, T2 new/enlarging lesions, and CALs were lower than in GA+CS group. **(C)** Mean T1 Gd+ lesions, T2 new/enlarging lesions, and CALs, adjusted by respective prenatalizumab values, were lower after natalizumab discontinuation only in GA group. * $P < 0.05$.

active scans of this group of patients, the mean number of T1 Gd+ lesions was 2.25 ± 1.50 , mean number of T2 new/enlarging lesions was 3.00 ± 2.16 , and mean number of CALs was 3.75 ± 2.21 . Because of the limited number of the subjects who completed the 6-month period of the study in the IFN group, we did not perform further analysis.

In the GA group, 18 of 32 patients (56%) undergoing P6 MRI had MRI evidence of disease activity (Figure 2A). In these patients, the mean number of T1 Gd+ lesions was 1.67 ± 1.23 , mean number of T2 new/enlarging lesions was 2.34 ± 1.28 , and mean number of CALs was 2.83 ± 1.29 [10] (Figure 2B).

Also on MRI parameters, combination of GA+CS was associated with worse outcome than GA alone ($P = 0.02$). In this group of patients, in fact, 22 of 26 subjects (84.6%) had MRI evidence of disease activity at P6. In the active scans of this group of patients, the mean number of T1 Gd+ lesions was 3.95 ± 3.91 , mean number of T2 new/enlarging lesions was 5.32 ± 5.93 , and mean number of CALs was 5.82 ± 5.85 ($P < 0.05$ for each parameters; Figure 2A,B). Accordingly, the probability to have an active MRI after NTZ withdrawal, adjusted for the number of CALs before NTZ therapy, baseline EDSS and age, was related to CS administration, being higher in GA+CS than GA group (Figure 2A).

MRI parameters of disease activity evaluated at P6 and adjusted by respective scans performed before NTZ were significantly lower after NTZ discontinuation only for the GA group (GA: $n = 32$, $P < 0.05$ for each parameter; GA-CS: $n = 26$, $P > 0.05$ for each parameter; Figure 2C), indicating that CS treatment nullifies the beneficial effects of GA in the post-NTZ period. Rebound of disease activity was detected in 0/32 (0%) subjects of GA group versus 7/26 (27%) subjects of GA-CS group ($P < 0.05$).

Discussion

NTZ therapy is well tolerated and causes rapid disease control in the majority of MS patients. NTZ discontinuation leads to disease return [4–6,18,19], but is sometimes necessary as it represents the only known strategy to restore immunosurveillance within the CNS and mitigates PML risk in JCV seropositive patients [2,20,21].

Several studies have tried to identify the best therapeutic strategy to prevent disease reactivation/rebound after NTZ suspension, but the optimal alternative treatment regimen has not been identified yet. Although variable in its clinical and radiological manifestations among different reports, in fact, a consistent return of

disease activity has been described by various authors 3–6 months following NTZ discontinuation [5,6,18]. A recent 24-week NTZ treatment interruption study explored the effects on clinical and MRI activity of NTZ continuation or placebo and of intramuscular INF β -1a, GA, or methylprednisolone in patients treated with NTZ for at least 12 months, and fully responsive to this medication [9]. The authors reported similar clinical and MRI reactivations in the CS and placebo arms (relapsing patients: 15% vs. 17%; MRI reactivation: 40% vs. 46%, respectively) despite patients in the CS arm having milder disease activity than the placebo patients (35% vs. 45% of the patients had at least 2 clinical relapses in the 12 months prior initiating NTZ) [9]. The same study also found in 17 patients that GA was not effective at all in preventing disease reactivation after NTZ. It is worth mentioning, however, that study greatly differs from the present investigation in terms of experimental design and definitions of disease reactivation, making hard any possible comparison.

We have recently found that although GA treatment was not able to maintain the same efficacy as NTZ, 62.5% of patients discontinuing NTZ were relapse-free 12 months after GA initiation [10], while in other studies, in patients with similar disease activity than our investigation, early recurrence/rebound of MRI and clinical disease activity was found to occur after abrupt discontinuation of NTZ in 70% of subjects [19] to 80% [4]. Here, the results in our cohort of 40 MS patients treated with GA after NTZ have been compared with those observed in a group of 25 patients treated with high-dose INF β -1b. Although the two groups of patients did not differ for their demographic and clinical characteristics, including the number of relapses the year before NTZ and clinical response to NTZ, we have found that INF β -1b therapy was associated with poorer protection against post-NTZ MS recurrence than GA. Accordingly, 76% of the patients of the INF group and 35% of the GA group relapsed within 6 months after NTZ suspension.

Far from enhancing the clinical efficacy of GA alone, combination of GA and pulse steroids was associated with impressively frequent and early MS return after NTZ. 60% of patients in the GA-CS group, in fact, relapsed within 6 months of NTZ suspension versus 35% in the GA group. Also, GA-CS patients relapsed about 1 month before the GA alone group and had MRI evidence of disease activity in larger proportion (85% of patients vs. 56% 6 months after NTZ discontinuation). Pulse steroids have already been shown not to protect MS patients from post-NTZ disease recurrence [9,22], and the results of the present investigation strongly suggest that they also negatively interfere with the action of GA in the post-NTZ period. Not only steroids, but also fingolimod can favor MS return after NTZ suspension [23,24]. Together, these observations indicate that post-NTZ MS disease reactivation is a clinical phenomenon whose immunological bases significantly differ from those of MS relapses occurring in never-treated

patients or in other therapeutic contexts, where both steroids and fingolimod are certainly beneficial.

We have recently proposed that NTZ beneficial effects in MS patients might in part rely upon its ability to stimulate Akt-regulated lymphocyte survival pathway and that the risk of MS reactivation after NTZ discontinuation is higher in subjects with less lymphocytosis during the treatment [11]. Indeed, the mechanism at the basis of NTZ-induced “protective lymphocytosis” needs clarification, but it might indicate the need of some regulatory immune cell activation to contrast MS rebound. This might be relevant for the interpretation of our results, as corticosteroids and fingolimod have lymphocytostatic properties, in fact reduce lymphocyte count in peripheral blood [25,26], and accelerate lymphocytosis resolution in the post-NTZ period [23]. GA effects, on the other hand, promote immune activation and not immune suppression [1,27] and might therefore contrast MS return by potentiating, in the post-NTZ period, residual beneficial actions of NTZ on lymphocyte survival and proliferation.

Conclusion

In conclusion, the present investigation indicates that corticosteroids should not be used in combination with GA to prevent post-NTZ MS recurrence. The identification of the best therapeutic strategy to control disease activity after NTZ is essential to optimize the use of this potent anti-MS medication.

Disclosures

Dr. Silvia Rossi received honoraria for writing from Bayer Schering and funding for traveling from Novartis, Teva, Merck Serono. She acted as an Advisory Board member of Biogen Idec and is involved as subinvestigator in clinical trials for Novartis, Merck Serono, Teva, Bayer Schering, Sanofi-aventis, Biogen Idec, Roche. Dr. Valentina De Chiara received funding for traveling by Teva. She is involved as study coordinator in clinical trials for Novartis, Merck Serono, Teva, Bayer Schering, Sanofi-aventis, Biogen Idec, Roche. Dr. Giorgio Bernardi is the principal investigator in clinical trials for Merck Serono and Teva. Dr. Diego Centonze acted as an Advisory Board member of Merck Serono, Teva, Bayer Schering, Biogen Idec, Novartis and received funding for traveling and honoraria for speaking or consultation fees from Merck Serono, Teva, Novartis, Bayer Schering, Sanofi-aventis, Biogen Idec. He is the principal investigator in clinical trials for Novartis, Merck Serono, Teva, Bayer Schering, Sanofi-aventis, Biogen Idec, Roche.

Conflict of Interest

The authors declare no conflict of interest.

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