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BRIEF COMMUNICATION

Recurrence of disease activity after repeated Natalizumab withdrawals

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Abstract Natalizumab (NTZ) is extremely effective in reducing disease activity in multiple sclerosis (MS) patients but its long-term use is associated with the risk of progressive multifocal leukoencephalopathy (PML). Thus, many patients discontinue NTZ and, after drug withdrawal, most of them face disease reactivation despite immunomodulant (IMD) start. The aim of this study was to evaluate the efficacy of different therapeutic strategies in preventing post-NTZ disease recurrence in a small cohort of patients that underwent repeated NTZ courses. 15 patients underwent two distinct NTZ discontinuations and started IMD after first withdrawal and a second line therapy (mainly fingolimod, FTY) after the second one. They were followed with periodic clinical and neuroradiological evaluations. All patients showed disease reactivation after first withdrawal and 13 out of 15 relapsed after the second one. In both the occasions annualized relapse rate (ARR) significantly increased as compared to on-treatment period (from 0.03 to 1.5 and from 0.26 to 1.71) with no differences between the two NTZ-free periods. Likewise, the mean number of Gd enhancing lesions increased both times to similar values (3.1 and 2.9). Median time to disease recurrence was comparable (4.7 and 5.7 months, $p = 0.57$). This study demonstrated recurrence of disease activity after two distinct NTZ discontinuations despite the treatment with IMD or more aggressive therapy, when used according to recent safety recommendations. Therefore, we need different therapeutic strategies to cope with the risk of post-NTZ disease recurrence and a "bridging strategy" with an earlier switch to second line drugs should be taken into account.

Keywords Multiple sclerosis · Natalizumab · Discontinuation · Fingolimod

Introduction

Natalizumab (NTZ) is a monoclonal antibody directed against the α4-integrin which prevents T-cells penetration in the CNS [1]. NTZ has shown an impressive efficacy and tolerability in the treatment of Relapsing Remitting Multiple Sclerosis (RRMS), yet its long-term use in patients with subclinical JC virus infection is limited by the risk of developing progressive multifocal leukoencephalopathy (PML) [2]. For this reason, many patients at high risk decide to discontinue NTZ therapy and, despite beginning immunomodulant treatments (IMT), many of them face a disease reactivation [3–6]. We collected and analyzed data of 15 patients that discontinued NTZ treatment twice to evaluate the efficacy of different therapeutic strategies.

Patients and methods

Since October 2010 at the MS centre of the San Raffaele Hospital in Milan, Italy, a group of 174 patients, treated with at least 12 infusions, discontinued NTZ treatment and 41 of them suffered disease reactivation despite IMT start. To compare the different therapeutic efficacy, we selected fifteen patients that underwent a second NTZ withdrawal switching to a second line therapy and we followed their progress with periodic clinical and radiological

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assessments. Neurological visits were scheduled every 3 months and each time we supposed a disease reactivation. Brain MRI studies were planned at 3, 6 and 12 months after NTZ discontinuation (each patient performed MRI at a single center). All patients had first MRI scan after a mean of 3.7 months from last NTZ dosing.

The parameters evaluated were: ARR, mean number of Gadolinium enhancing lesions and/or new T2 lesions. The subjects were considered disease free when presenting neither clinical nor neuroradiological reactivation. For statistical analysis, parametric variables with a normal distribution were analyzed using the Student *t* test, while the Mann–Whitney test was applied for the non-parametric ones. The Wilcoxon test was preferred for ordinal measures. Finally, Kaplan–Meier curves have been used to evaluate the temporal profile of disease reactivation while the differences between the two discontinuation periods have been calculated using the log-rank test. The study was performed in accordance with the ethical standards of Declaration of Helsinki.

Results

All patients, 11 females and 4 males, had RRMS and they were started on NTZ therapy because of failure of interferon (IFN) treatment (14 pts) or for very active disease (1 pt); six patients had already been treated with immunosuppressants. ARR before NTZ start was 2.3 (1.62–3.24). Patients had, on average, 24 NTZ doses (12–44, median 24) before stopping therapy due to: fear of PML before the availability of STRATIFY testing (4 pts), proven anti-JCV positivity (10 pts) and pregnancy planning (1 pt).

At the time of first withdrawal, mean age was 37.9 years (21.9–57.6) and mean disease duration was 8.5 years (1.9–13.11). Fourteen patients started an IMT (12 patients Glatiramer Acetate and 2 patients IFN) approximately 1 month after the discontinuation. One patient did not start any drug for refusing injective therapy. All patients reactivated within 8 months from last NTZ infusion (average 4.7; range 1.3–8.7) and drug rechallenge was tried. They took on average 13 more infusions (4–27, median 10) before discontinuing NTZ for the second time due to: fear of PML (13 pts), sero-conversion to anti-Natalizumab antibodies (1 pt) and concurrent medical problems (1 pt). During this second NTZ-free period, twelve patients started fingolimod (FTY) therapy at about 4 months after last infusion, two subjects underwent immunosuppressive therapy and one was started on Rituximab.

The disease reactivation occurred in most of the patients in both times that NTZ was stopped: median time to disease recurrence was 4.7 months after first withdrawal and 5.7 after the second one (Fig. 1). Twelve patients (80 %) relapsed after first withdrawal and eleven patients (73.5 %) after the second one. ARR significantly increased each time to similar values being 1.5 (0.89–2.37) and 1.71 (1.07–2.64), respectively, after the first and the second withdrawal ($p < 0.05$). Similarly thirteen (87 %) and nine (60 %) patients had MRI evidence of disease activity after the first and second discontinuation. Likewise, the mean number of Gd+ lesions rose to 3.1 (0–11, median 1) and 2.9 (0–20, median 1), respectively, ($p < 0.05$) (Fig. 2).On the contrary, during both NTZ treatment periods ARR as well as radiological activity significantly decreased.

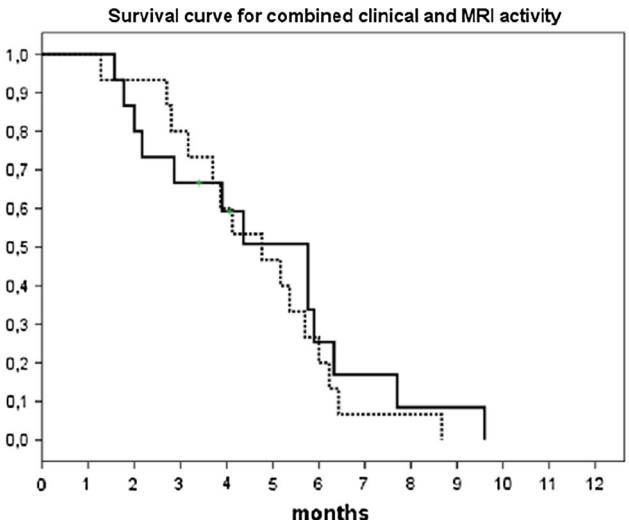

Fig. 1 KM curves relative to disease activity free patients after first (*continuous line*) and second (*dotted line*) discontinuation

Discussion

The present study is the first report of a cohort of patients discontinuing NTZ twice and it demonstrates the recurrence of disease activity after each NTZ discontinuation, regardless the treatment with IMT or with more aggressive therapies: disease reactivation affected more than 80 % of patients within comparable time frames.

Although recent studies suggested that FTY (a molecule with functional immunosuppressive properties) had a good therapeutic benefit when discontinuing NTZ [7, 8], we observed a similar disease course in patients who discontinued NTZ and started either a first or a second line therapy. Nevertheless, according to the Italian RCP, FTY-treated patients had a minimum of three-month drug-free interval after NTZ stop and maybe an earlier therapy start could reduce the disease recurrence [9]. No data exist yet on safety, especially on PML risk and, possibly, an early and safe use of FTY, or any other immunosuppressive drug, could be possible to the condition that a brain MRI is

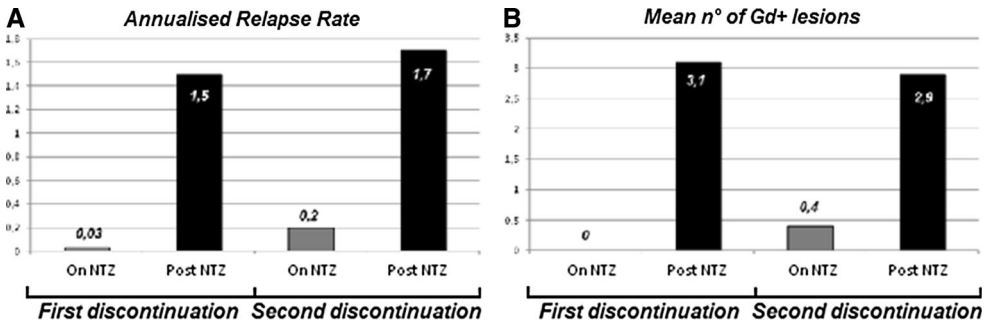

Fig. 2 **a** comparison between mean ARR during and after fist and second NTZ discontinuation; **b** comparison between mean number of Gd+ lesions during and after first and second NTZ discontinuation

performed 30–40 days after NTZ discontinuation to exclude any sign of PML. Such a "bridging" strategy could allow FTY to gradually become active by depleting circulating lymphocytes before the complete loss of NTZ-induced lymphocyte inhibition.

This study is limited by the relatively small number of patients, all of them presenting a highly active disease state, though it has shown that disease recurrence is expected each time NTZ is discontinued and it may persist overtime in patients who had had a first reactivation. Moreover, currently available treatments seem not to be effective in preventing disease activity recurrence when used according to recent safety recommendations.

Hence, while waiting for a more effective therapeutic strategy, the authors recommend evaluating very carefully the risk/benefit profile of each therapeutic choice after NTZ discontinuation for whatever reason [10], to prevent new MRI lesions and irreversible clinical disability.

Conflict of interest Dr. Ferrè, Dr. Sangalli, Dr. Radaelli and Dr. Barcella reported no disclosures. Dr. Moiola received speaker honoraria from Biogen-Dompè. Prof. Comi has in the past year received honorarium for speaking and consulting activities from Bayer Schering, Serono Symposia International Foundation, Merck Serono International, Sanofi-Aventis, Biogen-Dompè, Teva Pharmaceutical Ind. Ltd., Novartis. Dr. Martinelli received speaker honoraria or funding for travels from Biogen-Dompè. SG, Merck Serono, Bayer Schering Pharma, Novartis and Sanofi-Aventis.

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