Loss of the Cognitive Functions Improvement after Natalizumab Discontinuation: Is This a Rebound Effect?

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Background

Natalizumab (NTZ) treatment exerts a positive impact on cognitive functions in Relapsing Multiple Sclerosis (RRMS) patients[1]. Clinical and radiological disease reactivation has been described after NTZ discontinuation[2]. Whether this disease reactivation involves also cognitive functions is not known to date.

Objectives

The aims of our study were:

- To evaluate the effect of NTZ on cognitive functions of RRMS patients;
- To assess the persistence of the effect of NTZ treatment on cognitive functions 1 year after NTZ discontinuation.

Methods

- Brief Repeatable Battery [BRB], and the Stroop Test [ST] were performed at baseline, at the end of treatment and 1 year after the NTZ discontinuation in 30 RRMS patients.
- Outcome measures:
  - Cognitive Impairment Index (CII);
  - Annualized relapse rate (ARR);
  - Gadolinium enhancing lesions (GD);
- The Wilcoxon test for paired samples was used to assess the significance of the changes over time of the mean CII, the mean ARR and of the mean number of GD lesions.
- Patient' cognitive functions at 1 year after NTZ stop were classified based on the median delta CII. Patients with a delta CII ≥ the median of the delta CII of the entire population were classified as worsened, whereas the others were classified as stable/ameliorated. Differences of clinical and MRI features between groups were evaluated using the Mann-Whitney U-test and the $\chi 2$ test, as appropriate. A multivariate binary logistic regression analysis was then performed including only relevant data as covariates.

Results

- Changes of clinical and MRI disease activity at 1 year prior NTZ, at the end of NTZ and at 1 year from its suspension are shown in table 1
- The mean ARR significantly increased after NTZ stop (0.9±0.8 vs 0.5±0.6, p=0.04), but it remained significantly lower than the ARR in the year prior NTZ (1.5±0.8, p=0.003).
- During the NTZ treatment the mean number of GD lesions was close to zero (0.1±0.3). At 1 year after NTZ stopping the mean number of GD lesions significantly increased (0.9±1.4, p=0.002).
- The mean CII significantly (p<0.0001) decreased during the NTZ exposure (9.3±8.1 vs 12.6±7.9), but this positive effect on cognitive functions was completely lost (p<0.0001) at 1 year after NTZ suspension (12.2±7.9) (fig.1).

Table 1. Changes of disease activity prior, during and after NTZ therapy

Variable	
N. of NTZ infusions, Median (Min-Max)	24 (18-62)
ARR 1 year prior NTZ Mean (SD)	1.5 (0.8)
ARR during NTZ Mean (SD)	0.5 (0.6)
ARR 1 year after NTZ, Mean (SD)	0.9 (0.8)
GD + lesions 1 year prior NTZ, Mean (SD)	1.1 (1.1)
GD + lesions during NTZ, Mean (SD)	0.1 (0.3)
GD + lesions 1 year after NTZ, Mean (SD)	0.9 (1.4)

Results

- The median delta CII at 1 year after NTZ suspension was 3.0, and 18 (60%) patients were classified as cognitively worsened.
- No differences were found between patients with or without cognitive worsening in terms of age, EDSS score, sex, number of NTZ infusions, number of relapses and GD lesions during the NTZ treatment, CII at the end of treatment and washout duration. Patients showing a cognitive worsening had the longest MS duration, and had more active disease prior NTZ treatment, both in terms of relapse and of GD lesions in comparison to patients without cognitive worsening (p=0.022, p=0.009 and p=0.011, respectively).
- The Multivariate model demonstrated that patients with a longer disease duration and with a higher clinical disease activity before NTZ treatment were at higher risk of cognitive worsening after NTZ suspension (odds ratio (OR) 1.28; 95% Confidence Interval (CI) 1.03 - 1.60; p = 0.028; OR 14.63; 95% CI 1.01 - 211.32; p = 0.049; respectively). (Table 2)

Figure 1. The mean CII prior, during and at 1 year after NTZ discontinuation

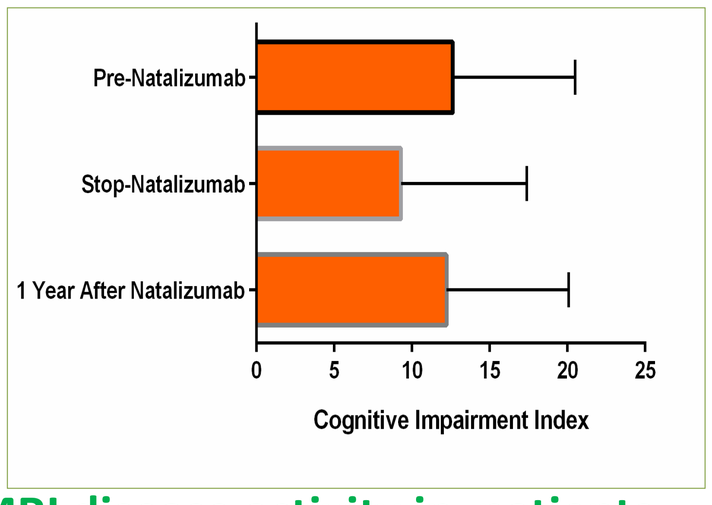

Table 2. Clinical and MRI disease activity in patients with and without Cognitive Deterioration (CD) at 1 year after NTZ suspension

Variable	CD	No CD	P Value
Disease duration, years, Mean (SD)	14.9 (6.8)	9.5 (5.0)	0.022
ARR 1-year prior NTZ, Mean (SD)	1.8 (0.9)	1.1 (0.3)	0.009
GD+ lesions 1-year prior NTZ, Mean (SD)	1.6 (1.2)	0.5 (0.5)	0.011
Multivariate Model	**Odds Ratio (95% CI)**		**P Value**
Disease duration	**1.28 (1.03 - 1.60)**		**0.028**
ARR 1-year prior NTZ	**14.63 (1.01 - 211.32)**		**0.049**

Conclusions

The beneficial effect of NTZ on cognitive functions is lost after the discontinuation of the drug.

Patients with a longer disease duration and with higher disease activity prior NTZ treatment are at higher risk of cognitive impairment rebound.

The rebound of the cognitive impairment after NTZ discontinuation goes in parallel with the clinical and radiological disease reactivation.

Our data reinforce the hypothesis that, in the short-term, NTZ exerts its positive impact on cognitive functions by means of its anti-inflammatory properties.

References

1. Iaffaldano P, Viterbo RG, et al. (2012) Impact of Natalizumab on Cognitive Performances and Fatigue in Relapsing Multiple Sclerosis: A Prospective, Open-Label, Two Years Observational Study. PLoS ONE 7(4): e35843. doi:10.1371/journal.pone.0035843
2. Havla J, et al. Bridging, switching or drug holidays - how to treat a patient who stops natalizumab? Ther Clin Risk Manag. 2013;9:361-9.