The analysis of cognitive decline in natalizumab treated RRMS suggests differential effects linked to the degree of disability, further pointing out EDSS=3 as a critical clinical milestone.

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Background and aim

Natalizumab (NTZ) has proved to be highly effective in arresting inflammation in MS, improving clinical outcomes (annualized relapse rate (ARR) and EDSS), but its effect on cortical atrophy, the major substratum of cognitive impairment (CI), is still debated. We evaluated the efficacy of NTZ throughout NEDA 3 at 24 months , integrating these data with neuropsychological assessment.

Materials and Methods

39 RRMS patients (26 females, 13 males; mean age 36.1±10.2 years, mean disease duration (DD) 8.1±7.9 years, mean education 12±3 years, median EDSS=3.0.) were included in a 2-year longitudinal study. At baseline (T0) and after two years of therapy (T1), they underwent a detailed clinical and cognitive assessment, including BRB-NT, FSS, MSNQ, BDI-II and brain MRI. Paired t-test, Pearson's correlation and Chi-square were used for statistical analysis.

Results

Clinical follow-up

All but one (97.4%) patient had no clinical event between T0 and T1. At T1, the EDSS score increased in 2 patients (5.1%), decreased in 30.7% and was stable in 25 (64.1%).

Neuropsychological follow-up

At T1, 9 patients showed a further cognitive decline, while 10 patients improved. However, considering all the patients together, no difference was found in neuropsychological test mean values between T1 to T0 (Table 1). MSNQ significantly increased at T1 (T0 vs. T1 = 13.9 vs. 19.3, $p<0.05$) and its variation (difference between T0 and T1 value) and percentage (T0–T1 value)/T0 value) strongly correlated with the FSS score (r 0.5, $p<0.001$ and r 0.9, $p<0.000001$, respectively).
EDSS scores, ARR, DD at T0 did not influence this correlation. Z-score analysis on BRB-NT disclosed no difference between T0 and T1 in the percentage of patients having at least one impaired item. However, when MS patients were divided into two groups on the base of the EDSS score, ≤3.0 (23 patients) and >3.0, EDSS (16 patients), patients with EDSS>3.0 showed a decline in at least one item (44% vs. 8%, $p<0.02$).

	Baseline	p	Follow-up
LTS g	46.15 ± 13.9	n.s.	47.2 ± 15.15
LTS c	46.5 ± 13.5	n.s.	47.2 ± 13.7
CLTR g	34.8 ± 15.9	n.s.	39.3 ± 17.4
CLTR c	34.8 ±15.7	n.s.	38.3 ± 14.8
SPART g	21.5 ± 4.6	n.s.	21.7 ± 5.3
SPART c	21.3 ± 4.4	n.s.	21.3 ± 5.2
SDMT g	51.5 ± 14.1	n.s.	52.2 ± 15.1
SDMT c	51.7 ± 13.1	n.s.	51.6 ± 14.3
PASAT g	42.9 ± 9.9	n.s.	44.1 ± 11.0
PASAT c	43.1 ± 10.3	n.s.	44.1 ± 10.5
SRT-D g	9.1 ± 2.4	n.s.	9.2 ± 2.4
SRT-D c	9.1 ± 2.3	n.s.	9.0 ± 2.2
SPART-D g	6.9 ± 2.5	n.s.	7.8 ± 2.3
SPART-D c	6.9 ± 2.5	n.s.	7.6 ± 2.3
WLG g	26.0 ± 6.9	n.s.	25.1 ± 7.1
WLG c	26.2 ± 7.0	n.s.	26.5 ± 7.0
MSNQ	13.9 ± 10.2	<0.05	19.3 ± 11.1
FSS	3.4 ± 1.6	n.s.	3.5 ± 1.4
BDI-II	8.6 ± 7.9	n.s.	7.1 ± 7.1

Table 1. Neuropsychological tests at baseline and at T1.

MRI follow-up

Compared to baseline scan, 8 patients (20.5%) presented almost one new white matter lesion after one year of treatment, while 3 (7.7%) patients presented almost one new white matter lesion between 1 and 2 year of treatment. At T1, ten patients (25.6%) presented almost one new white matter lesion. Figure 1 summarizes these data.

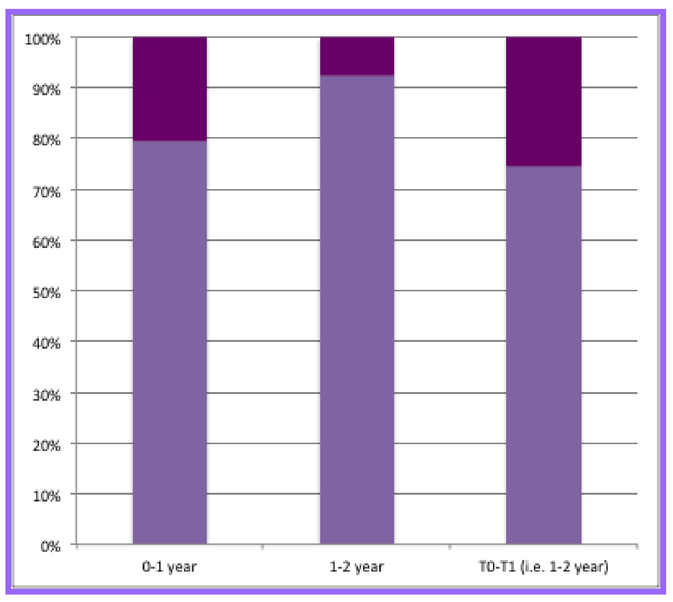

Figure 1. Patients with evidence of new white matter lesion after 1 year and 2 years of NTZ therapy.

NEDA 3

At T1, 27 (69%) patients met NEDA3 condition. No difference in the percentage of NEDA3 status was observed between patients with EDSS≤3 or EDSS>3 (75% vs. 65%, $p=0.8$).
However, among these patients, 14 (52%) were cognitively stable, 9 (33%) improved and 4 (15%) worsened.
Including these data, 23 patients presented no evidence of clinical (relapse free, no EDSS or cognitive assessment worsening) or radiological (new white matter lesions) disease activity. Finally NEDA 3 patients presented less frequently a worsening in cognitive impairment (23/27, 85%) than not NEDA 3 patients (7/12, 58%, $p=0.06$).

Conclusions

Our study further confirms the high anti-inflammatory effect of NTZ, which induced a NEDA3 status in 69% of very active RRMS, regardless the EDSS score. However, NTZ effect on cognition varied according to the degree of disability: patients with EDSS>3.0 continued to worse in cognitive performance. These findings suggest that, once reached a certain level of disability (i.e., EDSS=3), grey matter (especially cortical) pathology proceeds independently from inflammation. MS patients should be early treated with the more effective therapy in order to prevent grey matter damage and cognitive decline.

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