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Extended Interval Dosing Natalizumab and impact on neuropsychological deficits in Relapsing-Remitting Multiple Sclerosis

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Abstract

Background: Cognitive impairment and neuropsychiatric symptoms are frequently reported in Relapsing-Remitting Multiple Sclerosis (RRMS). Natalizumab (NTZ) is usually administered on a 4-weekly Standard Interval Dosing (SID) schedule. However, Extended Interval Dosing (EID) at 6–8 weekly intervals has been proven non-inferior regarding relapse risk, with a lower risk of Progressive Multifocal Leukoencephalopathy (PML). The impact of EID NTZ on neuropsychological deficits in RRMS has not been studied. **Objective:** To determine if EID NTZ demonstrates an improvement in neuropsychological parameters in RRMS patients. **Method:** We performed a retrospective, observational analysis of 34 RRMS patients treated between August 2015–2017. Patients underwent baseline neuropsychological testing before commencing EID NTZ. A second evaluation was performed, on average 28 months after commencing treatment. **Results:** Z scores at the initial assessment showed baseline cognitive impairment in multiple domains. 14/20 Z-scores showed an improvement post-NTZ and 5/14 reached statistical significance; namely Trails A (visual attention/processing speed), Line-orientation (visual-spatial), Picture-naming (word finding), Digital-Span (attention, executive function and memory) and Story-recall (memory). The Hospital Anxiety and Depression Scale (HADS) data remained unchanged. Correlation matrix showed no association between HADS scores, the time between assessments and the changes in Z scores. **Conclusion:** This data suggests the efficacy of EID NTZ in improving cognitive impairment in RRMS. A prospective observational study is warranted.

Keywords: multiple sclerosis, natalizumab, extended interval, cognition, psychology

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Introduction

Cognitive impairment can be present even at the onset of multiple sclerosis (MS); deficits in attention, executive functioning, abstract conceptualization, short term memory, word recall, and information processing speed are commonly described.[1] Some of this cognitive decline has been attributed to atrophy of cortical and deep grey matter (particularly of the corpus callosum and thalamus).[2] However, depression can also impact cognitive performance in MS, especially executive function e.g. working memory, planning ability and information processing speed. Depression and the presence of cognitive impairment have been shown to correlate with one another in MS cohorts, independent of the level of physical disability.[3–4]

Natalizumab [NTZ] is a humanized monoclonal antibody against α4β1 subunit of Very Late Antigen-4 (VLA4). VLA4 is expressed on the membrane of leucocytes and is involved in leucocyte migration to the central nervous system (CNS). NTZ is usually administered on a monthly (4 weekly) standard interval dosing [SID] schedule. Its efficacy in reducing the annualized relapse rate in RRMS is well established.[5–6] More recently, there is evidence that NTZ

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also improves cognitive deficits. Mattioli et al.; demonstrated a global improvement in cognitive function after 3 years of NTZ. In particular, executive function, information processing and memory domains showed significant improvement. Improvement was seen after 1 year and was sustained at 3 years. The MR data in this cohort not only demonstrated substantial sparing of grey matter, but also a significant increase in the grey matter density in the prefrontal and parahippocampal regions.[7] Grey matter volume changes are considered a better marker of brain atrophy than white matter volume changes, as the grey matter is considered insensitive to pseudoatrophy effects.[8,9] The authors postulated that their preliminary findings may represent an anatomical correlate of the cognitive improvement seen in their cohort and may be due to the anti-inflammatory and thus neuroprotective properties of NTZ.

NTZ has also been shown to improve depression and anxiety (although not statistically significant).[10] Neuroinflammation is postulated to play a role in the pathogenesis of depression and anxiety in MS, therefore improvements in mood in RRMS patients may also be due to the anti-inflammatory effects of NTZ.[10–12]

The risk of NTZ -associated PML has resulted in the concept of Extended interval dosing (EID) schedules.[13–14] Several published retrospective reviews show there is no increase in clinical or radiological relapses with six weekly NTZ dosing in RRMS patients.[15–20] To date, the effect of EID NTZ on both psychological and cognitive parameters has not been investigated. We hypothesized that EID NTZ is non-inferior to SID NTZ in improving cognitive and psychological parameters in RRMS patients. Therefore, we aimed to investigate the impact of EID NTZ on cognition and mood.

Methodology

34 RRMS patients were analysed in this retrospective, monocentric cohort study at Waikato Hospital, New Zealand between August 2015- August 2017 (see Figure 1). All patients were recruited from the outpatient neurology clinic. Inclusion criteria included: a) a diagnosis of RRMS as defined by the revised Mc Donald's diagnostic criteria b) participants were treatment naïve to NTZ prior to the study c) participants were receiving EID NTZ defined as six weekly 300mg intravenous infusions with no interruptions to NTZ treatment d) patients were aged 18 or above. Exclusion criteria included: a) progressive MS, previous exposure to NTZ, interruptions to NTZ therapy or a relapse before the second neuropsychological assessment.

Neuropsychological assessment

Before starting EID NTZ, all patients underwent a baseline neuropsychological assessment. A second evaluation was performed on average 28 months after the initial NTZ infusion (range 13–64 months). A screening battery of neuropsychological tests was used at both assessments to assess multiple aspects of cognition (verbal and non-verbal memory, attention, naming, language, reading, inhibition and executive functions). This included a wide panel of tests including Figure Copying, Line Orientation, Picture Naming, Semantic Fluency, Digit Span, Coding, List recall, List Recognition, Story recall, Figure recall, Letter fluency, Category Fluency, Category Switching, Colour Naming, Word Reading, Inhibition and Inhibition Switching. The Hospital Anxiety and Depression Scale (HADS) was used to assess mood. The second neuropsychological assessment was performed by the same neuropsychologist All patients underwent a second neuropsychological assessment.

Statistical analysis

Univariate analysis of pre-and post- NTZ neuropsychological test scores was performed. The raw data values were converted into Z scores. A nonparametric Wilcoxon test was applied ($p < 0.05$). A correlation matrix between a) HADS and the changes between pre-and post-NTZ cognitive testing Z-scores and b) duration of time between assessments and the changes between pre-and post-NTZ cognitive testing scores were applied.

Results

Patient demographics

The mean age of patients in our cohort was 42.8 years (range 24–59), M: F ratio: 6:28 and mean baseline Expanded Disability Status Scale (EDSS): 2.87 (range 1.5–4).

RRMS patients showed cognitive impairment at baseline

At first assessment, Z scores in our cohort showed baseline impairment in multiple domains, in particular, attention and abstraction (Trail A and B), executive functioning (Digit span, Figure copy, Letter fluency and Inhibition, Inhibition Switching) and short term Memory (List memory, Story memory, Digit memory, List recall and List recognition) (See Table 1).

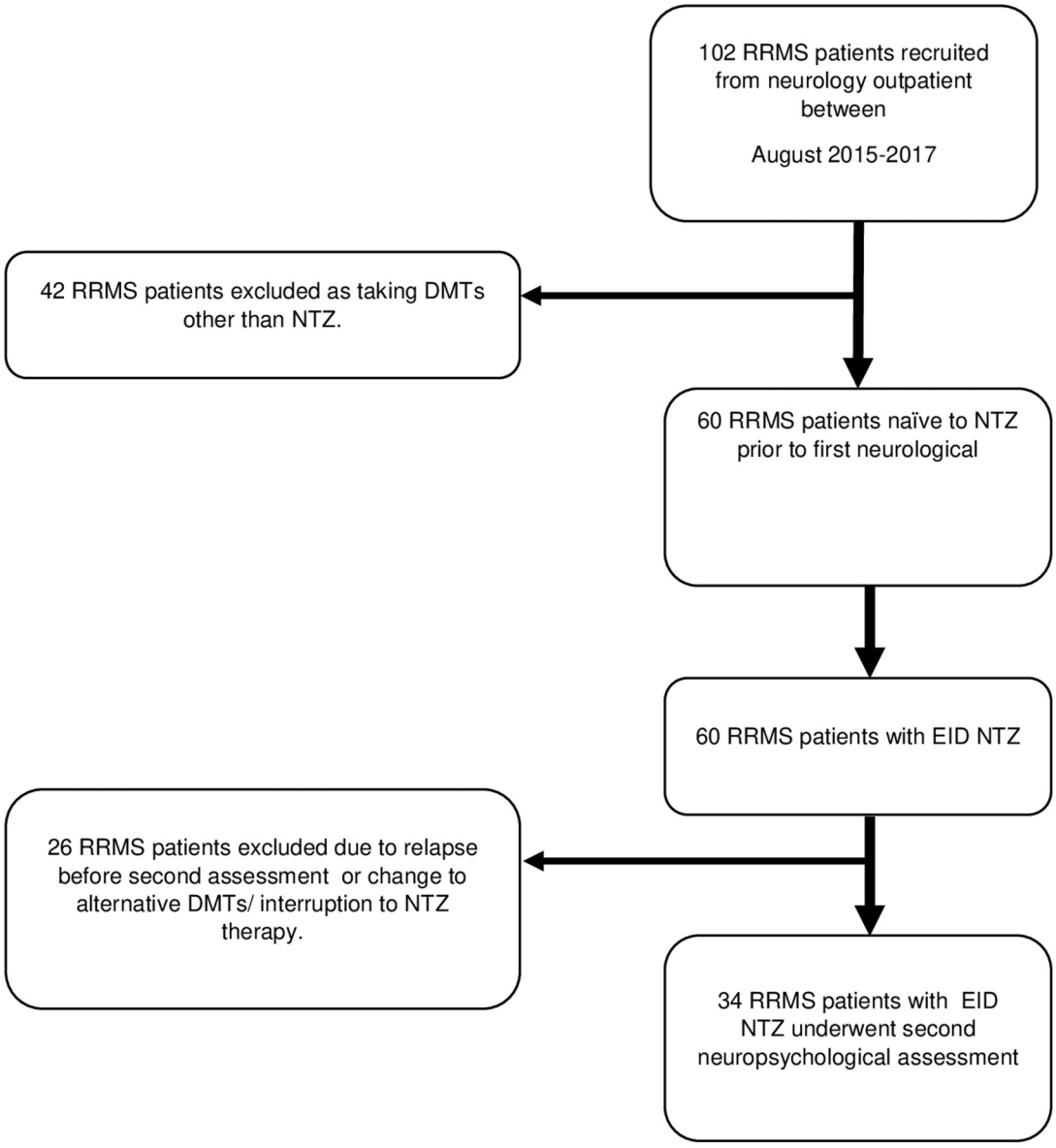

Figure 1. Flow chart showing the recrutiment process of patient from Neurology outpatients. DMTs = Disease Modifying Therapies.

Attention, memory and executive function showed statically significant improvements with EID NTZ.

Of the 20 cognitive parameters assessed, 6/20 Z-scores did not change (Figure-recall, Word-reading, Category-fluency, Colour-naming, Inhibition and Inhibition-switch), 14/20 Z-scores showed an improvement post-NTZ and 5/14 reached statistical significance $p < 0.05$ (See Table 1). Trails A (visual attention/processing speed), Line-orientation (visual-spatial), Picture-naming (word finding), Digital-Span (attention, executive function and memory) and Story-recall (memory) improved with statistical significance (See Figure 2). Correlation matrix analysis showed no association between time between assessments and changes in cognitive testing Z scores.

There was no association between depression/anxiety scores and cognitive performance.

Depression and anxiety was not an issue in our patient cohort with a mean pre- NTZ HADSs depression score of 4 and post NTZ HADs depression score of 4. The mean pre-NTZ HADS anxiety score was 7 and post-NTZ score 6, (HADS score: 0–7 = Normal, 8–10 = Borderline abnormal 11–21 = Abnormal).

Table 1. Pre, Post and changes: Stats significance.

	Paired Samples Statistics				Paired Differences								Non−parametric
					95% Confidence Interval of the Difference								
	Mean	N	Std. Deviation	Std. Error Mean	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df		p-value
PRE- Trails A	-0.956	34	1.2877	0.2208	−0.5471	1.1043	0.1894	−0.9324	−0.1617	−2.889	33	0.007	0.003
POST- Trails A	−0.409	34	1.0530	0.1806									
PRE-Trails B	−0.650	34	1.2263	0.2103	−0.1441	0.7632	0.1309	−0.4104	0.1222	−1.101	33	0.279	0.202
POST-Trails B	−0.506	34	1.2601	0.2161									
PRE-List learning	−0.259	34	1.2015	0.2061	−0.2265	1.0109	0.1734	−0.5792	0.1263	−1.306	33	0.201	0.227
POST-List Learning	−0.032	34	0.9641	0.1653									
PRE- Story Memory	−0.512	34	1.4103	0.2419	−0.0882	1.1499	0.1972	−0.4895	0.3130	−0.447	33	0.657	0.530
POST- Story memory	−0.424	34	1.3078	0.2243									
PRE-Figure Copy	−0.673	33	1.2948	0.2254	0.1545	1.1085	0.1930	−0.2385	0.5476	0.801	32	0.429	0.365
POST-Figure Copy	−0.827	33	1.2936	0.2252									
PRE-Line Orientation	0.135	34	0.8205	0.1407	−0.2676	0.7243	0.1242	−0.5204	−0.0149	−2.155	33	0.039	0.047
POST-Line Orientation	0.403	34	0.7082	0.1215									
PRE-Picture Naming	0.279	34	0.7227	0.1239	−0.2294	0.5906	0.1013	−0.4355	−0.0233	−2.265	33	0.030	0.022
POST-Picture Naming	0.509	34	0.5282	0.0906									
PRE-Semantic Fluency	0.524	34	1.0419	0.1787	−0.0618	0.8856	0.1519	−0.3708	0.2472	−0.407	33	0.687	0.762
POST-Semantic Fluency	0.585	34	1.0706	0.1836									
PRE-Digit Span	−0.259	34	1.0742	0.1842	0.4559	1.2671	0.2173	0.0138	0.8980	2.098	33	0.044	0.026
POST-Digit Span	−0.715	34	1.5234	0.2613									
PRE-Coding	−0.624	34	1.1407	0.1956	−0.0853	0.6679	0.1146	−0.3183	0.1478	−0.745	33	0.462	0.380
POST-Coding	−0.538	34	1.2053	0.2067									
PRE-List recall	−0.174	34	1.1725	0.2011	−0.1206	0.8048	0.1380	−0.4014	0.1602	−0.874	33	0.389	0.293
POST-List recall	−0.053	34	1.0103	0.1733									
PRE- List Recognition	−0.068	34	0.9181	0.1574	−0.0794	1.0168	0.1744	−0.4342	0.2754	−0.455	33	0.652	0.636
POST-List Recogniton	0.012	34	0.6596	0.1131									
PRE-Story recall	−0.500	34	1.5156	0.2599	−0.4000	0.9547	0.1637	−0.7331	−0.0669	−2.443	33	0.020	0.024
POST-Story recall	−0.100	34	1.2463	0.2137									
PRE-Figure recall	−0.194	34	1.0795	0.1851	0.0412	0.9032	0.1549	−0.2740	0.3563	0.266	33	0.792	0.862
POST-Figure recall	−0.235	34	1.1757	0.2016									
PRE-Letter fluency	−0.403	34	1.4288	0.2450	−0.1176	0.9324	0.1599	−0.4430	0.2077	−0.736	33	0.467	0.752
POST-Letter fluency	−0.285	34	1.2654	0.2170									
PRE-Category Fluency	0.194	34	1.2562	0.2154	0.1412	0.9605	0.1647	−0.1939	0.4763	0.857	33	0.398	0.223
POST-Category Fluency	0.053	34	1.4961	0.2566									
PRE-Category Switching	−0.026	34	1.2285	0.2107	−0.0206	0.8164	0.1400	−0.3054	0.2643	−0.147	33	0.884	0.954
POST-Category Switching	−0.006	34	1.2468	0.2138									
PRE-Color Naming	−0.294	34	0.9387	0.1610	0.0912	0.6828	0.1171	−0.1471	0.3294	0.779	33	0.442	0.369
POST-Color Naming	−0.385	34	0.9541	0.1636									

(continued)

Table 1. Continued.

	Paired Samples Statistics			Paired Differences						Non−parametric	
					95% Confidence Interval of the Difference						
	Mean	N	Std. Deviation	Std. Error Mean	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	p-value	
PRE-Word Reading	−0.556	34	1.0886	0.1867	0.0706	0.8744	0.1500	−0.2345	0.3757	0.471	33	0.641	0.863
POST-Word Reading	−0.626	34	1.0220	0.1753									
PRE-Inhibiton	−0.135	34	1.0436	0.1790	−0.0294	0.9756	0.1673	−0.3698	0.3110	−0.176	33	0.862	0.756
POST-Inhibition	−0.106	34	0.9008	0.1545									
PRE-Inhibition Switching	−0.259	34	0.8962	0.1537	−0.0206	0.5830	0.1000	−0.2240	0.1828	−0.206	33	0.838	0.724
POST-Inhibition Switching	−0.238	34	1.0290	0.1765									
PRE-HADS Depression	4.29	34	2.725	0.467	0.735	2.632	0.451	−0.183	1.654	1.629	33	0.113	0.070
POST-HADS Depression	3.56	34	2.776	0.476									
PRE-HADS Anxiety	7.03	34	4.789	0.821	0.353	2.784	0.477	−0.618	1.324	0.739	33	0.465	0.594
POST-HADS Anxiety	6.68	34	4.312	0.739									

Correlation matrix analysis showed no association between HADS scores and cognitive testing Z-scores.

Discussion

EID NTZ schedules are now utilized worldwide.[20] EID does not diminish the effectiveness of NTZ, in terms of relapse rates, new lesion development or brain parenchymal volume loss in RRMS.[15–20] The recently published results from the NOVA 3b study (NCT03689972) show that six-weekly NTZ is non-inferior with both clinical and neuroradiological outcomes in RRMS patients who switched from a previous four-weekly SID schedule. The use of EID schedules is further justified by the pharmacokinetic studies that demonstrate EID schedules likely mitigate the overall burden of adverse events (especially PML) by reducing the α4 β1 integrin receptor saturation on the surface of mononuclear cells.[13,14,20]

Cognitive impairment is common in RRMS. Even at the first assessment, cognitive Z scores in our cohort showed baseline impairment in multiple domains, in particular, attention and abstraction, executive functioning and short term memory. These deficits are consistent with those described in RRMS.[1] Our cohort showed improved cognitive Z scores in attention, memory and executive function. This is also consistent with existing literature, as SID NTZ schedules have been shown to improve deficits in these domains.[7,21] There is a paucity of evidence on the effectiveness of EID NTZ regarding the cognitive deficits in RRMS. Our data suggests that EID NTZ may be non-inferior to SID NTZ in regard to the improvement of cognitive deficits. Multivariate analysis did not find a correlation between the time between both assessments or the depression or anxiety scores and cognitive importance. Thus, the length of time between assessments did not seem to influence the cognitive testing scores. Depression often negatively impacts cognition in RRMS patients[4] but this was not the case in our retrospective analysis. However, this study has several limitations. Firstly, there is a limited number of 34 patients. Secondly, there is no control group. Thirdly it is a retrospective analysis, therefore causality can not be determined. There is a wide range from 13 to 64 months between assessments due to practical considerations, such as under-resourcing and not all the second neuropsychology assessments could be completed at the preferred 24 months (as per local protocol), which is a significant limitation of this retrospective study.

Therefore, although our results indicate that EID NTZ may be non-inferior to SID regarding cognition, a

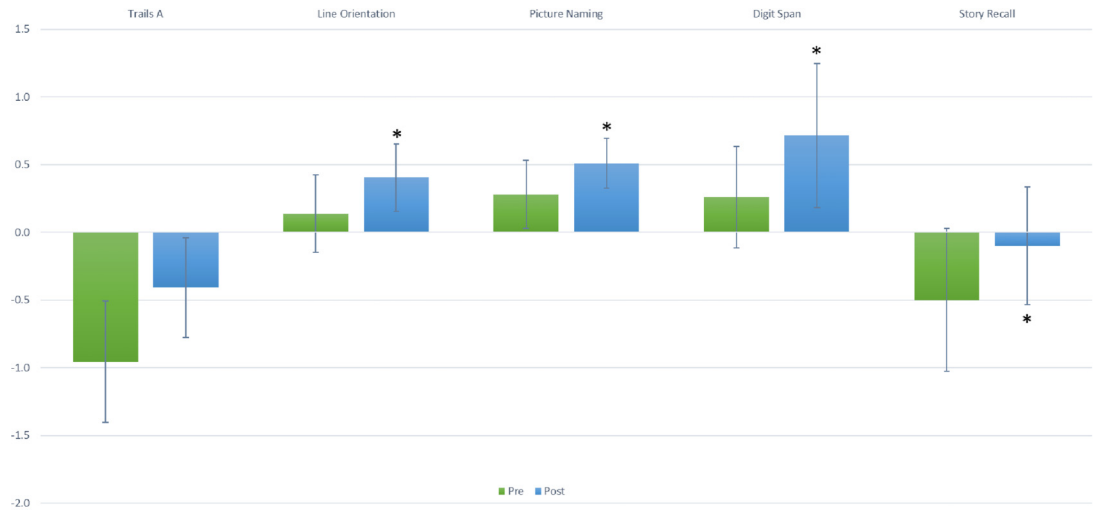

Figure 2. Shoeing the changes in pre- and post- NTZ cognitive testing. *Z Scores with statistical significance $p \leq 0.05$, **Z Scores with statistical significance $p \leq 0.01$.

larger prospective analysis is warranted to investigate this finding further.

Declaration of Conflicting Interests

Dr Jan Schepel has been compensated to speak on advisory committees for Biogen and Roche. He has had travel expenses for congresses paid by Merck, Beyer, Biogen and Roche. The other authors have no disclosures.

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