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

Eileen J. McManus, Karen M. Clark, Christopher Frampton, Jamie A.B. Macniven, and Jan Schepel

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...
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 pseudoarophy 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 McDonald’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).
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).

Figure 1. Flow chart showing the recruitment process of patient from Neurology outpatients. DMTs = Disease Modifying Therapies.
Table 1. Pre, Post and changes: Stats significance.

| Paired Samples Statistics | Paired Differences | 95% Confidence Interval of the Difference | Non-parametric |
|---------------------------|-------------------|------------------------------------------|----------------|
|                           | Mean N Std. Deviation | Std. Error Mean N Std. Deviation Std. Error Mean Lower Upper t df p-value | Non-parametric |
| 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 Recognition     | 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)
Correlation matrix analysis showed no association between HADS scores and cognitive testing Z-scores.

**Discussion**

EID NTZ schedules are now utilized worldwide. EID does not diminish the effectiveness of NTZ, in terms of relapse rates, new lesion development or brain parenchymal volume loss in RRMS. 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.

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. 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. 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 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 underresourcing 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
larger prospective analysis is warranted to investigate this finding further.

Declaration of Conflicting Interests
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ORCID iD
Eileen J. McManus https://orcid.org/0000-0002-4521-805X

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Figure 2. Shoing the changes in pre- and post- NTZ cognitive testing. *Z Scores with statistical significance p ≤ 0.05, **Z Scores with statistical significance p ≤ 0.01.
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