Cognitive Evolution in Tysabri (natalizumab)-Treated Multiple Sclerosis Patients

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Introduction

Cognitive dysfunction affects up to 65 % of Multiple Sclerosis (MS) patients. It can occur at any stage of the disease and even precede physical disability. Once present it tends to progress with time and is unlikely to improve or resolve (1). Cognitive impairment most commonly involves memory, information processing speed and executive skills (1-3).

A number of open label studies have shown over the short term (<1year) an immediate benefit in cognition with initiation of Tysabri in MS patients (4). Some of the benefit seen in theses open label trials could be attributed to a regression to the mean phenomenon and or learning effect. These shortcomings could be minimized with better cognitive testing and studies of longer duration.

It has yet to be determined if the benefit on cognitive evolution in MS is maintained beyond two years of continuous Tysabri therapy. We initiated an open label, two-year study comparing cognitive function in patients who at baseline had received two years or less of Tysabri therapy with patients with more than two years of Tysabri therapy. We present here the 12 months interim analysis.

Methods

This is a pilot, single-center, observational study. Sixty three (63) patients with MS (60 with RRMS and 3 with SPMS) and receiving Tysabri were recruited from our MS clinic.

Patient demographics, MS treatment history, EDSS, MSSS, and natalizumab treatment duration were collected at baseline. The Symbol Digit Modalities Test (SDMT) and a Cogstate battery of tests (Detection (DET), Identification (IDN), One Back (ONB), Groton Maze Learning Test (GMLT), International Shopping List Test (ISLT)) were performed every 4 weeks just prior to Tysabri infusion for a period of 24 months. A Beck depression questionnaire was administered at screening and at every 4th month. Patients with cognitive decline from other causes (i.e., PML or depression) were excluded.

In order to minimize practice effects, five different versions of the SDMT were used in five-month cycles. The baseline was calculated by averaging test scores over the first four months and intra-class correlations were calculated over this time period.

A series of Repeated Measures ANOVAs were also conducted with time on natalizumab as a between-subjects factor, time point as a within-subjects factor, and MSSS as a covariate. The current data are from the 12-month interim analysis. Clinically significant decline was defined as a decline in performance of >=1.96 SD on one or more tests or >=1 SD on two or more tests and sustained for 3 months.

Results

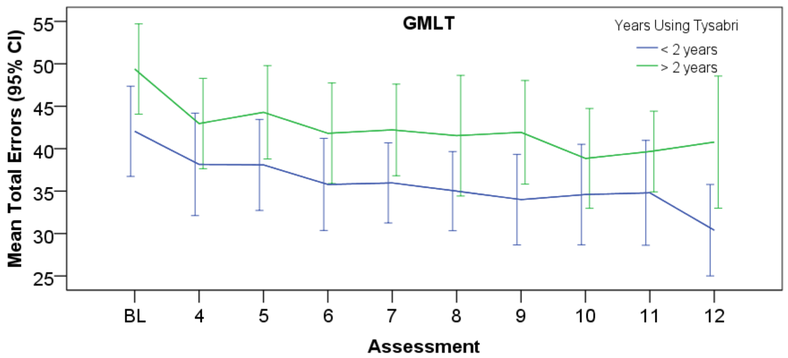
Demographics Table Split by Years on Tysabri

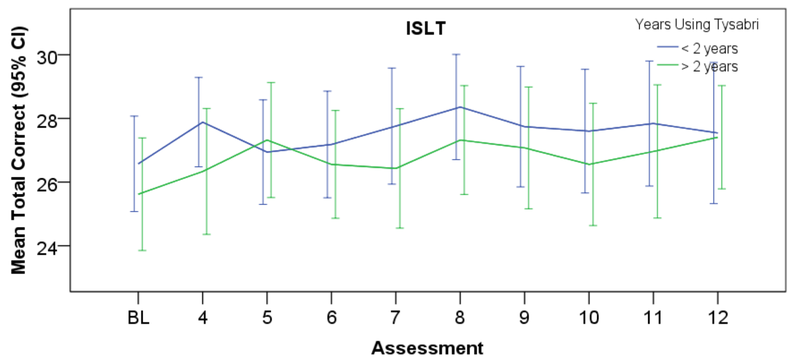
	Years Using Tysabri		
	<= 2 years (N=34)	> 2 years (N=28)	
Demographic	**Mean (SD)**	**Mean (SD)**	**P-value**
Age	44.44 (10.00)	47.11 (10.21)	0.31
MS Duration	11.65 (9.84)	14.46 (7.73)	0.22
EDSS	3.09 (1.06)	2.84 (1.48)	0.44
MSSS	4.22 (2.08)	2.88 (1.63)	0.007
Baseline Depression	6.35 (3.64)	6.35 (5.40)	0.99

Note: EDSS = Expanded Disability Status Scale, MSSS = Multiple Sclerosis Severity Score.

Changes in GMLT & ISLT Performance Over 12 Months

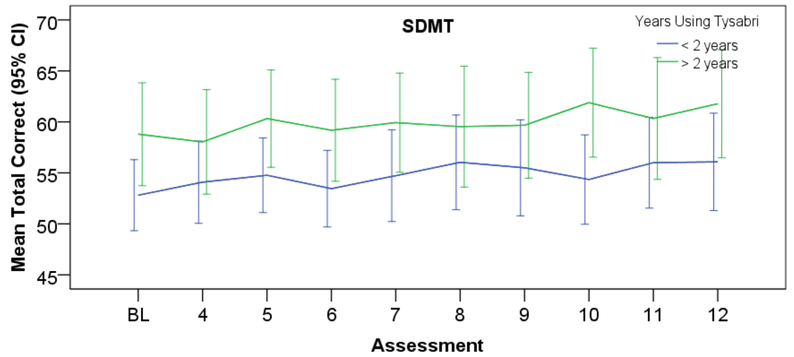
Irrespective of time on natalizumab, significant improvements were observed on the within-subjects factor (assessment) on the GMLT (p=.01), ISLT (p=.01), and SDMT p<.0001), whereas DET(p=.33), IDN (p=.72) and ONB (p=.11) remained unchanged.





Results

Changes in SDMT Performance Over 12 Months



Intraclass Correlation Coefficients

Task	DET	IDN	ONB	GMLT	ISLT	SDMT
ICC	0.86**	0.90**	0.88**	0.91**	0.92**	0.97**

**p < 0.001

Note: ICC computed over the first four months of assessment, incorporating the Baseline, Month 1, Month 2 and Month 3 assessments.

Conclusions

Subject-level analysis revealed only one patient with clinically meaningful decline, however this was attributable to concurrent depression. No difference was found between the two groups (≤2 years or >2 years on natalizumab) in regards to cognitive preservation and the capacity to learn after 12 months.

Although not statistically significant, the ≤2 years on natalizumab group tended to perform better on the Cogstate battery while the opposite was true for the SDMT.

The strong magnitude of the Intraclass correlations for each Cogstate task and the SDMT indicates a high level of test-retest reliability on these cognitive tests over the first four months of testing.

References

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