

Improved tremor outcomes in patients with natalizumab-treated multiple sclerosis

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Abstract

Background: Tremor is among the most physically disabling symptoms associated with multiple sclerosis (MS). Symptomatic therapies provide at best a modest benefit to affected patients. The effect of MS disease modifying therapies (DMTs) on the severity of MS tremor is unclear.

Objectives: To compare the change over time in scores of tremor-related activities of daily living (TRADL) between subjects treated with natalizumab (NTZ) and other MS DMTs.

To compare changes over time in visual analog scale (VAS) of tremor severity and tremor related handicap (TRH) by DMT

Methods: Questionnaires were sent to North American Research Committee on MS (NARCOMS) participants reporting mild or greater tremor on the Tremor and Coordination Scale during semiannual updates between Fall 2010 and Spring 2012. Three groups of subjects were invited to participate: Current NTZ recipients, previous NTZ recipients, and a random sample of patients on other MS DMTs. Respondents answered questions regarding their experience of tremor, including history, location, and symptomatic treatment, as well as tremor-specific scales (TRADL, TRH, VAS) to indicate both current tremor severity and tremor severity when the current DMT was initiated. For both TRADL (range 25-100) and VAS (range 1-10) higher scores reflect worse tremor. Changes were compared by NTZ treatment history using ANOVA.

Results: Respondents were 96.0% white, 78.1% female, and the mean age was 55.5 ± 9.3 years. Of 567 subjects, 202 were taking NTZ, 136 were previously on NTZ, and 229 had never taken NTZ and were on other DMTs. Subjects on NTZ were more likely to report tremor improvement on their DMT (28.7% on NTZ vs. 14.0% previously on NTZ vs. 14.4% on other DMT, p=0.0007). Mean baseline TRADL score was 43.5 ± 15.8, and did not differ between treatment groups (p=0.475). Over a mean recall period of 6.2 ± 4.6 years, the TRADL score increased by 1.8 points among NTZ subjects, 3.3 points in those previously on NTZ, and 5.4 points in those never on NTZ (p=0.009). The VAS score improved among NTZ-treated subjects and worsened in prior NTZ and other DMT groups (d, 1.1 vs. 0.1 vs. 0.3, p=0.027). TRH responses did not yield associations between change in tremor-related embarrassment or physical handicap with current DMT.

Conclusions: NTZ is associated with less worsening in MS-associated tremor compared to other MS DMTs. Longitudinal studies will be needed to confirm these results in prospective fashion.

Background

- Ataxia and tremor in multiple sclerosis are frequently disabling and rarely remit with time¹
- Symptomatic treatments of MS-associated tremor are at best modestly beneficial for most patients
- Changes in tremor or ataxia in response to treatment with approved MS disease modifying therapies (DMTs) have not been extensively described
- Natalizumab has been associated with symptom regression in MS-associated cognitive impairment² and improvement in other patient-reported outcomes³
- The NARCOMS registry includes a large population of patients on MS DMTs and also tracks symptoms of tremor and ataxia

Methods

- Search of NARCOMS registry identified participants reporting both mild or greater symptoms on Tremor and Coordination Scale (TACS)⁴ and use of natalizumab or other approved MS DMT
- Surveys based on tools developed by Bain and Findley developed and mailed to selected participants. In addition to descriptive questions about tremor^{1,5} symptoms, respondents also asked to complete some scales based on their recollections of symptom severity at start of current DMT
- Returned surveys were compiled into a de-identified database. Primary endpoint compared recalled change in Tremor Related Activities of Daily Living Scale (range 25-100) by current disease modifying therapy⁵

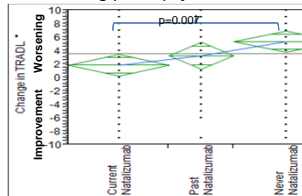
Results

Participant characteristics

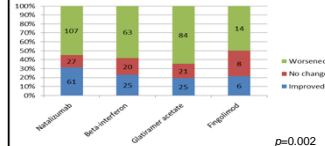
| | Natalizumab (n=202) | Never on Natalizumab (n=229) | Prior Natalizumab (n=136) | p |
|----------------------------------|---------------------|------------------------------|---------------------------|---------|
| Female, n (%) | 186 (82.6) | 170 (74.2) | 105 (77.8) | 0.113 |
| White, n (%) | 170 (96.1) | 215 (96.9) | 113 (94.2) | 0.641 |
| Age at MS diagnosis, y (SD) | 37.2 (9.6) | 38.6 (10.0) | 39.1 (8.3) | 0.154 |
| Disease duration, y (SD) | 16.2 (8.4) | 19.5 (8.7) | 15.0 (6.3) | <0.001* |
| Family history of tremor, n (%) | 33 (16.3) | 34 (14.9) | 18 (13.2) | 0.681 |
| Median PDDS (IQR) | 4 (3,6) | 5 (3,6) | 5 (4,6) | 0.180 |
| Tremor duration, y (SD) | 11.0 (9.0) | 12.5 (7.8) | 9.7 (7.0) | 0.005* |
| Baseline TRADL, mean (SD) | 43.7 (15.2) | 42.5 (16.9) | 44.6 (14.8) | 0.475 |
| Duration current DMT use, y (SD) | 3.1 (1.9) | 9.2 (4.8) | 4.9 (3.9) | <0.001* |
| Taking symptomatic meds, n (%) | 86 (42.6) | 82 (35.8) | 70 (51.5) | 0.065 |

DMT: Disease modifying therapy; TRADL: Tremor Related Activities of Daily Living; PDDS: Patient Determined Disease Steps

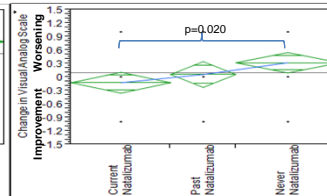
Change in Tremor Related Activities of Daily Living (TRADL) by Current DMT



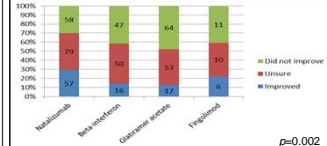
Improvement vs. worsening of TRADL over time



Change in Visual Analog Scale by Current DMT



Did current DMT improve your tremors?



Results, cont.

Regression estimates of parameters explaining change in TRADL*

| Parameter | Estimate | p-value |
|----------------------|-----------|---------|
| Treatment group | | |
| Never Natalizumab | reference | |
| Current Natalizumab | -1.2 | 0.013 |
| Current Age | 0.2 | 0.001 |
| Tremor Duration | -0.1 | 0.125 |
| PDDS (most recent) | 2.2 | <0.001 |
| Baseline TRADL Score | 0.4 | <0.001 |

*Model accounts for 39.5% of variance in change in TRADL

TRADL: Tremor Related Activities of Daily Living; PDDS: Patient Determined Disease Steps

Conclusions

- NARCOMS respondents reporting mild or greater tremor and currently receiving natalizumab experienced less worsening and were more likely to indicate improvement on patient-report measures of tremor and ataxia than respondents taking other MS disease modifying therapies
- The association of natalizumab with improved tremor and ataxia outcomes remains significant after adjustment for subject age, tremor duration, current PDDS, and baseline TRADL score
- In this cohort, current use of natalizumab also associates with shorter disease duration and duration of current DMT usage, which may confound results
- Prospective, observational studies are needed to definitively demonstrate whether natalizumab may effect regression of tremor and ataxia in the MS population

References

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