Poster DX42

Prospective Longitudinal Study of Natalizumab Treatment in MS Patients

Ellen Lathi, MD; Joshua Katz, MD; Allison Walczyk from The MS Center at St. Elizabeth's, Boston, MA

Background

- Natalizumab (Tysabri®, Biogen Idec) is a selective alpha-4 integrin antagonist that prevents leukocyte migration into the central nervous system (CNS) and subsequent inflammatory activity (Yednock et al. *Nature* 1992;356:63-66).
- The efficacy of natalizumab in relapsing-remitting multiple sclerosis (RRMS) patients was demonstrated in the 2-year randomized, controlled AFFIRM trial (Polman et al. *NEJM* 2006;354:899-910).
  - Natalizumab significantly reduced the rate of clinical relapse by 68% and the risk of sustained disability progression by 42% over 2 years (*P*<0.001).
- Real-world data are needed to confirm the efficacy and safety of natalizumab in a clinical setting and beyond 2 years of treatment.

Objective

To evaluate the efficacy and safety of long-term natalizumab treatment in MS patients in a clinical setting.

Methods

- Patients were enrolled consecutively into this open-label, single-center, prospective, observational study.
- Patients initiated natalizumab at a monthly dose of 300 mg intravenously.
- Patients were assessed for efficacy parameters and adverse events at 6-month intervals.
  - Efficacy parameters included relapse rate, MRI results, Expanded Disability Status Scale (EDSS), and timed 25-foot walk (T25FW) scores.
- Data on adverse events, laboratory results, 9-hole peg test, cognitive function, fatigue, and low-contrast vision were collected.

Results

Patient Disposition

- 69 patients continue to receive natalizumab (6 transferred to another site)
- 65 patients discontinued natalizumab for the following reasons:
  - 35 due to anti-JCV antibody positive status and concern for PML
  - 14 for anti-natalizumab antibodies with or without clinical hypersensitivity
  - 9 secondary-progressive MS (range of natalizumab doses = 3 to 22, median =6); limited benefit
  - 1 death (cardiac)
- 5 unknown status (lost to follow up)

Anti-Natalizumab Antibodies

- 17 patients tested positive for anti-natalizumab antibodies
- 4 patients had MRI activity and 3 of these had a clinical relapse

Table 1. Demographics and Baseline Characteristics

Characteristics	Total (N=133)
Age, y, (n=131)	
Mean (SD)	44.3 (10.8)
Range	18-74
Female, n (%)	102 (76.7%)
Race, n (%), (n=132)	
Caucasian	123 (93.2%)
Hispanic	6 (4.5%)
African American	2 (1.5%)
Asian	1 (0.8%)
Disease Stage, n (%)	
RRMS	115 (86.5%)
SPMS	10 (7.5%)
PRMS	8 (6.0%)
No. of relapses in 1 year before natalizumab, n (%), n=132	
0	80 (60.6%)
1	49 (37.1%)
2	3 (2.3%)
No. of relapses in 3 years before natalizumab, n (%), n=131[a]	
0	31 (23.7%)
1	53 (40.5%)
2	25 (19.1%)
3	11 (8.4%)
>3	11 (8.4%)
History of prior immunosuppressant use, n (%), n=132	30 (22.7%)
EDSS score, mean (SD), n=42	3.6 (1.8)
T25FW, sec, mean (SD), n=108	8.1 (7.9)
Anti-JCV antibody positive, n (%), n=85[b]	36 (42.4%)

EDSS=Expanded Disability Status Scale; JCV=JC virus; PRMS= progressive-relapsing MS; RRMS=relapsing-remitting MS; SPMS=secondary-progressive MS; T25FW=timed 25-foot walk.
[a]1 patient started natalizumab soon after diagnosis and was treatment naïve; and 1 patient reported "1 or 2 relapses"; these 2 patients are not included in relapse history.
[b]Anti-JCV antibody testing was not available in 16 of 85 patients.

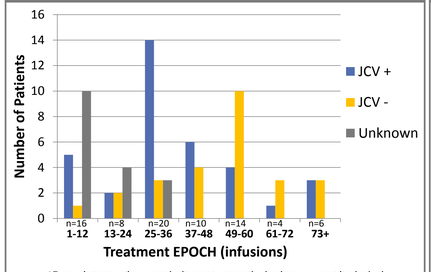
Natalizumab Treatment

- Of 132 patients with dosing data available, 86 (65.2%) patients received natalizumab with no dose interruption.
  - The mean (SD) number of doses before any interruption was 17.9 (14.9), with a range of 1 to 54 doses.
  - The mean total number of doses including all re-dosing after interruptions was 23.0 (15.6).
  - Patients were exposed to natalizumab for a mean of 1.8 years and up to 4.2 years at the time of analysis.

Long-term Continuous Natalizumab Treatment

- Figure 1 shows the distribution of 78 patients who received monthly natalizumab by treatment epoch and anti-JCV antibody status.
- Of those 78 patients who received continuous treatment, no patient has had a clinical relapse (Figure 2).
- Changes from baseline in EDSS score and T25FW are shown in Figure 3.

Figure 1. Patients receiving continuous monthly natalizumab by treatment EPOCH and anti-JCV antibody status (n=78)*



*Dose interruptions and alternate month dosing are not included.

Figure 2. Percentage of patients free of disease activity by natalizumab treatment frequency

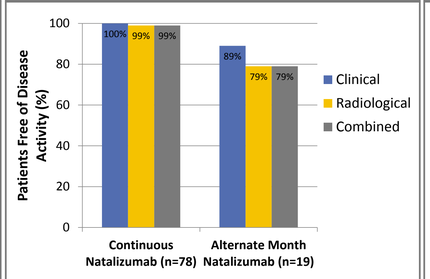
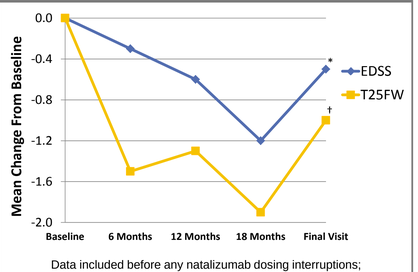


Figure 3. Mean change from baseline in EDSS and T25FW over longitudinal assessment



Data included before any natalizumab dosing interruptions; at final visit EDSS, n=32; T25FW, n=82; *P=0.009; †P=0.0005.

Alternate Month Dosing (n=19)

- 8 patients remained stable.
- 4 patients had a breakthrough (2 radiographic) and switched back to monthly dosing (Figure 2).
- 4 patients were stable but switched therapy due to anti-JCV antibody positive.
- 3 patients used alternate month dosing for 6 months, followed by a 2- to 3-month washout and switched to fingolimod (Gilenya™) and subsequently had a clinical relapse or new MRI activity on fingolimod after ≥ 6-12 months.

Clinical Relapse

- All clinical relapses occurred in patients who were anti-natalizumab antibody positive (4 clinical relapses in 3 patients).

Table 2. Adverse Events

	n (%)
Clinical hypersensitivity reaction*	11 (8.3%)
Headache	5 (3.8%)
Arthralgia	2 (1.5%)
Majocchi Granulomas (dermatophyte infection with rash)	1 (0.8%)
Cancer (1 patient each): Malignant glioma (7 doses) Colon cancer and basal cell carcinoma† Prostate cancer† Breast cancer (5 doses) Uterine cancer (1 dose, anti-natalizumab antibody positive)	5 (3.8%)
Progressive multifocal leukoencephalopathy (PML)	0

*Of 17 (65%) patients who were positive for anti-natalizumab antibodies.
†Patient continues to receive natalizumab.

Patients with Multiple Risk Factors for PML

- 5 patients had received prior immunosuppressants and were anti-JCV antibody positive at natalizumab initiation.
  - 3 patients continue to receive natalizumab .
    - At time of analysis, 1 patient has received 30 doses and 2 patients have received 74 doses.

MRI Relapse

- 3 new T2 lesions were seen in 2 patients on continuous natalizumab after 21 months of treatment; both patients continue to receive natalizumab.
- 2 patients on alternate month natalizumab developed contrast-enhancing lesions (CEL) after at least 5 doses.
- 4 anti-natalizumab antibody positive patients had MRI activity while on natalizumab.
  - 1 patient had 1 T2 lesion.
  - 1 patient had 2 T2 lesions.
  - 1 patient had 1 T2 and 1 CEL lesion (no clinical relapse).
  - 1 patient had 6 T2 and 3 CEL lesions.

Conclusions

- In this cohort of MS patients with active disease at baseline, as evidenced by prior treatments, relapses, and MRI lesions, continuous natalizumab treatment was associated with substantial and sustained improvement in clinical and radiological parameters.
  - Some patients, including anti-JCV antibody positive patients, have received natalizumab for more than 4 years with sustained efficacy and safety.
- Significant decreases were observed in EDSS scores and T25FW.
- Clinical relapses were limited to patients with anti-natalizumab antibodies and therefore, not unexpected.
- MRI activity occurred in patients receiving alternate month dosing and in patients who were positive for anti-natalizumab antibodies.
- Alternate month natalizumab dosing was associated with more breakthrough disease activity compared with continuous monthly natalizumab.
- This study provides useful clinical information on the long-term efficacy and safety of natalizumab treatment.