Multicenter retrospective study of extended dosing of Natalizumab in Multiple Sclerosis: a strategy for mitigating risk of Progressive Multifocal Leukoencephalopathy while Maintaining Efficacy?

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Objectives

- **To evaluate efficacy and safety of extended dosing of Natalizumab (NTZ).**

Background

- Progressive multifocal leukoencephalopathy (PML) caused by JC virus (JCV) , is a potentially fatal complication of NTZ.
- PML risk in JCV Ab sero-positive long – term NTZ recipients is 0.7%, if there was no prior immunosuppression and 1.3% ,if there was prior immunosuppression [1].
- PML susceptibility may reflect NTZ –induced blockade of α4β1 integrin receptor that leads to excessive reduction in discrete tissue compartment trafficking of immune cells required for JCV surveillance[2]. Treatment also mobilizes bone marrow CD19+ and CD 34+ cells containing JC virions into the periphery.[3]
- Current guidelines utilize a standard NTZ 300 mg dose administered every 4 weeks, but saturation of α4β1 integrin receptor on circulating lymphocytes is contingent upon NTZ serum concentrations, which may be influenced by individual metabolism, body mass[5] , and dosage amount and frequency[6,7].

Rationale

- After IV administration of a single 300 mg dose of NTZ, serum *concentrations* rapidly rise to 50-70 µg/dl and then gradually fall to 3-5 µg/dl over 4 weeks[4]
- After single dose NTZ infusion, $\alpha_4\beta_1$ integrin *saturation* reaches >80% (maximal saturation) and does not fall below 75% over 4 weeks[2].$\alpha_4\beta_1$ integrin desaturation occurs when NTZ serum concentrations fall below 1-2 µg/dl[6].
- At 6-8 weeks post-infusion $\alpha_4\beta_1$ saturation falls to approx. 70%[3] and at 8-10 weeks to about 40%[6,7].

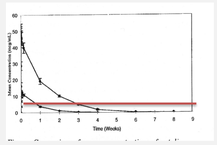


Figure 1. Serum concentration after single IV infusion[4]. Red line indicates 3 µg/ml[3] concentration (approximately) where receptor saturation is 70% or greater[6].

- **We hypothesized that extension of NTZ dosing schedule may produce an intermediate α4β1 integrin saturation that is sufficient to block auto-reactive T-cells from crossing the blood – brain – barrier ("MS-protective"), yet permit anti-JCV lymphocyte immune surveillance in CNS and/or the peripheral circulation (PML- protective) .**

Methods

- Retrospective analysis of data on patients treated with extended NTZ dosing
- from 6 large MS Centers across the US.
- Extended dosing was defined as 4weeks 3 days to 8weeks and 5 days (q32 – 61 days) for ≥ 3 consecutive doses.
- All patients were initially treated with standard q4 weeks dosing for ≥6 months, followed by extended dosing.
- Our analysis is restricted to extended dosing treatment period.
- Various treatment schedules were utilized by individual centers:
  - **Early Extended Dose only** (EED)* = 4w3d – 6w6d
  - **Late Extended Dose only** (LED) *= 7w0d – 8w5d
  - **Variable Extended Dose** (VED)* = exposure to both EED and LED schedules for variable durations

**Note: EED and LED were analyzed separately. VED is included together with EED and LED in total value calculations.*

- Chi square and Wilcoxon Rank Sum test was utilized to calculate the categorical and continuous variables, respectively. Annualized Relapse Rate was calculated using the negative binomial regression.

Results

Table 1. Baseline Demographic and Disease Characteristics

	Total	EED* only	LED* only	EED vs LED p- value
# of patients (n):	601	222	221	n/a
Female (%):	72%	80%	63%	<0.001
Age: mean ± st. dev. (range)	44.9 ± 12.2 (20-81)	47.2± 11.5 (20-77)	42.5 ±12.3 (20-78)	<0.001
JC Virus Detected status (%):	64%	63%	63%	0.61
Dz duration(years): mean ± st. dev (range)	12.1±7.4 (1-44)	13.5 ±7.7 (1-44)	10.7 ±6.8 (1-35)	<0.001
BMI: mean ± st. dev (range)	25.8 ±5.2 (13.7-51.2)	26.2± 5.2 (19.3-42.4)	25.4 ±4.5 (16.1-49.2)	0.18
Prior immunosuppression (% of patients):	21%	10%	33%	<0.001
Total NTZ Doses: mean ± st. dev (range)	39 ±20.3 (3-93)	47 ± 23.2 (8-92)	33 ±13.2 (10-71)	<0.001
Longest duration of ED schedule (months): mean ± st. dev (range)	21 ± 11.4 (3-72)	16 ±9.9 (3-39)	23±11.7 (3-27)	<0.001

**Note: EED and LED were analyzed separately. VED is included together with EED and LED in Total data calculations.*

Summary:

- **Annualized relapse rate in our cohort (n=601): 0.12 (Fig. 2)**
- **IV Steroids used:16% of patients (Fig. 3)**
- **New T2 Lesions were observed: 11% of patients (Fig.3)**
- **New Gadolinium-enhancing lesions: 5% of patients (Fig. 3)**
- **No evidence of clinical/MRI disease activity: 62% of patients (Fig. 4)**
- **Extended dosing discontinued: 32% of patients (Fig. 5)**
- **Current therapy: NTZ ED 68%, NTZ q4wks 5% (Fig.5)**
- **No cases of PML (0/601)**

Figure 2. Adjusted Annualized Relapse Rate

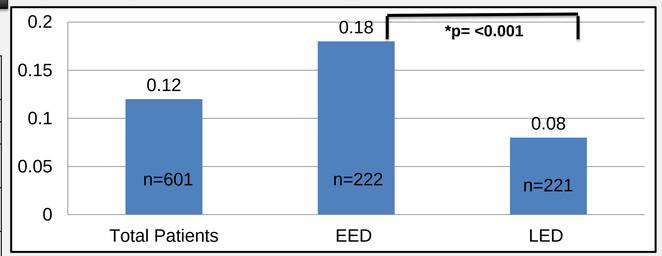


Figure 3. % of patients with clinical and/or radiographic Activity.

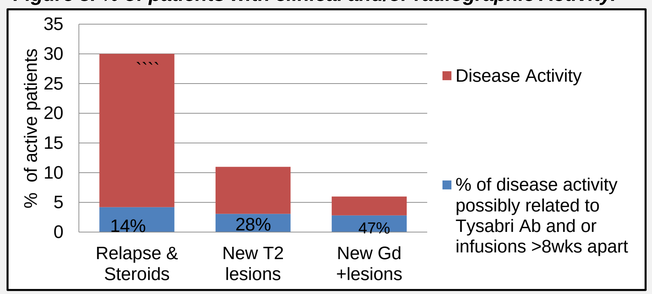


Figure 4. % of patients with No Evidence of Disease Activity (NEDA)

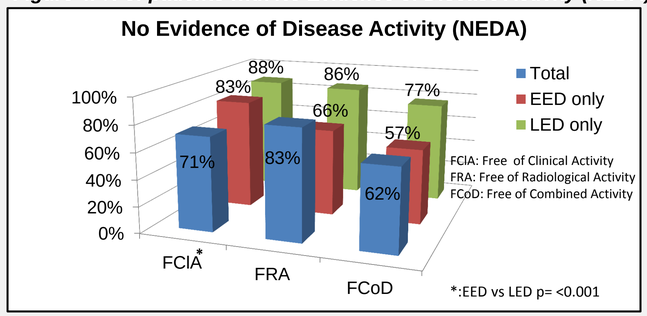


Figure 5. Current Therapy

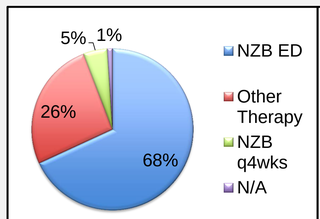
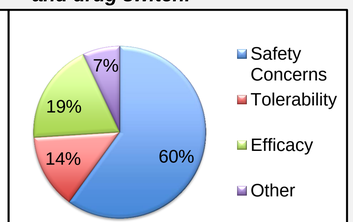


Figure 6. Reason for NZB d/c and drug switch.



PML Risk Calculation

- No cases of PML have been encountered so far.
- PML JCV-ab positive post-marketing incidence rate is 424 over 173,324 (crude but conservative estimate) person-years = 2.4 per1,000[8]
- Our cohort comprises 680 JCV-antibody positive person-years, so expected PML incidence so far is 1.6.
- Despite the promising trend, statistical significance not yet attained.
- For significance at 0.05 level we would need to observe zero PML cases over 1248 person-years. We are half-way there!

Discussion/Conclusions

- Extending the NTZ dosing schedule to q6-8 weeks does not appear to affect the excellent efficacy profile of drug.
- For reference purposes, we present comparative efficacy measures from the 2 pivotal NTZ phase 3 studies and TOP post-marketing study. We recognize the limitations inherent in differences in study design, data collection and disease-free definition

Clinical Trial	Relapse Rate	% relapse free	% free of new lesions	% free of combined activity
AFFIRM[9,10]	0.23	67%	57.7%	36.7%
SENTINEL[9,10]	0.34	54%	65.5%	31.7%
TOP[11]	0.31	56%	n/a	n/a
Current Cohort	0.12	71%	83%	62%

- Differences in EED and LED may reflect in part selection bias favoring patients who tolerate and are disease-free on q8 week NTZ, while others discontinue NTZ or transitioned to VED.
- Thus far no major unexpected adverse effects and no cases of PML have been reported. Although the PML trend is favorable, it has not yet achieved statistical significance. If the zero-PML trend continues to significance, it would support the concept of a dosing 'safety zone' which is protective of MS relapse but is also non-permissive of JC Virus activation.
- Further monitoring of this cohort and a prospective NTZ ED study are planned.

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- PML susceptibility may reflect NTZ-induced blockade of α4β1 integrin receptor that leads to excessive reduction in discrete tissue compartment trafficking of immune cells required for JCV surveillance.
- Current guidelines utilize a standard NTZ 300 mg q28 day regimen, but saturation of α4β1 integrin is maintained beyond 4-week period: at 6-8 weeks post-infusion $\alpha_4\beta_1$ saturation is ~70%[3] and at 8-10 weeks - ~40%[2,3].

We hypothesized that extension of Natalizumab dosing schedule may produce an intermediate α4β1 integrin saturation that is sufficient to block auto-reactive T-cell from crossing the blood-brain-barrier ('MS-protective'), yet permit anti-JCV lymphocyte immune surveillance in CNS (PML-protective).