Reducing Rebound Disease Activity in Relapsing Multiple Sclerosis Patients Electively Transitioned From Natalizumab to Teriflunomide

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Background/Objective

Natalizumab (NTZ) has proven to be an extremely effective therapy for patients with relapsing forms of Multiple Sclerosis (RMS). However, its use has been associated with increased risk of progressive multifocal leukoencephalopathy (PML) in patients exposed to John Cunningham virus (JCV). Discontinuance of NTZ in such patients has been associated with high rates of rebound relapse (RBR), particularly in the first 3-6 months post-NTZ discontinuation. Due to this increased post-NTZ RBR risk, which increases with washout duration, we initiated a prospective study of patients with clinically stable RMS, in whom teriflunomide (TFM) 14 mg daily was started within 4 weeks of their last dose of NTZ. We aim to determine if early introduction of teriflunomide (TFM) treatment would be safe and effective in reducing the risk of post-NTZ breakthrough MS disease activity. Here, we present the results of an interim analysis of patients who completed ≥ 6 months of TFM.

Methods

Adult patients with RMS, who had remained relapse-free for ≥ 12 consecutive months of NTZ treatment and were electively taken off NTZ due to the presence of serum anti-JCV antibodies were eligible to participate. After being successfully consented and screened, patients were switched to oral TFM, 14 mg daily, 4 ± 1 weeks after their last NTZ infusion. Physical and neurological exams, Expanded Disability Status Scale (EDSS), 3T brain MRI and labs were performed at baseline, monthly for 6 months, and 12, 18 and 24 months after initiating TFM.

Patient characteristics and discontinuation rates were summarized and reported. Changes in the EDSS, Symbol Digit Modality Test (SDMT), and Beck Depression Inventory (BDI-II) from baseline to 6 months and 12 months were tested with paired t or Wilcoxon rank sum, as appropriate after initiating TFM.

The risk of first relapse and first new lesion from baseline to 24 months were analyzed using Kaplan Meier analysis. Survival curves were plotted for all patients and by gender, age (<50 vs ≥50 years), disease duration (<15 vs ≥15 years), duration of prior NTZ treatment (<2 vs ≥2 years), baseline EDSS(<3 vs ≥3) , and number of relapses prior to NTZ treatment (0 vs ≥1). Log rank tests were used to compare survival curves between strata. Patients who either discontinued study or have not yet completed 24 months of follow up were considered censored.

Table 1. Patient demographic and baseline information

Demographics (N=50)	
Age, mean (SD)	48.2 (9.0)
Female, % (n)	76.0 (38)
White, % (n)	98.0 (49)
Disease Duration in years, mean (SD)	18.2 (7.6)
Duration of Teriflunomide use in months, mean (SD)	17.4 (6.1)
Duration of prior Natalizumab in months, median [IQR]	34.0 [20.5, 62.3]
Relapses in year prior to Natalizumab start, median [IQR]	1.0 [0.0, 2.0]
Years of formal education, median [IQR]	14.0 [12.0, 16.0]
Working at baseline, % (n)	58.0 (29)

Results

- 50 subjects, 76% female, baseline mean age of 48.2 ± 9 years, and completed ≥ 6 months of TFM therapy have been included in the analysis. Patient demographic and clinical information are presented in Table 1.
- 18 patients had a total of 26 new and/or enlarging T2 and/or gadolinium enhancing T1 brain MRI lesions: 9 within the first 6 months, 9 between months 7 and 12, and 8 between months 13 and 24 of TFM therapy.
- 7 patients had a total of 8 relapses: 2 relapses occurring within the first 12 months, and 6 occurring between months 13 and 24 of TFM therapy.
- 19 patients have discontinued TFM: 14 within first 12 months and 5 between 13 and 24 months. 16 patients had mild, non-critical (< 3 x ULN) hepatic liver enzyme elevations and 19 had hair thinning. No cases of PML have been observed.
- We found no significant changes in EDSS, SDMT, or BDI-II between baseline and 6 months (n=50) (Table 2) or between baseline and 12 months (n=44) (Table 3).

Table 2. EDSS, SDMT, and BDI for patients who completed 6 months (n=50)

	Baseline	Month 6	Change from baseline to month 6	P-Value
EDSS[a]	2.5 [2.0, 3.9]	2.5 [2.0, 3.4]	0.0 [-0.5, 0.0]	0.103
SDMT[b]	52.0 (11.5)	52.8 (11.7)	0.8 (-2.5, 1.0)	0.389
BDI[a]	5.0 [1.0, 10.8]	5.0 [2.0, 10.8]	0.0 [-2.8, 2.0]	0.739

[a]Median [IQR] reported and Wilcoxon signed rank test used
[b]Mean (SD) or (Lower CI, Upper CI) reported and paired t-test used

Table 3. EDSS, SDMT, and BDI for patients who completed 12 months (n=44)

	Baseline	Month 12	Change from baseline to month 12	P-Value
EDSS[a]	2.5 [2.0, 3.6]	2.5 [2.0, 4.0]	0.0 [-0.5, 0.5]	0.417[a]
SDMT[b]	52.2 (11.7)	53.2 (12.4)	1.0 (-0.9, 2.9)	0.278
BDI[a]	4.0 [1.0, 9.5]	5.0 [1.8, 11.3]	0.0 [-4.0, 4.0]	0.791

[a]Median [IQR] reported and Wilcoxon signed rank test used
[b]Mean (SD) or (Lower CI, Upper CI) reported and paired t-test used

- Kaplan Meier estimates for the risks of first relapse and first new lesion are shown in Figure 1 and Figure 2.
- Age, duration of disease, duration of NTZ treatment, and baseline EDSS had no significant impact on the risk of relapse during TFM therapy.
- Having ≥ 1 relapse prior to NTZ treatment significantly increased the risk of developing new MRI lesions (Figure 3) but it had no impact on the risk of having clinical relapses (Figure 4).
- We have observed trends of higher risk of relapse during TFM therapy in male patients (Figure 5) and higher risk of new MRI lesion in patients with longer disease duration (Figure 6).

Conclusion

Because of the heightened risk of PML occurring in NTZ-treated patients exposed to JCV, there is need for a strategy to transition such patient onto other disease modifying therapy. However these patients bear an increased risk of clinical relapses, which may exceed 30% of patients, particularly in the first 3-6 month post-NTZ interval (1, 2). Risk appears to be related, at least in part, to the duration of post-NTZ "washout" (2, 3). Our results demonstrate that elimination of the post-NTZ washout period entirely, combined with early TFM treatment initiation, was associated with only a 4.5% relapse rate during the first 12 months following NTZ withdrawal, a period during which the vulnerability to NTZ breakthrough relapses would be greatest. This relapse rate is well below the previously reported 30% or higher (1). Our study size is small, unblinded, and does not include active comparators, but has the advantages of being prospective, with frequent scheduled clinical and MRI assessments, and its results clearly argue for early initiation of an effective disease modifying therapy such as TFM, yielding better outcomes in reducing the risk of post-NTZ MS disease activity than with longer duration post-NTZ washouts.

Figure 1. Kaplan Meier Estimates for Risk of Relapse

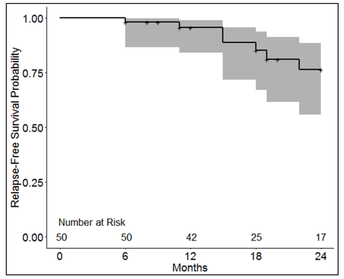


Figure 2. Kaplan Meier Estimates for Risk of New Lesion

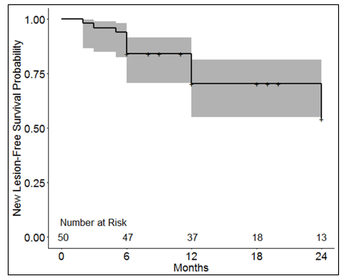


Figure 3. Kaplan Meier Estimates of New Lesion by Patient Relapse Prior to NTZ

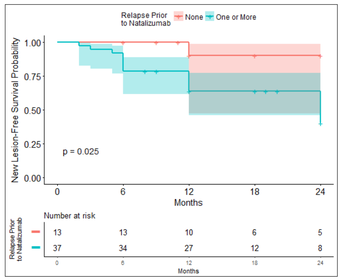


Figure 4. Kaplan Meier Estimates of Relapse by Patient Relapse Prior to NTZ

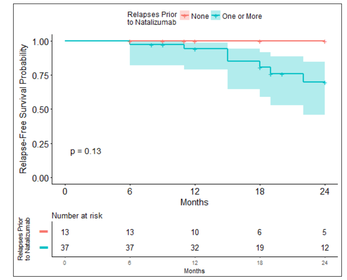


Figure 5. Kaplan Meier Estimates of Risk by Gender

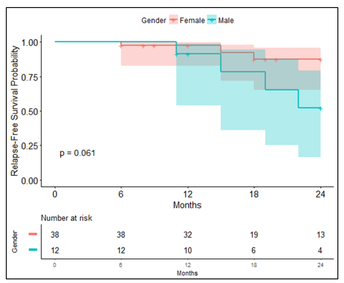
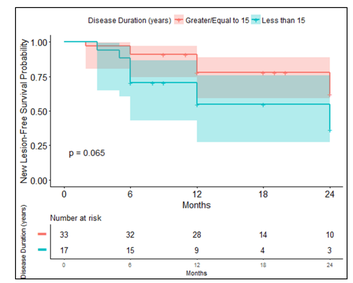


Figure 6. Kaplan Meier Estimates of Risk of New Lesion by Disease Duration



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