Original Research Paper

Reducing return of disease activity in patients with relapsing multiple sclerosis transitioned from natalizumab to teriflunomide: 12-month interim results of teriflunomide therapy

Stanley L Cohan, Keith Edwards, Lindsay Lucas, Tiffany Gervasi-Follmar, Judy O'Connor, Jessica Siuta, Vineetha Kamath, Lore Garten, Chiayi Chen 🄳, James Thomas, Kyle Smoot, Kiren Kresa-Reahl 🄳, Kateri J Spinelli

Abstract

Background: Natalizumab is an effective treatment for relapsing multiple sclerosis. Return of disease activity upon natalizumab discontinuance creates the need for follow-up therapeutic strategies.

Objective: To assess the efficacy of teriflunomide following natalizumab discontinuance in relapsing multiple sclerosis patients.

Methods: Clinically stable relapsing multiple sclerosis patients completing 12 or more consecutive months of natalizumab, testing positive for anti-John Cunningham virus antibody, started teriflunomide 14 mg/day, 28 ± 7 days after their final natalizumab infusion. Physical examination, Expanded Disability Status Scale, laboratory assessments, and brain magnetic resonance imaging were performed at screening and multiple follow-up visits.

Results: Fifty-five patients were enrolled in the study. The proportion of patients relapse-free was 0.94, restricted mean time to first gadolinium-enhancing lesion was 10.9 months and time to 3-month sustained disability worsening was 11.8 months. The mean number of new or enlarging T2 lesions per patient at 12 months was 0.42. Exploratory analyses revealed an annualized relapse rate of 0.08, and a proportion of patients with no evidence of disease activity of 0.68. Forty-seven patients (85.5%) reported adverse events, 95% of which were mild to moderate.

Conclusions: Teriflunomide therapy initiated without natalizumab washout resulted in a low rate of return of disease activity. Clinicians may consider this a worthwhile strategy when transitioning clinically stable patients off natalizumab to another therapy.

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Introduction

Cell-mediated inflammation is a hallmark of multiple sclerosis (MS) that contributes to neurological impairment and has prompted the development of disease-modifying therapies (DMTs) that destroy, suppress, or alter the pro-inflammatory behavior of cells, primarily lymphocytes and monocytes. Natalizumab, an effective monoclonal antibody therapy for relapsing multiple sclerosis (RMS),[1] inhibits migration of these cells into the central nervous system (CNS),[2] but increases the risk of developing progressive multifocal leukoencephalopathy (PML)

Correspondence to:
Stanley L Cohan,
Providence Multiple Sclerosis Center, Providence Brain and Spine Institute, 9135 SW Barnes Road, Suite 461, Portland, OR, USA 97225.

stanley.cohan@
providence.org

Stanley L Cohan,
Providence Multiple
Sclerosis Center, Providence
Brain and Spine
Institute, USA

Keith Edwards,
Multiple Sclerosis Center of
Northeastern
New York, USA

Lindsay Lucas,
Providence Multiple
Sclerosis Center, Providence
Brain and Spine
Institute, USA

Tiffany Gervasi-Follmar,
Providence Multiple
Sclerosis Center, Providence
Brain and Spine
Institute, USA

Judy O'Connor,
Multiple Sclerosis Center of
Northeastern
New York, USA

Jessica Siuta,
Multiple Sclerosis Center of
Northeastern
New York, USA

Vineetha Kamath,
Multiple Sclerosis Center of
Northeastern
New York, USA

Lore Garten,
Multiple Sclerosis Center of
Northeastern
New York, USA

Chiayi Chen,
Providence Multiple
Sclerosis Center, Providence
Brain and Spine
Institute, USA

James Thomas,
ImageCare, Medical Imaging
of Community Care
Physicians, USA

Kyle Smoot,
Providence Multiple
Sclerosis Center, Providence
Brain and Spine
Institute, USA

Kiren Kresa-Reahl,
Providence Multiple
Sclerosis Center, Providence
Brain and Spine
Institute, USA

Kateri J Spinelli,
Regional Research,
Providence Health and
Services, USA

in patients infected by John Cunningham virus (JCV).[3] Evidence of JCV exposure is found in more than 50% of the adult MS population.[4] PML risk in JCV-infected patients increases with the duration of natalizumab use, rates approximating 3/1000 for 2–4 years' use, 6/1000 for 4–6 years' use, and 12–13/1000 for patients who had also been treated with cytotoxic or immunosuppressant chemotherapeutic agents.[5]

PML risk has prompted the discontinuation of natalizumab in a large percentage of patients. However, studies have reported heightened MS disease activity after natalizumab withdrawal, including increased relapse frequency,[6–14] increased disease activity on magnetic resonance imaging (MRI),[8–10,14,15] increased relapse severity,[6,7] and relapse-related fatalities.[12,13] Several studies have not substantiated these observations.[15–17] To date there are few data on successful therapeutic strategies to transition patients off natalizumab while reducing the risk of disease reactivation.

The post-natalizumab use of glatiramer acetate, interferon beta or methylprednisolone was not beneficial for patients.[8] In a post-hoc, cross-sectional analysis, initiating dimethyl fumarate sooner than 90 days after the last natalizumab dose was associated with a lower risk of relapse.[18] In a retrospective study of patients switching to fingolimod, 61% of patients experienced relapse after discontinuing natalizumab, 48% of whom relapsed while receiving fingolimod, mostly occurring after 13–24 weeks of natalizumab washout.[7] In a prospective study of patients switching from natalizumab to fingolimod, 11.5% of patients relapsed within 6 months.[10] The odds ratio of relapse was 7.2 for patients with washout of 8–12 weeks versus those with 4 or fewer weeks' washout. A placebo controlled prospective study of fingolimod demonstrated a 9–12% and 16% relapse risk with natalizumab washout of up to 12 and 16 weeks, respectively, but a 61% relapse risk after a 3-month natalizumab washout.[19] Evidence of reduced disease activity on MRI was observed with fingolimod initiation within 8–12 weeks of stopping natalizumab.[15] These studies suggest that a longer duration of post-natalizumab washout increases the risk of resumed disease activity. In comparing fingolimod to rituximab, only 1.8% of rituximab-treated patients had a relapse, compared to 17.6% of fingolimod-treated patients, with no significant effect of differing natalizumab washout duration.[20]

This study examined teriflunomide as replacement therapy for clinically stable RMS patients taken off natalizumab because of prior JCV exposure. Teriflunomide, an approved medication for RMS treatment that inhibits de-novo pyrimidine synthesis by blocking mitochondrial dihydroorotate dehydrogenase, was selected because of its acceptable safety profile.[21,22] Higher efficacy medications such as alemtuzumab and ocrelizumab were not yet approved when this study began.

Materials and methods

Study design
This is a prospective, observational cohort study conducted at three US community-based MS clinics. Data from study initiation (July 2013) until the final patient completed month 12 (31 August 2017) are included. Eligibility criteria included age of 21–60 years, diagnosis of RMS, being relapse free for 12 months prior to screening visit, baseline Expanded Disability Status Scale (EDSS) between 1.0 and 6.0, no evidence of significant cognitive limitation or psychiatric disorder, stable brain MRIs in the 12 months prior to the screening visit, defined as no new or enlarged T2 or gadolinium-enhancing lesions, receiving at least 12 consecutive months of natalizumab treatment, and a positive serum anti-JCV IgG titer. After providing informed consent and completing study screening, patients started oral teriflunomide, 14 mg a day 28 ± 7 days after their last natalizumab infusion.

Physical examination, EDSS, adverse event (AE) and laboratory assessments, and concomitant medication review were performed at screening and baseline visits, monthly for 6 months, then at 9 and 12 months. Brain MRI was completed at screening, monthly for 6 months, and at 12 months. Symbol digit modality test (SDMT) and Beck depression inventory-II (BDI-II) were completed at baseline, 6 months and 12 months.

Patients at each site were studied on the same 3T scanner throughout the study. MRI sequences included axial and sagittal T2 fluid-attenuated inversion recovery (FLAIR), axial T1, axial T2, axial diffusion-weighted images, and axial spin-echo T1 following gadobutrol 0.1 mmol/kg administration. Axial and sagittal T2 FLAIR three-dimensional (3D) images were contiguous non-gapped 1 mm thick sections. Other images were contiguous non-gapped, 3 mm thick. Gadolinium T1 images were obtained after a 10-minute post-infusion delay,

with 1 mm 3D T1 magnetization prepared rapid acquisiton gradient echo (MPRAGE) sequences and 3 mm axial spin-echo T1-weighted sequences. Scans were reviewed by neuroradiologists with extensive experience in MRI MS assessment.

Study AEs were reported according to International Conference of Harmonization guidelines. Study approval was obtained from each site's institutional review board (IRB), and written informed consent was obtained from all participating patients. Continuing review for safety was performed by the IRBs throughout the study.

Trial endpoints

The primary study endpoint was the proportion of relapse-free patients at 12 months. Secondary endpoints included time to first gadolinium-enhancing lesion, time to 3-month sustained disability worsening (SDW), and the number of new or enlarging T2-weighted lesions. Non-pre-specified exploratory endpoints at 12 months included annualized relapse rate (ARR), mean number of gadolinium-enhancing lesions, the proportion of patients with no new or enlarged T2 lesions, no gadolinium-enhancing lesions, no evidence of SDW, and no evidence of disease activity (NEDA-3), defined as no occurrence of clinical relapses, SDW, gadolinium-enhancing, or new or enlarging T2 lesions. Changes in SDMT and BDI-II from baseline to 6 and 12 months were also examined (see Supplementary Figure 1).

A relapse was defined as new or worsened neurological symptoms, unassociated with fever or evidence of infection, lasting at least 24 hours, and an increase of 1 or more points in two or more functional scales, or 2 or more points in one functional scale. All patients reporting suspected relapse symptoms were evaluated within 7 days of onset by their study treating neurologist. All relapses were confirmed by the principal investigators (KE and SLC). SDW was defined as an increase of 1.5 or more points for patients with a baseline EDSS of 0, 1 or more points for patients with EDSS of 1–5, and 0.5 or more points for patients with EDSS of 5.5–6.0, sustained for 3 months. Patients with a 1 or more point increase in EDSS in whom a second measure was not obtained 3 months later were not included as SDW.

Statistical analysis

Analysis was based on an intention-to-treat model and included all enrolled patients who received at least one dose of teriflunomide. Patient characteristics were summarized as percentages, means (SD) or medians (interquartile range), as appropriate. Kaplan–Meier analysis was used to estimate the proportion of patients relapse free at 12 months. For secondary endpoints, restricted mean time to- first gadolinium-enhancing lesion and time to SDW were calculated as the area under the Kaplan–Meier curve up to 12 months and interpreted as the number of months, out of 12, a patient would be event free.[23] The mean number of new or enlarging T2 lesions at 12 months was calculated using negative binomial regression, with the number of lesions as the dependent variable and the natural logarithm of follow-up time as an offset.

In exploratory analyses, negative binomial regression was used to estimate the ARR and mean number of gadolinium-enhancing lesions at 12 months, with the number of events as the dependent variable and the natural logarithm of follow-up time as an offset. Kaplan–Meier analyses were used to estimate the proportion of patients with no new or enlarging T2 lesions, no gadolinium-enhancing lesions, no SDW at 12 months, and NEDA-3. Log rank tests were used to compare survival curves by the following subgroups: gender, age ($<$50 vs. $\geq$50 years), disease duration ($<$15 vs. $\geq$15 years), duration of natalizumab treatment ($<$2 vs. $\geq$2 years), baseline EDSS ($<$3 vs. $\geq$3 years), and the number of relapses in the year prior to starting natalizumab (0 vs. $\geq$1). Subgroup analyses were not pre-specified for this exploratory analysis, and no post-hoc adjustments for multiple comparisons were used.

Linear mixed-effects models (LMMs) were used to analyze the change in SDMT and BDI-II from baseline to months 6 and 12. Each model included time as a categorical fixed effect, patient as a random intercept, and an unstructured variance–covariance matrix. LMMs provide unbiased estimates in the presence of missing data under the assumption that the model is correctly specified and data are missing at random. Scatter plots of residuals were examined to assess lack of fit. Least squares means with standard errors and changes with 95% confidence intervals and *P* values were reported.[24] R packages MASS, survival, survminer, lme4, lmerTest, and ggplot2 were used for analyses and figures.

Results

Sixty-two patients were screened and 55 patients completed the baseline visit. Reasons for not completing the baseline visit included wanting to become pregnant (one), and as per protocol eligibility criteria, enhancing MRI lesions at screening
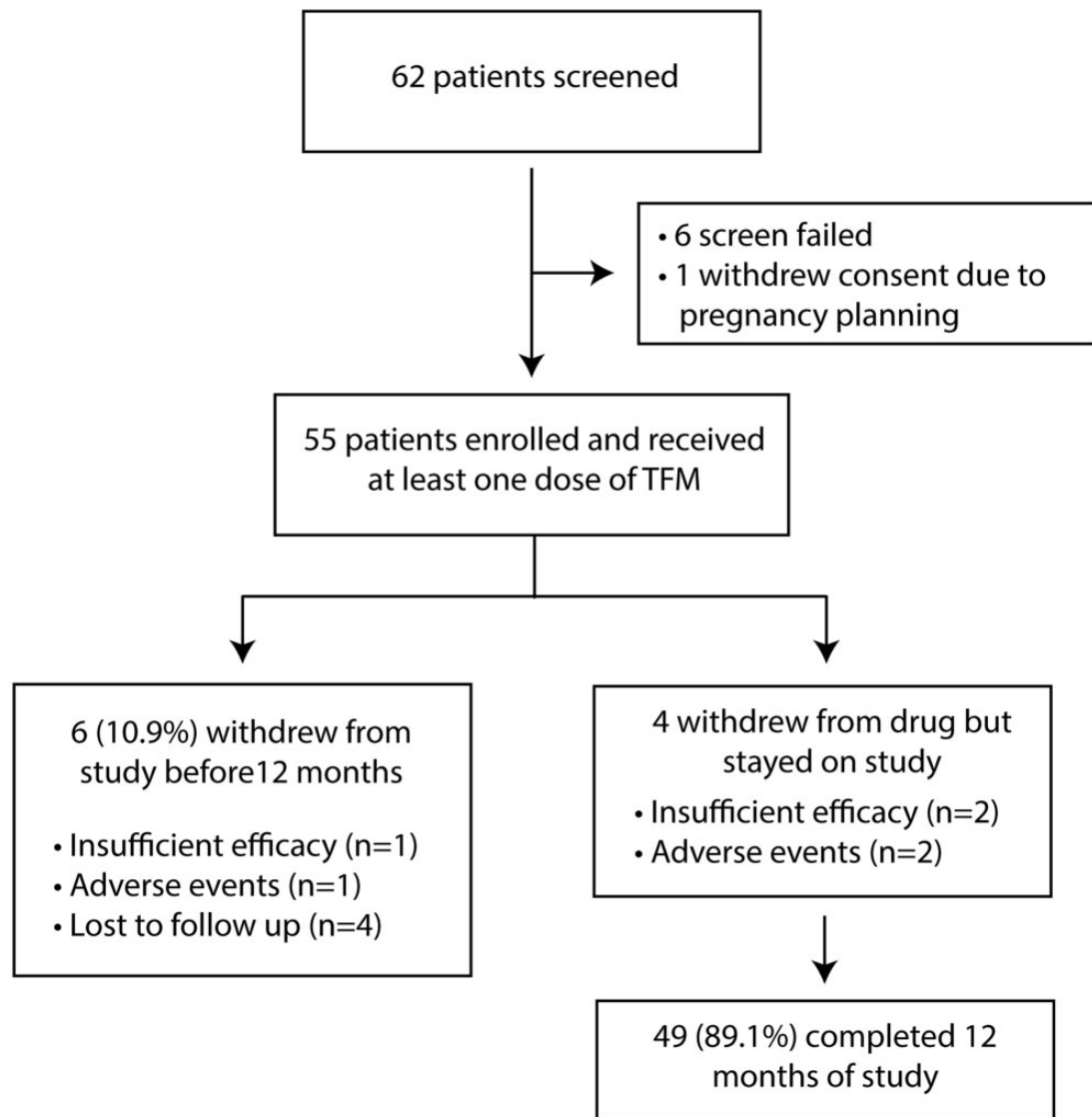
Figure 1. Patient attrition diagram. TFM: teriflunomide.

(four), negative JCV status (one), and severe depression at screening (one) (Figure 1). Of 55 patients completing the baseline visit, 49 (89.1%) completed 12 months of study. Two patients from site 1 withdrew at month 4 due to MRI progression (one) and severe diarrhea (one). All four patients from site 3 had no verifiable clinical or MRI data past the date of the site coordinator's unexpected death, however their clinical, safety, and imaging data were included in the analyses up to the date of the coordinator's death (follow-up of 2 months for two patients and 4 months for two patients), during which no relapses, MRI changes, or AEs were reported. Four of the 49 patients completing 12 months of study discontinued teriflunomide before 12 months: one at month 5 due

to relapse, one at month 5 due to MRI worsening, and two at months 9 and 11 due to AEs (Figure 1).

Of the 55 enrolled patients, 53 (96.4%) were white and two (3.6%) were African American, 42 (76.4%) were women, and the mean age was 47.2 years (±10.1, range 19–64 years) (Table 1). By 12 months, two patients had experienced one clinical relapse (months 3 and 5), and one patient had two clinical relapses (months 6 and 9) resulting in a relapse-free proportion of 0.94 (95% confidence interval (CI) 0.83, 0.98) (Table 2). Secondary endpoints included a restricted mean time to first gadolinium-enhancing lesion of 10.9 months (95% CI 10.1, 11.7), with first gadolinium-enhancing

Table 1. Demographic and disease characteristics of patients at baseline.

Characteristic	Value
Number of patients	55
Age in years, mean (SD); range	47.2 (10.1); 19–64[a]
Women, % (*n*)	76.4 (42)
Race, % (*n*)	
African American	3.6 (2)
White	96.4 (53)
Disease duration in years, mean (SD)	18.6 (8.4)
Years of formal education, median (IQR)	14 (12, 16)
Working at baseline, % (*n*)	58.2 (32)
Duration of prior natalizumab in years, median (IQR)	2.8 (1.5, 5.3)
ARR in year prior to natalizumab start	1.53
No relapses in year prior to natalizumab start, % (*n*)	23.6 (13)
EDSS at baseline, mean (SD); median (IQR)	3.0 (1.4); 2.5 (2.0, 3.8)
SDMT at baseline, mean (SD)	51.8 (11.3)
BDI-II at baseline, median (IQR)	5.0 (2.5, 11.0)

[a]Waivers were obtained to include one 19-year-old, one 62-year-old, two 63-year-olds, and one 64-year-old who did not meet inclusion criteria for age range of 21–60 years.

IQR: interquartile range; ARR: annualized relapse rate; EDSS: Expanded Disability Status Scale; SDMT: symbol digit modalities test; BDI-II: Beck depression inventory-II.

lesions found for 11 patients: three at month 3, one at month 4, four at month 6, and three at month 12. Two patients had SDW (months 4 and 9), resulting in a restricted mean time to SDW of 11.8 months (95% CI 11.4, 12.0). Thirteen patients had at least one new or enlarging T2 lesion: one at month 2, three at month 3, one at month 4, two at month 5, three at month 6, and nine at month 12, resulting in a mean number of new or enlarging T2 lesions per patient at 12 months of 0.42 (95% CI 0.23, 0.77) (Table 2).

Exploratory endpoints included an ARR of 0.08 (95% CI 0.02, 0.26) and a mean number of gadolinium-enhancing lesions per patient at 12 months of 0.34 (95% CI 0.18, 0.63). The 12-month new or enlarging T2 lesion-free proportion was 0.74 (95% CI 0.60, 0.84), the gadolinium-enhancing lesion-free proportion was 0.78 (95% CI 0.64, 0.87), and the SDW-free proportion was 0.96 (95% CI 0.85, 0.99). NEDA-3 was achieved in 39 patients by 12 months, resulting in a disease activity-free proportion of 0.68 (95% CI 0.53, 0.79) (Table 2; Figure 2). Patients with disease duration of less than 15 years were more likely to have gadolinium-enhancing lesions than those with 15 or more years (gadolinium-enhancing lesion-free proportion at 12 months 0.58 vs. 0.88; log rank *P*=0.011) (Figure 2). No other significant differences

in survival curves were found for gender, age, disease duration, duration of prior natalizumab treatment, baseline EDSS, or the number of relapses in the year prior to starting natalizumab. There were no significant changes in SDMT or BDI-II from baseline to 6 or 12 months (Table 2).

Forty-seven patients (85.5%) reported AEs, of which 95% were mild to moderate and 5% were severe (see Supplementary Table 1). Serious, most commonly reported (five or more occurrences), and AEs causing teriflunomide withdrawal are presented in Table 3. There were 10 serious AEs reported in five patients, six of which occurred in the same patient: *Staphylococcus aureus* empyema, pleural effusion, pneumothorax and secondary brain abscess with subfalcial herniation, and obstructive hydrocephalus. This patient at no time had leukopenia, but had absolute lymphocyte counts of $0.7 \times 10^{9/L}$ before, and $0.3–1.1 \times 10^{9/L}$ during and after resolution of the AEs (reference range $1.0–4.8 \times 10^{9/L}$). In the remaining four patients, there was one case each of ruptured gangrenous appendicitis, pneumonia, pyelonephritis, and localized squamous cell carcinoma (Table 3). All five patients recovered.

The top five most reported AEs included hair thinning or loss (36.4%), diarrhea or loose stool (30.9%), headache (21.8%), nausea/vomiting

Table 2. Clinical endpoints during 12-month study (intention-to-treat population).

	No. of patients 55	
	By month 6	By month 12
Primary endpoint		
Patients relapse-free,		52
Proportion (95% CI)		0.94 (0.83, 0.98)
Number of relapses, *n* (%)		
0	52 (95%)	52 (95%)
1	3 (5%)	2 (4%)
2	0 (0%)	1 (2%)
Secondary endpoints		
Mean time to first-GAD+ lesion (95% CI), in months[a]		10.9 (10.1, 11.7)
Mean time to 3-month sustained disability worsening (95% CI), in months[a]		11.8 (11.4, 12.0)
Mean number of new or enlarging T2 lesions (95% CI)		0.42 (0.23, 0.77)
Number of new or enlarging T2 lesions, *n* (%)		
0	48 (87%)	42 (76%)
1	4 (7%)	9 (16%)
≥2	3 (5%)	4 (7%)
Exploratory endpoints		
Annualized relapse rate (95% CI)		0.08 (0.02, 0.26)
Mean number of GAD+ lesions (95% CI)		0.34 (0.18, 0.63)
Number of GAD+ lesions, *n* (%)		
0	47 (85%)	44 (80%)
1	5 (9%)	6 (11%)
≥2	3 (5%)	5 (9%)
Patients free of new or enlarging T2 lesions, *n*		42
Proportion (95% CI)		0.74 (0.60, 0.84)
Patients free of GAD+ lesions, *n*		44
Proportion (95% CI)		0.78 (0.64, 0.87)
Patients free of 3-month sustained disability worsening, *n*		53
Proportion (95% CI)		0.96 (0.85, 0.99)
Patients achieving NEDA-3,[b] *n*		39
Proportion (95% CI)		0.68 (0.53, 0.79)
Symbol digit modalities test		
Mean (SE)[c]	53.2 (1.6)	52.9 (1.6)
Change from baseline (95% CI)	1.4 (−0.4, 3.1) *P*=0.134	1.0 (−0.8, 2.8) *P*=0.254
Beck depression inventory-II		
Mean (SE)†	7.0 (1.0)	8.3 (1.0)
Change from baseline (95% CI)	−0.2 (−2.5, 2.0) *P*=0.828	1.1 (−1.1, 3.4) *P*=0.314

[a]Restricted mean with upper limit of 12 months estimated from Kaplan–Meier survival curve.
[b]NEDA-3 defined as no occurrence of clinical relapses, sustained worsening in EDSS, GAD+ lesions, or new or enlarging T2 lesions.
[c]Least squares mean with standard error estimated from linear mixed model.
GAD+: gadolinium enhancing; CI: confidence interval; IQR: interquartile range; SE: standard error.
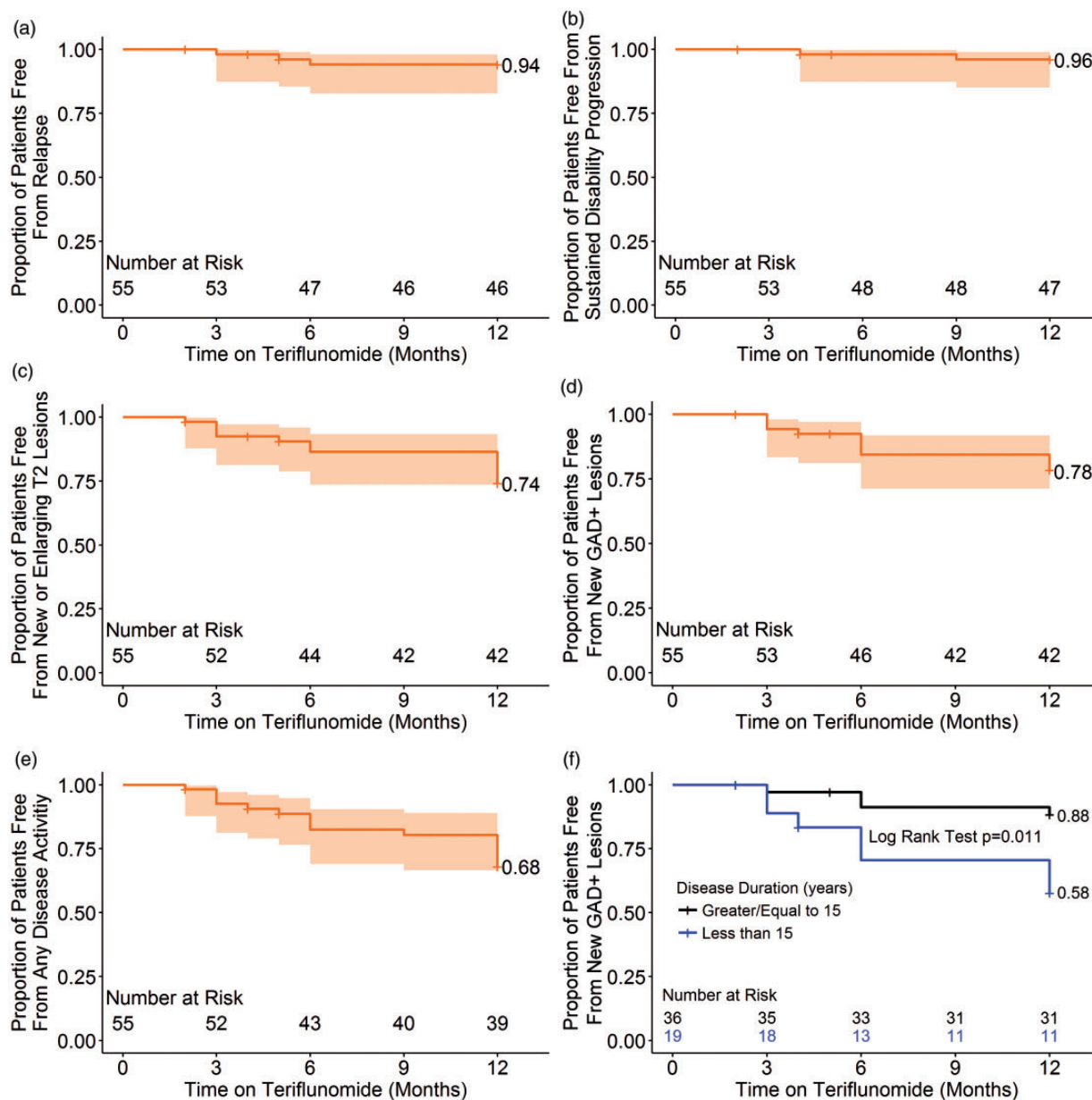
Figure 2. Survival analysis. Results indicate a high proportion of patients free from (a) relapse, (b) sustained disability worsening, (c) new or enlarging T2 lesions, (d) new gadolinium-enhancing lesions, and (e) evidence of disease activity. (f) Subgroup analyses indicate that patients with disease duration of less than 15 years are more likely to have new gadolinium-enhancing (GAD+) lesions. For panels (a) to (e), solid lines denote Kaplan–Meier estimate and shaded areas denote 95% confidence intervals.

(20.0%), and vertigo/balance difficulties/dizziness (20.0%) (Table 3). Additional common side effects of teriflunomide included elevated transaminases (none greater than $3\times$ upper limit of normal) (14.6%), leukopenia (1.8%), and peripheral neuropathy (3.6%) (see Supplementary Table 1). There were no cases of PML, other opportunistic infections or deaths. Three patients discontinued teriflunomide due to AEs, one due to diarrhea, one due to

leukopenia, abscessed tooth, and dental infection after implant, and the patient with empyema, pleural effusion, and moderate lymphopenia (Table 3).

Discussion

Strategies are needed for transitioning natalizumab-treated, JCV-positive MS patients to other therapeutic agents to mitigate PML risk, while reducing the

Table 3. Adverse events.

	Mild–moderate No. of patients (%)	Severe No. of patients (%)
Serious adverse event		
Brain abscess	0 (0)	1 (1.8)
Empyema[a]	0 (0)	1 (1.8)
Gangrenous appendicitis, ruptured	0 (0)	1 (1.8)
Obstructive hydrocephalus	0 (0)	1 (1.8)
Pleural effusion[a]	0 (0)	1 (1.8)
Pneumonia	0 (0)	1 (1.8)
Pyelonephritis	1 (1.8)	0 (0)
Right pneumothorax	0 (0)	1 (1.8)
Squamous cell carcinoma, left ankle	0 (0)	1 (1.8)
Subfalcial herniation	0 (0)	1 (1.8)
Adverse events with five or more patients		
Hair thinning/loss	20 (36.4)	0 (0)
Diarrhea[b]/loose stool	17 (30.9)	1 (1.8)
Headache	12 (21.8)	0 (0)
Nausea/vomiting	11 (20.0)	0 (0)
Vertigo/balance difficulty/dizziness	11 (20.0)	0 (0)
Fatigue	10 (18.2)	0 (0)
Tingling/paresthesia	10 (18.2)	0 (0)
Upper respiratory infection	10 (18.2)	0 (0)
Cognitive changes	8 (14.6)	0 (0)
Elevated transaminases	8 (14.6)	0 (0)
Extremity joint pain	8 (14.6)	0 (0)
Other infections	8 (14.6)	0 (0)
Sensory decrease/disturbance	8 (14.6)	0 (0)
Urinary tract infection	8 (14.6)	0 (0)
Depression	7 (12.7)	1 (1.8)
Rashes/eczema	7 (12.7)	0 (0)
Abdominal pain/discomfort	6 (10.9)	0 (0)
Anxiety	6 (10.9)	0 (0)
Ophthalmic changes	6 (10.9)	0 (0)
Decreased appetite	5 (9.1)	0 (0)
Heartburn	5 (9.1)	0 (0)
Hypertension	5 (9.1)	0 (0)
Stiffness/spasticity	5 (9.1)	0 (0)
Migraine	3 (5.5)	2 (3.6)
Additional adverse events causing teriflunomide withdrawal		
Abscessed tooth, left molar[c]	1 (1.8)	0 (0)
Dental infection secondary to implant[c]	1 (1.8)	0 (0)
Leukopenia[c]	1 (1.8)	0 (0)
Lymphopenia[a]	1 (1.8)	0 (0)

Percentages are based on total number of enrolled patients ($N=55$). All adverse events ($N=342$) reported for those who experienced adverse events as of the date the final patient completed the month 12 visit ($N=47$). Relapse and progression of multiple sclerosis were not reported as adverse events, as these were categorized separately for reporting in the main text.
[a]One patient discontinued due to severe empyema, severe pleural effusion, and mild to moderate lymphopenia.
[b]One patient discontinued due to severe diarrhea.
[c]One patient discontinued due to mild to moderate leukopenia, abscessed tooth and dental infection.

risk of MS activity recurrence. Based on pharmacodynamics, clinical and MRI data, natalizumab retains therapeutic activity for 3 or more months after the last dose,[17,25] leading some clinicians to employ post-natalizumab washout periods of 3 or more months because of potential risks of substituting another DMT while natalizumab is still therapeutically active. However, the return of MS disease activity may correlate with longer post-natalizumab washout durations.[7,8,15,18] Analyses of immune cell populations during natalizumab therapy suggest potential mechanisms to explain the timing of returned, and in some cases heightened, MS disease activity following natalizumab discontinuation. Sustained natalizumab treatment was associated with increased circulating T cells, B cells and monocytes,[26–30] possibly from impaired cell migration into the CNS, and elevated mobilization of T and B cell stem cells.[31] Return to baseline lymphocyte levels and subtherapeutic alpha 4 integrin saturation required up to 16 weeks after the last natalizumab dose.[32] Natalizumab-treated patients had upregulation of interleukin (IL)-17 and IL-22-producing CD4+ and CD8+ T cells,[27,29] preferential transmigration of T-helper 17 cells into the CNS,[33] upregulation of IL-17 receptors on endothelial cells,[33] increased mRNA expression and circulating levels of pro-inflammatory cytokines.[27] These changes may set the stage for elevated disease activity following natalizumab discontinuation.

The introduction of a new DMT can be guided by the timing of the therapeutic onset of that DMT before the efficacy of natalizumab ceases, which is estimated to be approximately 16 weeks.[32] Pharmacodynamic studies of teriflunomide have demonstrated therapeutic effects on MRI activity and relapses within 6 weeks of its initiation.[34] This largely informed our strategy to eliminate natalizumab washout and introduce teriflunomide at the time patients would have received their next natalizumab infusion. Although there may be concern for the risks of adding a second DMT while natalizumab is still biologically active, only one reported patient developed PML after 3 months of teriflunomide and 8 months after discontinuing natalizumab.[35] To our knowledge, there are no reports of the risk of other opportunistic infections.

To increase our ability to detect disease reactivation, we obtained monthly brain MRIs for the first 6 months, a time interval that has a high risk of post-natalizumab relapse.[6–11] Initiating teriflunomide at the time patients were due for their next natalizumab infusion was associated with low 12-month relapse risk (proportion of relapse-free patients 0.94), and only two patients (4%) experienced SDW, in contrast to some post-natalizumab outcomes previously reported.[6–9,12,13] While direct comparisons to other reported studies of post-natalizumab DMT cannot be made, the low risks of relapse and SDW we observed may provide potential guidelines for transitioning patients off natalizumab. Although 15% of our patients had gadolinium-enhancing scans within the first 6 months, most of these would have gone undetected if the common practice of MRI scanning 6–12 months after changing therapy had been followed. The safety and side-effect profile in our study was similar to those of larger teriflunomide controlled clinical trials,[15,16,] further supporting no increased risk from initiating teriflunomide without natalizumab washout.

The potential shortcomings of this study include its open label design, the absence of a comparator DMT, and the small number of subjects. The proportion of relapse-free patients (94%) is higher than the approximately 76% reported in the pivotal teriflunomide clinical trials,[21,22] but may reflect our smaller cohort size and only 12 months of observation, and may increase as we extend the study duration to 24 months. Excluding patients with enhancing MRI lesions at screening may introduce selection bias, which would not be likely to occur in routine clinical practice and did not occur in the teriflunomide placebo controlled trials.[21,22] No cases of PML or other opportunistic infections were observed, which may be related to the small cohort and only one year of observation, but is consistent with the sole report of PML in a patient being treated with teriflunomide.[35] This study was not designed to examine the comparative efficacy and safety of other DMTs, nor were clinical neurologists or the patients blinded to the treatment employed.

The strengths of this study include high frequency, rigorous attention to consistency and quality of MRI scanning, and the reading of all MRIs by pre-designated neuroradiology MS experts. All patients at each site were studied on the same 3T scanner throughout the study. Each patient was clinically assessed at every visit by the same neurologist, who had extensive experience in MS patient care, evaluation and clinical research, using prespecified criteria for relapses and disability progression.

Our results suggest that teriflunomide use without washout is a potentially effective therapy for stable

patients being taken off natalizumab, with a low risk of post-natalizumab relapses and an acceptable safety profile. This is the first prospective study of teriflunomide that addresses the issue of recurrent or increased MS disease activity following natalizumab withdrawal. These results may prompt further investigation of 'no washout' strategies with other DMTs in the post-natalizumab setting.

Author contribution

SLC, KE, and JT contributed to the study design; TGF, JO, JS and VK contributed to data collection and management; LL performed statistical analyses; SLC, KE, LL, TGF, CC, LG, KS, KKR and KJS contributed to the interpretation of results; SLC, KE, JT, LL, TGF, CC and KJS participated in writing the manuscript; and SLC, KE, LL, TGF, JO, JS, VK, LG, CC, JT, KS, KKR and KJS critically reviewed the manuscript.

Conflict of Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SLC has served on advisory boards or steering committees for Biogen, Novartis, Sanofi Genzyme; has received research support from Biogen, Novartis, Sanofi Genzyme, MedDay, Mallinckrodt, Genentech, IMS Health, and Roche; has received speaker honoraria from Biogen, Novartis, Sanofi Genzyme, Roche Genentech and Acorda. KE has received consulting fees from Biogen, Genzyme, EMD Serono and research support from Biogen, Eli Lilly, Genentech, Novartis and Sanofi-Genzyme. KS has received research support from Biogen, MedDay, and IMS Health and speaking and consulting fees from Biogen, EMDSerono, Genentech, Genzyme, Novartis, and Teva. KKR has received speaking honoraria from Biogen, Novartis, TEVA, Mallinckrodt, and Sanofi Genzyme and research support from Biogen, Novartis, Mallinckrodt, and Genzyme and consulting fees from EMDSerono and Genentech. LL, TGF, JO, JS, VK, LG, CC, JT and KJS have no disclosures to report.

Supplemental Material

Supplemental material for this article is available online.

ORCID iD

Chiayi Chen http://orcid.org/0000-0001-6636-5203
Kiren Kresa-Reahl http://orcid.org/0000-0001-7095-1520

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