

Effectiveness of teriflunomide in patients with relapsing multiple sclerosis who switched from other disease-modifying therapies

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Abstract

To examine effectiveness of teriflunomide in patients with multiple sclerosis (MS) who switched to teriflunomide from other disease-modifying therapies (DMTs). Retrospective, observational, pre-post analysis of adults with relapsing MS (RMS; relapsing-remitting MS or active secondary progressive MS [aSPMS]) with prescription for teriflunomide between September 1, 2012, and March 31, 2019, and had been treated with another disease-modifying therapy ("switched"). Data were extracted from medical-chart data from a single US neurology center in California. Index was the date of teriflunomide initiation. Data were extracted at 1-year pre-index, index, and 1- and 2-years post-index. Patients were observed until death, loss to follow-up, or study end. A subgroup of patients with aSPMS were also examined. For inferential comparisons, significance was assessed using paired *T*-test or Wilcoxon rank sum test, as appropriate. *P* < .05 was considered significant. Eighty patients with RMS formed the main analysis. At index, mean (±SD) age was 44.0 ± 14.6 years, 71.3% were female, mean duration of MS was 9.3 ± 6.4 years. Mean duration of teriflunomide use was 24.9 ± 14.2 months. Magnetic resonance imaging of lesions were "stable" or "improved" in most patients at baseline (92.5%), at 1-year (95.1%) or 2-years (97.6%). Mean annualized relapse rate decreased by 80.8%, from 0.26 at 1-year pre-teriflunomide initiation to 0.05 at 2-years post-index (*P* < .001). Mean Expanded Disability Status Scale (EDSS) score slightly increased from 1-year pre-index to 1-year post-index (3.84 vs 3.90, respectively; difference: −0.06 [*P* = .033]) but was nonsignificant from index to 2-years post-index (3.84 vs 3.94; difference: −0.06 [*P* = .058]). Montreal Cognitive Assessment and timed 25-foot walk test scores remained stable through follow-up. A decrease in proportion of patients with lymphopenia was recorded from index (30.0%) to 2-years post-index (1.3%). In the subset of patients with aSPMS (*n* = 32), mean annualized relapse rate reduced from 1-year pre-index to 2-years post-index (0.4 vs 0.03; change: −0.38 [*P* < .001]). EDSS, Montreal Cognitive Assessment, and timed 25-foot walk test scores remained stable in patients with aSPMS. After switching to teriflunomide, patients with RMS (relapsing-remitting MS or aSPMS) experienced a reduction in relapses and evidence for recovery from lymphopenia. Other markers of disability worsening, including EDSS, remained stable after switching to teriflunomide.

Abbreviations: ARR = annualized relapse rates, aSPMS = active secondary progressive MS, DMTs = disease-modifying therapies, EDSS = Expanded Disability Status Scale, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, MS = multiple sclerosis, RMS = relapsing MS, RRMS = relapsing-remitting MS, T25FW = timed 25-foot walk.

Keywords: active secondary progressive multiple sclerosis, effectiveness, observational, real world, relapsing remitting multiple sclerosis, teriflunomide

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1. Introduction

Multiple sclerosis (MS) is a chronic, incurable, neurodegenerative disorder, with a heterogeneous disease course that generally results in accumulation of disability.^[1,2] The burden of MS is substantial and is further exacerbated by comorbidities including depression, anxiety, and chronic pain.^[3] The most common MS phenotype is relapsing-remitting MS (RRMS), which accounts for approximately 85% of the MS population.^[4] RRMS is typically defined by episodes of acute worsening of neurologic functioning followed by periods of total or partial recovery (remission) but no apparent progression of disease.^[2,5] Progressive MS phenotypes are categorized as primary progressive MS and secondary progressive MS (SPMS).^[1] Importantly, each MS phenotype allows a time-specific assessment of the disease within an individual, and these have been successfully used by clinicians, clinical trialists, and regulatory authorities to aid clinical study and drug development.^[1] For example, at least 50% of RRMS patients progress over ~10 years to SPMS,^[6,7] although progression may be slowed by disease-modifying therapies (DMTs).^[8] MS diagnosis should be regularly monitored and assessed.^[1,5,9]

DMTs are the cornerstone of MS treatment and are used to suppress focal inflammation, thereby reducing the frequency and severity of relapses and MS lesions.^[10,11] However, while DMTs can reduce disease activity and slow the accumulation of disability, most patients still experience disability progression.^[12] Teriflunomide, an oral DMT taken once daily, has demonstrated efficacy in clinical trials in patients with relapsing MS (RMS), including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.^[13–17] Clinical observations have consistently shown improvements in annualized relapse rates (ARRs), disability (using the Expanded Disability Status Scale [EDSS]), and improved magnetic resonance imaging (MRI) outcomes.^[13–17] Real-world studies have supported these data to demonstrate improvements in treatment satisfaction and stability of disability measures in patients treated with teriflunomide across different areas of the world.^[18,19] In particular, the advantages of teriflunomide's oral administration over injectable therapies have previously been highlighted in relation to patient convenience, preference, and adherence.^[20–22]

In real-world clinical practice, switching DMTs when establishing a treatment regimen occurs in approximately 45% to 85% of patients with existing MS,^[18,19,23] and in approximately 35% of patients with newly diagnosed MS.^[24] The reasons for switching DMTs are multifaceted and are influenced by both clinical factors like treatment efficacy, safety, and tolerability, as well as personal considerations such as lifestyle and convenience.^[25–28] While some real-world studies have reported on switching to teriflunomide from other DMTs, these studies are somewhat limited in scope. For example, studies have focused on patient-reported outcomes,^[18] included data solely on relapses as the only surrogate measure of effectiveness,^[29] had a limited sample size,^[30] or focused on switching from natalizumab for reasons of safety.^[31,32] As such, real-world data in patients with RMS (incorporating patients with RRMS and active secondary progressive MS [aSPMS]) who have switched therapy to teriflunomide from other DMTs are relatively limited, and little is known about the range of characteristics in these patients, including assessment of mobility, cognitive scores, and/or relapses. This study sought to describe characteristics of patients with MS who switched to teriflunomide from another DMT, within a single neurology center in California, and to examine the effectiveness of teriflunomide among these patients with RMS.

2. Materials and methods

2.1. Study design and data source

This was a retrospective, observational, pre-post analysis using medical-chart data of patients with RMS (incorporating patients

with RRMS and aSPMS) from a single US neurology center. The deidentified dataset contained information on patient characteristics (e.g., demographics, comorbidities, and treatment patterns) and on clinical outcomes and MRI. The study was approved by a central Institutional Review Board. The Board found that this research met general requirements for a waiver of informed consent under 45 CFR 46.116(d).

2.2. Patient population and time frame

Adults (aged > 18 years) with MS were identified who had a prescription history for teriflunomide (current or past) between September 1, 2012, and March 31, 2019, and who had been treated with other DMTs but then were “switched” to receive teriflunomide treatment. The index date was defined as the date of teriflunomide initiation (prescription filled). All screened patients (N = 80) were eligible for inclusion in the study. Data were extracted at 4 time points (for applicable measures): 12 months before index date (1 year pre-index), index (date of switching to teriflunomide), 12 months after index date (1 year post-index), and 24 months after index date (2 years post-index). Patients were observed until death, loss of follow-up, or end of study period; thus, sample sizes varied for certain measurements. Patients who were pregnant or wished to become pregnant were excluded. A planned subanalysis examined a subgroup of patients with aSPMS with a prescription history for teriflunomide and who were switched from other DMTs to teriflunomide therapy within the extraction window.

2.3. Study measures and analysis

At 1 year pre-index and at index, demographics and disease- and treatment-related characteristics (i.e., duration of MS, MS subtype, family history, smoking status, comorbidities, symptomatic medication, and latest DMTs) were extracted. Other measures assessed at index and/or at 1 or 2 years post-index (depending on duration of follow-up) included teriflunomide dose-modification details, duration of therapy, and concomitant medication use. The following outcomes were measured at all 4 time points: disability (EDSS score [higher score denotes greater disability] administered by a certified neurologist; ambulatory-aid use, timed 25-foot walk [T25FW] test administered by an MS-experienced registered nurse), number of relapses, MRI lesions (comparing 1-year and 2-year post-index MRI scans with the previous year [worsened, stable, improved]), cognition (Montreal Cognitive Assessment [MoCA; lower score denotes greater cognitive impairment] administered by an MS-experienced nurse),^[33] and lymphopenia.

2.4. Statistical analysis

Descriptive statistics are reported for all measures. Patient demographics and other characteristics were summarized before or at the time of teriflunomide initiation. For the clinical and imaging outcomes, unadjusted statistical comparisons were performed comparing measures at the following time points (where applicable): 1 year pre-index versus 1 year or versus 2 years post-index; index versus 1 year or versus 2 years post-index. Use of concomitant medications and teriflunomide use were reported descriptively over 1- and 2-year follow-up periods. For inferential comparison of outcomes pre- versus post-teriflunomide use, a paired T-test was used to assess statistical significance for continuous variables (such as EDSS), and a Wilcoxon rank-sum test if the data were not normally distributed, as appropriate. $P < .05$ was considered significant for all analyses. Missing data were excluded from the statistical analyses. All data transformations and statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC).

3. Results

3.1. RMS analysis

3.1.1. Demographic and clinical characteristics. A total of 80 patients with RMS were included in the analysis (Table 1). At index, the mean ($\pm$ SD) age was 44.0 ± 14.6 years, the majority of patients were female (71.3%) and covered by private medical insurance (72.5%), and 51.3% and 20.0% were self-categorized as White or multiracial, respectively. Average duration of MS was 9.3 ± 6.4 years and mean ($\pm$ SD) EDSS score was 3.88 ± 1.76 . The most prevalent comorbidities in the 1-year pre-index period were depression (63.8%), neurogenic bladder (30.0%), and spasticity (26.3%). The majority of patients ($n = 76$ [95.0%]) remained on a stable dose of 14-mg teriflunomide throughout the study. Mean ($\pm$ SD) duration of teriflunomide use was 24.9 ± 14.2 months.

Before switching to teriflunomide, dimethyl fumarate was the most commonly used DMT (22.5%), followed by glatiramer acetate (18.8%) and natalizumab (16.3%; Table 1). Selective serotonin reuptake inhibitors were the most commonly used concomitant medication (50.0%) followed by dalfampridine (33.3%) and baclofen (19.2%). Infection (most commonly urinary tract infection) was cited as the most common reason for switching from a prior DMT (28.8%; Table 1). Of the 23 patients who switched because of recurrent infection on a prior DMT, only 3 patients still experienced infection after switching to teriflunomide.

3.1.2. Outcomes in RMS cohort. Mean ARR decreased by 80.8% following switching to teriflunomide, from 0.26 relapses at 1 year pre-index to 0.05 relapses at 2 years post-index (change: -0.21 [0.47]; $P < .001$; Table 2). MRI lesions were stable or improved in most patients following switching to teriflunomide (1 year post-index: 95.1%; 2 years post-index: 97.6%) compared with before switching to teriflunomide therapy (1 year pre-index, 80.1%; Table 2).

Mean EDSS score slightly increased between 1 year pre-index to 1 year post-index, but otherwise remained stable throughout (3.84 at 1 year pre-index to 3.90 at 1 year post-index; $P = .033$; Table 2). Ambulatory-aid use, T25FW test, and patient MoCA scores were also stable across the study period (Table 2).

The proportion of patients with lymphopenia decreased from 30.0% ($n = 24$) at index to 6.3% ($n = 5$) at 1 year post-index and 1.3% ($n = 1$) at 2 years post-index. Notwithstanding in the small number of patients who experienced lymphopenia, lymphocyte count increased from index across the 2-year follow-up period (Table 2).

3.2. aSPMS subgroup analysis

3.2.1. Demographic and clinical characteristics. A subgroup analysis included 32 patients with aSPMS, representing 40% of the main RMS cohort. Observations followed a similar pattern as those in the main RMS analysis, with a few notable differences: the mean (SD) age was slightly older (51.4 [13.8] years); the duration of MS was about 1 year longer (10.7 [6.5] years); and the mean (SD) EDSS score at index was higher (5.48 [0.97]; Table 1), as might be expected.

Before switching to teriflunomide, glatiramer acetate was the most widely used DMT (21.9%), followed by dimethyl fumarate, interferon beta-1a, and natalizumab (all 15.6%; Table 1). Similar to the main analysis, depression (50.0%) was common, while neurogenic bladder (50.0%), spasticity (46.9%), and pseudobulbar affect (34.4%) were all more frequently recorded than in the main RMS cohort (Table 1). Lack of efficacy was the most frequent reason cited for switching from the prior DMT (40.6%) to teriflunomide (Table 1).

Table 1

Index* characteristics for the relapsing multiple sclerosis (RMS) and active secondary progressive multiple sclerosis (aSPMS) cohorts

	RMS patients who switched to teriflunomide (N = 80)	aSPMS patients who switched to teriflunomide (N = 32)
Age, yr, mean (SD)	44.0 (14.6)	51.4 (13.8)
Female, n (%)	57 (71.3)	23 (71.9)
Race, n (%)		
Black or African American	6 (7.5)	3 (9.4)
Multiracial	16 (20.0)	9 (28.1)
White	41 (51.3)	15 (46.9)
Ethnicity, n (%)		
Hispanic or Latino	17 (21.3)	8 (25.0)
Insurance type, n (%)		
Medicare	16 (20.0)	14 (43.8)
Medicaid	6 (7.5)	3 (9.4)
Private	58 (72.5)	15 (46.9)
EDSS score at index date, mean (SD)	3.88 (1.76)	5.48 (0.97)
Time since diagnosis, yr, mean (SD)	9.3 (6.4)	10.7 (6.5)
MS subtype, n (%)		
RRMS	48 (60.0)	—†
aSPMS	32 (40.0)	32 (100.0)
Overall comorbidities (yes), n (%)	74 (92.5)	31 (96.9)
Depression	51 (63.8)	16 (50.0)
Neurogenic bladder	24 (30.0)	16 (50.0)
Spasticity	21 (26.3)	15 (46.9)
Pseudobulbar affect	15 (18.8)	11 (34.4)
Migraine	14 (17.5)	5 (15.6)
Anxiety	13 (16.3)	7 (21.9)
Thyroid disorder	12 (15.0)	5 (15.6)
Family history of MS (yes), n (%)	25 (31.3)	7 (21.9)
DMT before switch to teriflunomide, n (%)		
Dimethyl fumarate	18 (22.5)	5 (15.6)
Glatiramer acetate	15 (18.8)	7 (21.9)
Natalizumab	13 (16.3)	5 (15.6)
Interferon beta-1a (AVONEX)‡	9 (11.3)	5 (15.6)
Fingolimod	9 (11.3)	4 (12.5)
Interferon beta-1b	6 (7.5)	3 (9.4)
Interferon beta-1a (REBIF)§	6 (7.5)	2 (6.3)
Peginterferon beta-1a	2 (2.5)	—*
Alemtuzumab	1 (1.3)	—*
Unknown	1 (1.3)	1 (3.1)
Symptomatic medication use, n (%)		
SSRI	39 (50.0)	11 (35.5)
Dalfampridine	26 (33.3)	15 (48.4)
Baclofen	15 (19.2)	10 (32.3)
Modafinil	9 (11.5)	4 (12.9)
Dextromethorphan/quinidine	8 (10.3)	5 (16.1)
None	10 (12.8)	3 (9.7)
Switch reason, n (%)		
Safety–infection	23 (28.8)	9 (28.1)
Needle fatigue	21 (26.3)	6 (18.8)
Lack of efficacy	20 (25.0)	13 (40.6)
Safety–lymphopenia	15 (18.8)	4 (12.5)
Patient request	1 (1.3)	—*

RMS patients included those with relapsing-remitting multiple sclerosis (RRMS) and active secondary progressive multiple sclerosis (aSPMS).

aSPMS = active secondary progressive multiple sclerosis, DMT = disease-modifying therapy, EDSS = Expanded Disability Status Scale, MS = multiple sclerosis, RMS = relapsing MS, RRMS = relapsing-remitting MS, SSRI = selective serotonin reuptake inhibitor.

*Demographics and disease- and treatment-related characteristics (i.e., duration of MS, MS subtype, family history, smoking status, comorbidities, symptomatic medication, and latest DMTs) were extracted during 1 year pre-index period or at index.

†Data not available.

‡Biogen Inc, Cambridge, MA.

§EMD Serono Inc, Rockland, MA.

||Data available for N = 78 for the main analysis and N = 31 for the subanalysis.

Table 2**Main clinical assessments for evaluating patients with relapsing multiple sclerosis (RMS; N = 80)***

	1 yr pre-index	Index date	1 yr post-index	2 yr post-index
EDSS score, mean $\pm$ SD ^{†,‡}	3.84 $\pm$ 1.73	3.88 $\pm$ 1.76	3.90 $\pm$ 1.73	3.94 $\pm$ 1.79
Mean (95% CI) difference to 1 yr pre-index <i>P</i> -value			0.06 (0.01 to 0.10) <i>P</i> = .033*	0.06 (−0.00 to 0.13) <i>P</i> = .058
Ambulatory-aid use, n (%) [§]	21 (26.3)	20 (25.0)	20 (25.3)	16 (21.1)
T25FW test (s), mean $\pm$ SD	8.9 $\pm$ 2.8	8.8 $\pm$ 2.8	8.9 $\pm$ 2.7	9.0 $\pm$ 2.8
At least 1 annual relapse, n (%) [†]	21 (26.3)	— [¶]	14 (17.5)	4 (5.0)
Annualized relapse rate, mean $\pm$ SD	0.26 $\pm$ 0.44	— [¶]	0.18 $\pm$ 0.38	0.05 $\pm$ 0.22
Mean (95% CI) difference to 1 yr pre-index <i>P</i> -value			−0.09 (−0.20 to 0.03) <i>P</i> = .130	−0.21 (−0.32 to −0.11) <i>P</i> = .001
MRI lesion status				
Improved	7 (8.8)	0 (0)	3 (3.8)	1 (1.3)
Stable	57 (71.3)	74 (92.5)	73 (91.3)	77 (96.3)
Worsened	16 (20.0)	6 (7.5)	4 (5.0)	2 (2.5)
Cognition test (MoCA) [#] , mean $\pm$ SD**	27.6 $\pm$ 2.8	27.9 $\pm$ 2.4	27.9 $\pm$ 2.6	27.9 $\pm$ 2.4
Lymphopenia present, n (%)	— [¶]	24 (30.0)	5 (6.3)	1 (1.3)
Absolute lymphocyte count among patients with lymphopenia (<1000 lymphocytes/ μ L), mean $\pm$ SD	— [¶]	524.3 $\pm$ 238.1	883.2 $\pm$ 14.2	890.0 (N/A)

RMS patients included those with relapsing-remitting multiple sclerosis (RRMS) and active secondary progressive multiple sclerosis (aSPMS).

EDSS = Expanded Disability Status Scale, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, N/A = not applicable, T25FW = timed 25-foot walk.

*Changes in all measures were not statistically significant except where shown.

†Sample sizes for pre- and post-comparisons differed from those for measurements at single time points.

‡N = 77 at 2 years post-index.

§N = 79 at 1 year pre-index; N = 76 at 2 years post-index.

||N = 78 at 1 year pre-index; N = 79 at 1-year post-index; N = 75 at 2 years post-index.

¶Data not available.

#Scores on the MoCA range from 0 to 30. A score of 26 or higher is considered "normal."^[33]

**N = 55 at 1 year pre-index; N = 79 at index date; N = 76 at 1-year post-index; N = 74 at 2 years post-index.

Table 3**Main clinical assessments for evaluating patients with active secondary progressive multiple sclerosis (aSPMS) cohort (N = 32)***

	1 yr pre-index	Index date	1 yr post-index	2 yr post-index
EDSS score, mean $\pm$ SD [†]	5.42 $\pm$ 0.97	5.48 $\pm$ 0.97	5.47 $\pm$ 1.03	5.58 $\pm$ 0.97
Mean (95% CI) difference to 1 yr pre-index			0.05 (−0.04 to 0.13) <i>P</i> = .453	0.11 (0.01 to 0.22) <i>P</i> = .063
<i>P</i> -value [‡]				
Ambulatory-aid use, n (%) [§]	19 (59.4)	18 (56.3)	18 (56.3)	15 (50.0)
T25FW test* (s), mean $\pm$ SD	11.2 $\pm$ 2.4	11.1 $\pm$ 2.7	11.1 $\pm$ 2.4	11.1 $\pm$ 2.6
At least 1 annual relapse, n (%)	13 (40.6)	— [¶]	7 (21.9)	1 (3.1)
Annualized relapse rate, mean $\pm$ SD	0.4 $\pm$ 0.5	— [¶]	0.2 $\pm$ 0.4	0.03 $\pm$ 0.2
Mean (95% CI) difference to 1 yr pre-index <i>P</i> -value			−0.19 (−0.40 to 0.03) <i>P</i> = .146	−0.38 (−0.55 to −0.20) <i>P</i> < .001
MRI lesion status, n (%)				
Improved	1 (3.1)	0 (0)	1 (3.1)	0 (0)
Stable	21 (65.6)	28 (87.5)	29 (90.6)	32 (100)
Worsened	10 (31.3)	4 (12.5)	2 (6.3)	0 (0)
Cognition test (MoCA score), ^{†,‡} mean $\pm$ SD**	26.2 $\pm$ 3.3	26.7 $\pm$ 3.1	26.4 $\pm$ 3.1	26.7 $\pm$ 3.0
Lymphopenia present, n (%)	— [¶]	7 (21.9)	3 (9.4)	0 (0)
Absolute lymphocyte count among patients with lymphopenia (<1000 lymphocytes/ μ L), mean $\pm$ SD	— [¶]	582.0 $\pm$ 244.6	892.0 $\pm$ 3.5	N/A

EDSS = Expanded Disability Status Scale, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, N/A = not applicable, T25FW = timed 25-foot walk.

*Changes in all measures were not statistically significant except where shown.

†N = 31 at 2 years post-index.

‡Sample sizes for pre- and post-comparisons differed from those for measurements at single time points.

§N = 30 at 2 years post-index.

||N = 31 at 2 years post-index.

¶Data not available.

#Scores on the MoCA range from 0 to 30. A score of 26 or higher is considered "normal."^[33]

**N = 25 at 1 year pre-index; N = 31 at index date; N = 30 at 2 years post-index.

3.2.2. Outcomes within the aSPMS cohort. Similar to the main RMS cohort, a reduction in mean ARR was seen from 0.4 relapses at 1 year pre-index to 0.03 relapses at 2 years post-index (change: −0.38 [0.49]; *P* < .001; Table 3). No other

statistically significant changes were observed in the measured outcomes across the study follow-up period, including for EDSS score (Table 3). The proportion of patients with lymphopenia numerically decreased from 21.9% (n = 7) at index to 9.4%

($n = 3$) at 1 year post-index and 0% ($n = 0$) at 2 years post-index, although the change was nonsignificant in this small sample.

4. Discussion

This retrospective, observational analysis of medical records for 80 patients with RMS (incorporating patients with RRMS and active SPMS [aSPMS]) treated within a single US center demonstrates that switching to teriflunomide was associated with a reduced frequency of relapses, in addition to stabilized or improved MRI lesion status, and an increased mean EDSS score, compared with prior treatment with other DMTs (i.e., before switching). Consistent with the MRI and relapse data, stability in patient-reported disability and cognition assessments were also observed following switching to teriflunomide from existing DMTs. The efficacy and safety of teriflunomide have been demonstrated in clinical trials of patients with RMS or RRMS,^[13–17] including long-term extensions and postmarketing studies.^[34,35] Although real-world studies have explored the effectiveness in patients who switch to teriflunomide from other DMTs, this study included the MoCA test, which is a quick and effective assessment of cognitive function. The MoCA is highlighted as a simple to administer cognitive test in the clinical practice setting that addresses key shortcomings of the EDSS and SDMT, specifically insufficient coverage of the cognitive domain. For example, the SDMT covers mostly processing speed, whereas the MoCA addresses multiple aspects of the cognitive domain. The improvements in multiple measures of disease activity seen following switching to teriflunomide from other DMTs, both in patients with RMS and in the aSPMS subcohort, suggest teriflunomide may be an appropriate treatment option for patients with RMS who have experienced unsuccessful therapy with previous DMTs.

Our results have several important implications for the RMS population. For example, the mean ARR decreased significantly after switching to teriflunomide from other DMTs, from a mean of 0.26 relapses per year (at 1 year pre-index) to 0.05 at 2 years post-index. These observations compare favorably with other real-world analyses of patients with RMS taking teriflunomide, including the larger observational TAURUS-MS study ($N = 1128$), which reported a significant reduction in ARR from 0.87 (in the 2 years before study entry) to 0.35 during 2 years of teriflunomide treatment,^[30] and the smaller TACO study ($N = 47$), which reported an ARR of 0.14 during 2 years of teriflunomide treatment.^[31] Observations from the present study of 80 patients with RMS were taken from a single neurology center in California, and included 32 patients with SPMS. These data therefore add to growing evidence supporting the effectiveness of teriflunomide in the real-world clinical setting, specifically in patients who switched to teriflunomide from various DMTs for different reasons. The most commonly cited reason for switching in the overall RMS cohort being infection or needle fatigue.

Oral DMTs, including teriflunomide, offer a convenient route of administration compared with injectable counterparts. In addition, oral therapies are associated with better treatment satisfaction compared with injectable DMTs.^[18,36–38] For example, in the phase 4 Teri-PRO study, patients who had switched to teriflunomide from another DMT reported significantly improved satisfaction compared with baseline, and the highest satisfaction score was given for convenience.^[18,38] Indeed, the convenience of oral therapy was the most frequently cited reason given by physicians for selecting teriflunomide.^[18,38] There are a number of other reasons why patients switch DMTs, one being lymphopenia and subsequent risk of infection.^[39,40] While low rates (1%–3%) of serious infection have been associated with DMT use in clinical trials, some DMTs appear to carry a higher risk of serious opportunistic infections (such as progressive multifocal

leukoencephalopathy) in real-world clinical settings, and concerns about opportunistic or recurrent infections may be one reason that healthcare professionals suggest patients switch DMTs.^[39,41] Although data in the present study were limited, the proportion of RMS patients with lymphopenia decreased after switching to teriflunomide (from 30% of patients at the index [$n = 24$] to just 1.3% [$n = 1$] 2 years post-index), with similar observations seen in our subset of patients with aSPMS. Teriflunomide was also associated with an increase in absolute lymphocyte counts among patients who experienced lymphopenia before initiation of teriflunomide. These observations are in line with the safety profile known for the drug,^[42] and with observations from placebo-controlled clinical trials, where no increase in the risk of serious infections was observed with teriflunomide (2.2% at 7 mg, 2.7% at 14 mg) compared with placebo therapy (2.2%).^[42] Lymphopenia is thought to occur with DMTs, as their mechanism of action typically involves some form of immunomodulation that affects lymphocyte activation, proliferation, or cytokine secretion.^[39]

The current study also explored the effectiveness of teriflunomide in a small subgroup of patients with aSPMS ($n = 32$) and demonstrates a significant reduction in relapse, in line with observations from the full RMS cohort. It should be noted that not all patients with aSPMS experience relapses. Indeed, the disease course of aSPMS is not uniform and consists of periods of progression with possible relapse activity, but also periods of stability, where patients may improve or have fewer relapses without intervention.^[1,5] In the present study a range of additional disease activity measures (EDSS, T25FW test, and MoCA) remained stable after switching to teriflunomide from other DMTs in the subset of 32 patients with aSPMS, providing a range of important patient-reported data following a switch to teriflunomide. Data on the effectiveness of teriflunomide in patients with progressive MS are limited, and any additional data should help broaden our understanding of teriflunomide in aSPMS patients. Pooled data from the phase 3 TOWER and TEMSO trials indicated that the majority of patients with SPMS experiencing relapses ($n = 122$) did not show a worsening of disability scores with teriflunomide treatment after at least 12 weeks of treatment, and very few reached severe EDSS scores after at least 24 weeks of treatment with teriflunomide.^[43] Real-world studies generally report small sample sizes, reflecting the lower proportion of patients with SPMS than with RRMS within patient care settings.^[44,45] For example, an analysis of 20 patients with progressive MS (19 with SPMS) from 2 US centers who switched to teriflunomide from other DMTs demonstrated EDSS scores remained stable following switching to teriflunomide (14 mg) in 17 patients (85%; compared with the score at the start of teriflunomide treatment).^[44] These observations are in-line with observations from the current study, and suggested that treatment was associated with longer-term stability in this assessment of disability (follow-up 3–5 years).^[44] In patients with RMS, including those with aSPMS, switching to teriflunomide from other DMTs conferred a consistent benefit on markers of disease activity, not just assessments of relapse. However, further data in patients with different types of progressive MS are needed.

This study should be considered in light of its limitations. First, the sample size was small, and data were taken only from a single center in California; however, this did allow for consistent prescribing practices which kept variation in patient management to a minimum. Nevertheless, data are representative of only this one geographical population within the US. It is unclear if the sample size was sufficient to detect meaningful differences, as there were no predetermined power levels. Future studies should aim for a larger sample size, ideally with a multi-center study design, to allow for more robust conclusions and generalizations. A multi-center study with a larger sample size should also allow for a subgroup analysis between patients with RMS and aSPMS who switched to

teriflunomide, which was not feasible in this study due to the small number of patients with aSPMS. The statistical analyses did not include adjustments for potentially confounding factors such as age, baseline disease severity, or comorbidities, which might have influenced the outcomes. In addition, for some outcome measures, patients had some missing data or inconsistent data recording. For example, there were very few RMS patients with lymphopenia data during follow-up ($n = 5$ at 1 year post-index; $n = 1$ at 2 years post-index) compared with baseline ($n = 24$). Second, the descriptive comparisons in this study did not adjust for potential confounding factors, including previous DMT use (including type of DMT); therefore, the changes observed following a treatment switch to teriflunomide may include biases that were not controlled for. In the general population 12% are estimated to have progressive MS,^[4] whereas 40% of the MS study population had aSPMS. Finally, no direct comparisons were made between teriflunomide and other DMTs in clinical or imaging outcomes or between different routes of administration of DMTs as in other studies^[46]; however, such comparisons were not the focus of this real-world analysis, and we did not aim to provide an analysis based on the type of DMT patients were on prior to switching.

5. Conclusion

Compared with prior use of other DMTs, switching to teriflunomide was associated with a reduced frequency of relapses and a potential recovery from lymphopenia in patients with RMS, including those with RRMS or aSPMS. Stable assessment on multiple measures of disease activity was also seen following switching to teriflunomide treatment from other DMTs, including on disability and walking assessments (EDSS, T25FW test) and cognition assessment (MoCA), both in patients with RRMS and in the aSPMS subcohort. These real-world data suggest that teriflunomide may be an appropriate treatment option for patients with RRMS who have experienced unsuccessful therapy with previous DMTs.

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