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ORIGINAL RESEARCH

Sustained Effectiveness and Safety Over Time of Teriflunomide in Chinese Patients with Relapsing Multiple Sclerosis in the Greater Bay Area of China: Insights from Real-World Data

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ABSTRACT

Introduction: The real-world data on the medium- to long-term effectiveness and safety of teriflunomide in Chinese patients with relapsing multiple sclerosis (MS) is limited. Therefore, this study aims to assess the treatment outcomes of teriflunomide in Chinese patients with MS over a medium- to long-term period.
Methods: This cohort study was carried out in three tertiary hospitals and regional MS centers located in the Greater Bay Area of China. We obtained the historical clinical data of patients who underwent teriflunomide treatment for at least 6 months. The primary objective was to evaluate the proportion of patients achieving no evidence of disease activity (NEDA)-3 status, which is characterized by the absence of relapses, confirmed disability worsening, and new or enlarging MRI lesions, over time. Secondary objectives included assessing the proportion of patients meeting each NEDA-3 criterion, changes in motor and cognitive function, as well as the incidence of adverse events and treatment discontinuations.
Results: A total of 160 patients with MS were enrolled, including 125 patients treated with teriflunomide for at least 1 year (≥ 1-year completers) and 71 patients treated for at least 2 years (≥ 2-year completers). A total of 85.63% of the overall population achieved clinical NEDA-3 status at 6 months of teriflunomide treatment, and 71.20% of ≥ 1-year completers achieved NEDA-3 status at 12 months of teriflunomide treatment. The median timed 25-foot walk test (T25FW), nine-hole peg test (9-HPT), and paced auditory serial addition test (PASAT) results were relatively stable before and after treatment.
Conclusion: Medium- to long-term MS disease activity, as indicated by NEDA-3 status, is well controlled in patients treated with continuous teriflunomide treatment in real-world settings.

Keywords: Medium to long term; Teriflunomide; NEDA-3; Motor and cognitive function

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Key Summary Points

Why carry out this study?

Currently, no evidence of disease activity (NEDA) has become a new goal and outcome measure for multiple sclerosis (MS) treatment. Despite teriflunomide being available in China for 5 years, data on its medium- to long-term effectiveness and safety in Chinese patients with relapsing MS are lacking.

The objective of this analysis was to evaluate the medium- to long-term treatment outcomes of teriflunomide treatment.

What was learned from the study?

Medium- to long-term MS disease activity, as indicated by NEDA-3 status, is well controlled in patients receiving continuous teriflunomide treatment in real-world settings.

This study also showed that the regular use of teriflunomide may slow motor and cognitive impairments in patients with relapsing MS.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by demyelination and axonal loss in the central nervous system (CNS) [1]. Currently, there is no known cure for MS, so disease-modifying therapies (DMTs) are commonly used to slow down disease progression and alleviate associated symptoms [2]. Magnetic resonance imaging (MRI) is considered the most effective and sensitive diagnostic tool for detecting both new and ongoing disease activity in patients with MS [3]. An emerging treatment goal and outcome measures for MS is no evidence of disease activity (NEDA), which involves the absence of relapses, no lasting disability progression for minimum of 3 months, and no new MRI findings [4].

Teriflunomide is an oral immunomodulatory agent taken once daily, approved for treating relapsing MS (RMS) [5]. Phase III clinical trials, such as the TEMSO [6], TOWER [7], and TOPIC [8] trials, have provided evidence of its effectiveness and safety. Teriflunomide has demonstrated superiority over placebo in decreasing relapses, halting disability progression, and improving MRI outcomes pertaining to brain lesions and atrophy measures [7, 9]. Teriflunomide was the first oral DMT available on the Chinese market for the treatment of MS. Prior to the availability of teriflunomide, patients with MS in China often received treatment with interferons or traditional immunosuppressants such as mycophenolate mofetil. During the initial launch period of teriflunomide in China, there were limited other DMTs available on the Chinese market. Teriflunomide provided a therapeutic option for treating relapsing forms of MS, including clinically isolated syndrome, relapsing–remitting MS, and active secondary progressive MS, before additional DMT options became accessible. Real-world studies conducted in China have further confirmed the effectiveness of teriflunomide, widely used in the country, in reducing relapse rates and slowing down the progression of permanent disability among Chinese patients with MS [10, 11]. Nevertheless, limited research exists on the NEDA status or predictors of treatment response specific to teriflunomide. Furthermore, despite teriflunomide being accessible in China for 5 years, there remains a dearth of data on the medium- to long-term effectiveness and safety of this medication in Chinese patients with RMS. These factors play a crucial role in making informed decisions regarding personalized treatment.

The neurodegenerative process of MS leads to the continuous accumulation and progression of disabilities. Recently, there has been an increasing amount of data demonstrating that even when relapse activity appears to be effectively managed, patients with RMS frequently experience a progressive deterioration of disability over time [12, 13]. The use of composite confirmed disability accumulation, which

combines assessments of overall function (Expanded Disability Status Scale [EDSS]), upper extremity function (9-hole peg test [9-HPT]), and lower extremity function (timed 25 foot walk test [T25FW]), can provide a more comprehensive understanding of disease progression. This approach captures aspects that may be overlooked when relying solely on the EDSS alone [14]. Cognitive impairment is recognized as a significant symptom of MS as well, affecting up to 60% of patients [15]. While DMTs are considered the gold standard in MS treatment, there is a scarcity of studies examining the long-term effects of DMTs on both motor and cognitive functions. In particular, the motor and cognitive function assessment data from the population of Chinese patients with MS who have received DMT treatment remain limited.

Therefore, in the present study, we conducted a multicenter, real-world, retrospective study to evaluate the medium- to long-term treatment outcomes of teriflunomide treatment. The study also examined the safety and reasons for discontinuation of teriflunomide treatment. Moreover, we also analyzed the improvement in motor and cognitive function in patients with MS receiving teriflunomide treatment.

METHODS

Study Design

This retrospective, multicenter, observational study took place in three tertiary hospitals and regional MS centers within the Greater Bay Area of China. The study utilized anonymized medical records and electronic case report forms to extract historical clinical data of patients who received teriflunomide treatment between January 1, 2018 and July 1, 2023. Inclusion criteria for the study required a diagnosis of MS and a minimum treatment duration of 6 months with teriflunomide. Patients who took part in any interventional clinical studies during the specified period were excluded from the analysis.

To further assess the medium/long-term effectiveness of teriflunomide treatment, we divided the enrolled overall population into two other groups based on the duration of teriflunomide treatment: patients treated with teriflunomide for at least 1 year ($\geq$ 1-year completers) and those treated with teriflunomide for at least 2 years ($\geq$ 2-year completers). The $\geq$ 1-year completer group will primarily be used to evaluate the medium-term effectiveness of teriflunomide, while the $\geq$ 2-year completer group will mainly be used to test the sensitivity of the results and provide insights into the long-term real-world effectiveness of teriflunomide.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Third Affiliated Hospital, Sun Yat-sen University (approval number [2007] 33).

Data Collection

The baseline data for each patient, collected at initiation of teriflunomide treatment, included various factors such as demographic information, onset dates of the disease, type of MS, presence of cerebrospinal fluid oligoclonal bands (OB), number of relapses before treatment, symptoms experienced during previous attacks, EDSS scores, brain and spinal MRI results, prior treatment, results from 9-HPT, T25FW, and paced auditory serial addition test (PASAT).

The follow-up period in this study was defined as the duration from the initiation of teriflunomide treatment until either the patient discontinued teriflunomide treatment by the patient, was lost to follow-up, or reached the end of the study period (July 1, 2023). The data collected in the follow-up period included relapses experienced during teriflunomide treatment, EDSS scores, brain and spinal MRI outcomes, 9-HPT, T25FW, PASAT, and adverse events (AEs). The date and reasons for teriflunomide discontinuation were also recorded.

Definitions and Outcome Measures

The recovery from the first attack in this study was classified into three categories: complete recovery (no neurological signs compared to baseline), partial recovery (incomplete recovery

with persistent neurological signs compared to baseline), or no recovery (persistent neurological signs without any improvement compared to baseline). The affected regions of the central nervous system at the onset of MS were classified as isolated optic nerve, isolated cerebrum, isolated cerebellum/brainstem, isolated spinal cord, or poly-system. Patients who had experienced a minimum of two attacks within 1 year before starting treatment or at least three attacks within 2 years prior to treatment initiation were considered to have frequent relapses prior to treatment.

The primary outcome was the proportion of patients with RMS treated with teriflunomide who achieved NEDA-3 status over time. NEDA-3 was defined as a composite that consisted of no relapses and nonconfirmed disability progression (CDP) sustained for 12 weeks (an increase of ≥ 1.0 points from baseline EDSS score of < 5.5 or ≥ 0.5 points from baseline EDSS score of ≥ 5.5) and no new or enlarging MRI activity. The secondary outcomes included the proportion of patients with no relapse over time, the proportion of patients with no CDP over time, the proportion of patients with no MRI findings over time, the proportion of patients with reported AEs, and the proportion of patients with teriflunomide treatment discontinuation. The assessment of motor function improvements involved measuring changes in 9-HPT and T25FW results before and after teriflunomide treatment. Additionally, the evaluation of cognitive function improvement was based on changes in PASAT results before and after teriflunomide treatment.

Statistical Analysis

Continuous data in this study are reported using the mean, standard deviation (SD), median, and interquartile range (IQR). Categorical data are reported using counts with corresponding percentages. Patients with missing data were excluded from the calculations of means and percentages. When relevant, the number of patients with missing data is presented. The Shapiro–Wilk test was utilized to access normality in the data. Subsequently, the Wilcoxon signed-rank test was employed to compare pretreatment annualized relapse rate (ARR), EDSS, 9-HPT nondominant hand, and 9-HPT combined average to those post-treatment. Paired *t* tests were used to compare pretreatment T25FW, 9-HPT dominant hand, and PASAT scores to those post-treatment. Differences were considered statistically significant if the *P* value was less than 0.05. The time from the initiation of teriflunomide treatment to first NEDA-3 failure was estimated using Kaplan–-Meier survival analyses. To identify the demographic and clinical variables that are independently associated with NEDA-3 failure, both univariable and multivariable Cox proportional hazards regression analyses were performed. The time interval considered in these analyses was defined as the duration from the initiation of teriflunomide treatment to the occurrence of first NEDA-3 failure. The independent variables comprised age, sex, disease duration, MS type (relapsing disease from onset: relapsing remitting multiple sclerosis [RRMS] and secondary progressive multiple sclerosis [SPMS]), CSF oligoclonal bands result, the status of recovery from the first attack, regions involved at onset, spinal cord lesions (or not) before teriflunomide treatment. ARR before treatment, frequent relapses before treatment, EDSS before treatment, received treatment before teriflunomide initiation (or not), and received immunosuppressive agent before teriflunomide initiation. The status of recovery from the first attack (complete recovery; partial recovery; no recovery) and regions involved at onset (poly-system onset; isolated cerebrum; isolated brainstem/cerebellum; isolated spinal cord; isolated optic nerve) were both coded as dummy variables. Received immunosuppressive agent before teriflunomide initiation was defined as patients have received azathioprine, mycophenolate mofetil, tacrolimus, or methotrexate treatment before teriflunomide treatment. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated as effect measures. All variables that were significant ($P < 0.1$) in the univariable Cox regression analysis were entered into the multivariable model. All analyses were conducted using the R statistical package v.4.2.3 (R

Foundation for Statistical Computing [RRID:SCR_001905], Vienna, Austria).

RESULTS

Cohort Characteristics

A total of 160 patients with MS treated with teriflunomide for at least 6 months were enrolled in this study (Table 1). Of these, 125 patients had been treated with teriflunomide for at least 1 year (≥ 1-year completers). Seventy-one patients who were treated with teriflunomide for at least 2 years (≥ 2-year completers) were also included in a subgroup sensitivity analysis. The mean ages in the overall population and ≥ 1-year completer cohort were 28.78 and 28.92 years, respectively. Women accounted for 73.75% of the overall population and 74.40% of the ≥ 1-year completer cohort. The most common region involved at disease onset was the poly-system (70.49%), and a total of 50 (41.32%) patients recovered completely from the first attack. At the time of teriflunomide initiation, the overall population exhibited a mean disease duration of 3.32 years, a mean ARR of 0.91, and a mean EDSS score of 2.06. Corticosteroids (23.13%) were the most common treatment before teriflunomide initiation, followed by immunoglobulin (9.38%) and azathioprine (7.50%). The clinical characteristics of the two subgroups (≥ 1-year completers and ≥ 2-year completers) were similar to those of the overall population.

Treatment Duration

The median teriflunomide treatment duration in the overall population was 21 (12, 33) months (Table 2). In the ≥ 1-year completer and ≥ 2-year completer groups, the median durations of teriflunomide treatment were 25 (19, 34) months and 33 (27.50, 42) months, respectively.

Effectiveness Analysis

We first evaluated the changes in ARR and EDSS score in the overall population as well as in the subgroups of ≥ 1-year completers and ≥ 2-year completers (Table 3). In the overall population, there was a significant reduction in ARR (0.37 ± 0.55) after treatment compared to pretreatment (0.91 ± 0.73), with a decrease of 59.3%. The EDSS score also showed a significant decrease of 19.9% after treatment (1.65 ± 1.41) compared to pretreatment (2.06 ± 1.36). Similarly, in the subgroup of medium-term users of teriflunomide (≥ 1-year completers), there was a significant reduction in post-treatment ARR (0.30 ± 0.40) compared to before treatment (0.89 ± 0.72) as well as a significant decrease in post-treatment EDSS (1.71 ± 1.46) compared to before treatment (2.02 ± 1.41). These differences were statistically significant. In the subgroup of participants who used teriflunomide for over 2 years (≥ 2-year completers), we also observed a trend of reduced ARR and EDSS scores.

During the course of teriflunomide treatment, 85.63% of the overall population achieved clinical NEDA-3 status within 6 months (as shown in Table 4 and Fig. 1). Among medium-term users of teriflunomide (≥ 1-year completers), 85.60% of patients attained NEDA-3 status within a span of 6 months. Moreover, among ≥ 1-year completers, 71.20% of patients attained NEDA-3 status within a span of 12 months. Among patients who completed at least 2 years of treatment (≥ 2-year completers), the clinical NEDA-3 rates were comparable to those in the ≥ 1-year completers. Within 24 months of treatment, 73.24% of patients achieved NEDA-3 status.

The univariate analysis demonstrated a significant association between the pretreatment EDSS score (HR 1.23; 1.06, 1.44, $P = 0.007$) and the failure to achieve NEDA-3 status during teriflunomide treatment in the overall population (Table 5). Patients with SPMS had a 1.92 times higher risk of NEDA-3 failure compared to patients with RRMS. Additionally, patients with monocular optic nerve involvement had a 3.07 times higher risk of NEDA-3 failure compared to

Table 1 Demographic and clinical characteristics of patients

Characteristics	Overall population	≥ 1-year completers	≥ 2-year completers
Patients, *n*	160	125	71
Sex, *n* (%)			
Male	42 (26.25)	32 (25.60)	20 (28.17)
Female	118 (73.75)	93 (74.40)	51 (71.83)
Age, years			
Mean (SD)	28.78 (7.57)	28.92 (7.89)	28.99 (8.36)
Median (Q1, Q3)	27.00 (24.00, 34.00)	27.00 (24.00, 34.00)	27.00 (23.00, 34.50)
Disease duration, years			
Mean (SD)	3.32 (3.66)	3.43 (3.74)	3.13 (3.51)
Median (Q1, Q3)	1.92 (0.38, 5.27)	1.92 (0.40, 5.34)	1.92 (0.34, 5.16)
Missing	1	1	0
MS type, *n* (%)			
RRMS	130 (92.20)	106 (92.98)	62 (93.94)
SPMS	11 (7.80)	8 (7.02)	4 (6.06)
Missing	19	11	5
CSF oligoclonal bands, *n* (%)			
Negative	20 (20.20)	16 (20.25)	9 (18.75)
Positive	79 (79.80)	63 (79.75)	39 (81.25)
Missing	61	46	23
Recovery from the first attack, *n* (%)			
Complete recovery	50 (41.32)	43 (43.43)	25 (45.45)
Partial recovery	59 (48.76)	48 (48.48)	25 (45.45)
No recovery	12 (9.92)	8 (8.08)	5 (9.09)
Missing	39	26	16
Regions involved at onset, *n* (%)			
Poly-system onset	86 (70.49)	69 (70.41)	37 (67.27)
Isolated cerebrum	14 (11.48)	10 (10.20)	7 (12.73)
Isolated brainstem/cerebellum	6 (4.92)	6 (6.12)	3 (5.45)
Isolated spinal cord	13 (10.66)	11 (11.22)	6 (10.91)
Isolated optic nerve	3 (2.46)	2 (2.04)	2 (3.64)
Missing	38	27	16
ARR before treatment			
Mean (SD)	0.91 (0.73)	0.89 (0.72)	0.92 (0.75)

Table 1 continued

Characteristics	Overall population	≥ 1-year completers	≥ 2-year completers
Median (Q1, Q3)	0.97 (0.37, 1.00)	0.85 (0.35, 1.00)	0.89 (0.39, 1.00)
Missing	8	6	1
Frequent relapses before treatment, *n* (%)	35 (23.03)	25 (21.01)	13 (18.57)
EDSS before treatment			
Mean (SD)	2.06 (1.36)	2.02 (1.41)	1.88 (1.45)
Median (Q1, Q3)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	1.50 (1.00, 2.50)
Missing	21	19	13
Treatment before teriflunomide initiation, *n* (%)			
Corticosteroid	37 (23.13)	31 (24.80)	19 (26.76)
Azathioprine	12 (7.50)	11 (8.80)	6 (8.45)
Immunoglobulin	15 (9.38)	13 (10.40)	8 (11.27)
Mycophenolate mofetil	6 (3.75)	5 (4.00)	3 (4.23)
Tacrolimus	4 (2.50)	4 (3.20)	1 (1.41)
Mitoxantrone	1 (0.63)	1 (0.80)	0 (0.00)
Anti-CD20	4 (2.50)	4 (3.20)	1 (1.41)
Methotrexate	1 (0.63)	1 (0.80)	1 (1.41)
Dimethyl fumarate	1 (0.63)	1 (0.80)	0 (0.00)
Fingolimod	1 (0.63)	1 (0.80)	1 (1.41)

SD standard deviation, *Q1* 25% quantile, *Q3* 75% quantile, *ARR* annualized relapse rate, *EDSS* Expanded Disability Status Scale, *CSF* cerebrospinal fluid, *MS* multiple sclerosis, *RRMS* relapsing remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *anti-CD20* anti-cluster of differentiation 20

Table 2 Treatment duration of patients with MS

Characteristics	Overall population	≥ 1-year completers	≥ 2-year completers
Patients, *n*	160	125	71
Treatment duration, month			
Mean (SD)	24.32 (15.66)	28.70 (15.02)	37.37 (14.61)
Median (Q1, Q3)	21.00 (12.00, 33.00)	25.00 (19.00, 34.00)	33.00 (27.50, 42.00)

SD standard deviation, *Q1* 25% quantile, *Q3* 75% quantile

those without such involvement, and patients who received immunosuppressive agent before teriflunomide initiation had a 1.73 times higher risk of NEDA-3 failure compared to immunosuppressive naïve patients, although these differences did not reach statistical significance. The multivariate analysis provided additional support indicating that pretreatment

Table 3 Effectiveness outcomes of patients with MS (pretreatment versus post-treatment)

Characteristics	Pretreatment	Post-treatment	Difference	95% CI	*P* value
Overall population					
Patients, *n*	160	160			
ARR			− 0.54	− 0.69, − 0.39	< 0.001*
Mean (SD)	0.91 (0.73)	0.37 (0.55)			
Missing	8	10			
EDSS score			− 0.37	− 0.56, − 0.17	< 0.001*
Mean (SD)	2.06 (1.36)	1.65 (1.44)			
Missing	21	16			
≥ 1-year completers					
Patients, *n*	125	125			
ARR			− 0.59	− 0.74, − 0.44	< 0.001*
Mean (SD)	0.89 (0.72)	0.30 (0.40)			
Missing	6	6			
EDSS score			− 0.25	− 0.49, − 0.02	0.012*
Mean (SD)	2.02 (1.41)	1.71 (1.46)			
Missing	19	14			
≥ 2-year completers					
Patients, *n*	71	71			
ARR			− 0.73	− 0.92, − 0.54	< 0.001*
Mean (SD)	0.92 (0.75)	0.17 (0.24)			
Missing	1	4			
EDSS score			− 0.21	− 0.52, 0.10	0.077
Mean (SD)	1.88 (1.45)	1.61 (1.59)			
Missing	13	10			

95% CI 95% confidence interval, *ARR* annualized relapse rate, *EDSS* Expanded Disability Status Scale, *SD* standard deviation

*Statistical significance at the $P < 0.05$ level

EDSS score (HR 1.18; 95% CI 1.00, 1.40, $P = 0.057$) potentially served as an independent factor associated with the failure to achieve NEDA-3 status during teriflunomide treatment.

Changes in Motor and Cognitive Function

Furthermore, we explored the effects of long-term use of teriflunomide on the motor and cognitive function of patients with MS in those who had been using the medication for over 1 year (Table 6 and Fig. 2). There were 22 patients with complete pre- and post-treatment

Table 4 NEDA-3 outcomes of patients with MS

Characteristics	Overall population	≥ 1-year completers	≥ 2-year completers
Patients, *n*	160	125	71
No relapse, *n* (%)			
Within 6 months	145 (90.63)	113 (90.40)	67 (94.37)
Within 12 months	–	97 (77.60)	62 (87.32)
Within 24 months	–	–	56 (78.87)
No disability progression, *n* (%)			
Within 6 months	160 (100.00)	125 (100.00)	71 (100.00)
Within 12 months	–	124 (99.20)	71 (100.00)
Within 24 months	–	–	71 (100.00)
No new or enlarging MRI lesions, *n* (%)			
Within 6 months	148 (92.50)	116 (92.80)	68 (95.77)
Within 12 months	–	109 (87.20)	65 (91.55)
Within 24 months	–	–	60 (84.51)
NEDA-3, *n* (%)			
Within 6 months	137 (85.63)	107 (85.60)	65 (91.55)
Within 12 months	–	89 (71.20)	60 (84.51)
Within 24 months	–	–	52 (73.24)

NEDA no evidence of disease activity, *MS* multiple sclerosis, *MRI* magnetic resonance imaging

T25FW and 9-HPT assessments. The overall results of T25FW and 9-HPT assessments remained relatively stable in patients treated with teriflunomide for at least 1 year. The median T25FW walking time decreased from 6.08 s before treatment to 5.63 s after treatment. The median 9-HPT average time also slightly decreased from 23.49 s before treatment to 21.80 s after treatment, but these results were not statistically significant. Only a few patients (7 cases) underwent both pre- and post-treatment PASAT assessments, and the results also maintained relative stability. The median PASAT score increased from 53.00 before treatment to 56.00 after treatment, although this difference was not statistically significant.

Safety Analysis

The safety analysis was conducted on the basis of the overall population (Table 7). Among the 160 patients who used teriflunomide for at least 6 months, 61 cases (38.13%) reported experiencing safety events. Alopecia was the most common safety event, occurring in 44 cases (27.50%). Other commonly reported safety events included abnormal liver function test results in 10 cases (6.25%), leukopenia in 6 cases (3.75%), digestive symptoms in 5 cases (3.13%), and skin rash in 3 cases (1.88%), among others.

Analysis of Treatment Discontinuation

During the study period, a total of 64 patients in the overall population cohort discontinued the treatment (Table 8). Disease relapse was the

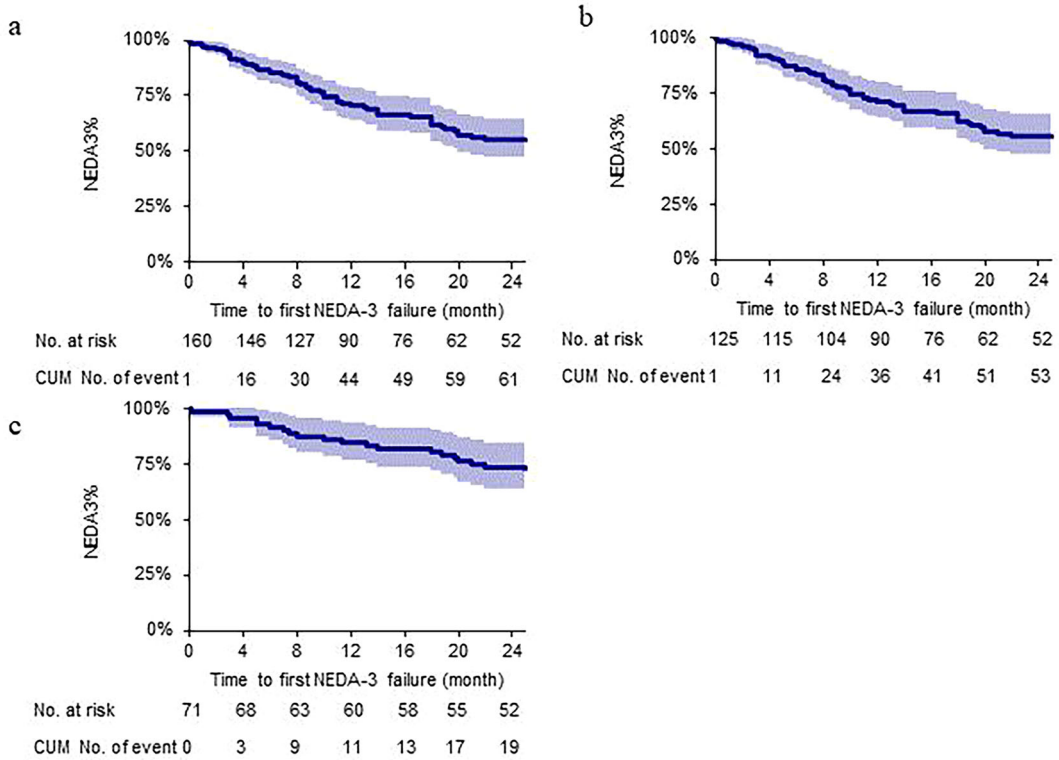

Fig. 1 Kaplan–Meier curve for NEDA-3 probability of overall population (**a**), ≥ 1-year completers (**b**), ≥ 2-year completers (**c**). The number of events and number at risk (censored) are displayed below the x-axis. NEDA-3, no evidence of disease activity

main reason for treatment discontinuation (51.56%). Other reasons included self-intention (14.06%), pregnancy or planning to become pregnant (14.06%), financial reasons (6.25%), adverse drug reactions (6.25%), and off-test (1.56).

DISCUSSION

In this study, we conducted a retrospective multicenter real-world study to evaluate the effectiveness and safety of teriflunomide treatment for a relatively long duration in Chinese patients with MS. The three participating MS centers were in southern China, covering most patients with MS in the Greater Bay Area of China. This study primarily focused on non-newly diagnosed patients, aiming to evaluate the proportion of patients who achieved NEDA-3 status with regular teriflunomide treatment, which has rarely been reported in Chinese real-world data. We also described, to a limited extent, the impact of teriflunomide on the upper and lower limb motor function and cognitive status of patients with MS. These findings can help fill the evidence gap in the comprehensive assessment of the long-term effectiveness of teriflunomide in Chinese patients with non-newly diagnosed MS.

To date, several single- or multicenter real-world studies have confirmed that teriflunomide significantly reduces disease relapse and slows disability progression in the Chinese population of patients with MS [10, 11]. In this study, we observed that in patients with non-newly diagnosed MS, there was a significant reduction in both the ARR and EDSS after at least 6 months of teriflunomide treatment, which is consistent with the trends reported in previous real-world data. Long-term data from the TEMSO, TOWER, and TOPIC extension studies (up to 9, 6.3, and 7.5 years of follow-up) have provided evidence in support of the

Table 5 Factors influencing NEDA-3 failure among the overall population

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age at onset	1.01	0.98, 1.04	0.658			
Sex						
Male	–	–				
Female	0.94	0.55, 1.59	0.814			
Disease course at treatment start	1.02	0.95, 1.08	0.612			
MS phenotype						
RRMS	–	–		–	–	
SPMS	1.92	0.91, 4.06	0.086*	1.27	0.56, 2.89	0.562
CSF oligoclonal bands						
Negative	–	–				
Positive	1.01	0.47, 2.16	0.989			
Recovery from 1st attack						
Complete recovery	1.12	0.69, 1.84	0.644			
Partial recovery	0.97	0.60, 1.58	0.907			
No recovery	1.56	0.71, 3.41	0.268			
Regions involved at onset (yes vs. no)						
Poly-system onset	1.10	0.69, 1.77	0.684			
Isolated optic nerve	3.07	0.96, 9.81	0.058*	2.20	0.64, 7.56	0.210
Isolated spinal cord	1.51	0.69, 3.31	0.300			
Isolated cerebrum	0.71	0.29, 1.78	0.468			
Isolated brainstem/cerebellum	0.30	0.04, 2.19	0.238			
Spinal cord lesion (or not) before teriflunomide treatment	1.51	0.85, 2.68	0.160			
ARR before treatment	1.01	0.73, 1.39	0.958			
Frequent relapse before treatment	1.27	0.72, 2.24	0.407			
EDSS before treatment	1.23	1.06, 1.44	0.007*	1.18	1.00, 1.40	0.057*
Received treatment before teriflunomide initiation	1.42	0.88, 2.31	0.154			
Received immunosuppressive agent before teriflunomide initiation	1.73	0.98, 3.03	0.057*	1.30	0.68, 2.47	0.428

NEDA no evidence of disease activity, *HR* hazard ratio, *CI* confidence interval, *MS* multiple sclerosis, *RRMS* relapsing remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *CSF* cerebrospinal fluid, *ARR* annualized relapse rate, *EDSS* Expanded Disability Status Scale

*Statistical significance at the $P < 0.1$ level

Table 6 Evaluation of motor and cognitive function in patients with MS with medium-term teriflunomide treatment (≥ 1-year completers)

Characteristics	Pretreatment	Post-treatment	Difference	95% CI	*P* value
Patients, *n*	22	22			
T25FW score, seconds			− 0.20	− 0.66, 0.26	0.372
Mean (SD)	6.02 (1.21)	5.81 (1.37)			
Median (Q1, Q3)	6.08 (5.39, 6.50)	5.63 (4.99, 6.41)			
9-HPT score—dominant hand, seconds			0.34	− 0.83, 1.52	0.549
Mean (SD)	22.76 (3.75)	23.10 (4.69)			
Median (Q1, Q3)	21.64 (20.05, 24.83)	21.58 (20.36, 24.59)			
9-HPT score—nondominant hand, seconds			0.38	− 3.43, 4.18	0.723
Mean (SD)	24.96 (4.98)	25.33 (10.13)			
Median (Q1, Q3)	23.71 (21.79, 26.28)	22.02 (21.16, 25.46)			
9-HPT score—combined average, seconds			0.360	− 1.81, 2.53	0.972
Mean (SD)	23.86 (3.33)	24.22 (6.75)			
Median (Q1, Q3)	23.49 (21.52, 25.33)	21.80 (20.29, 24.86)			
PASAT score			1.14	− 5.64, 7.93	0.695
Mean (SD)	51.00 (8.02)	52.14 (7.49)			
Median (Q1, Q3)	53.00 (49.00, 56.00)	56.00 (45.50, 58.00)			
Missing	15	15			

CI confidence interval, *SD* standard deviation, *Q1* 25% quantile, *Q3* 75% quantile, *T25FW* timed 25-foot walk test, *9-HPT* nine-hole peg test, *PASAT* paced auditory serial addition test

sustained long-term efficacy of teriflunomide in the treatment of MS [16–18], with EDSS remaining low and stable over the course of the disease and ARR remaining low and typically less than 0.3 at most time points. Here, we observed that in patients who were on medium- or long-term stable use of teriflunomide (defined as receiving treatment for at least 1 year or at least 2 years, respectively), there was a significant reduction in post-treatment ARR (≥ 1-year completers: 0.30, $P < 0.001$; ≥ 2-year completers: 0.17, $P < 0.001$) and EDSS (≥ 1-year completers: 1.71, $P < 0.012$; ≥ 2-year completers: 1.61, $P < 0.077$) compared to pretreatment. This is consistent with the results of previous prospective extension studies [19], indicating that the medium- to long-term use of teriflunomide in the real-world Chinese population can still produce good therapeutic effects that are maintained, reduce disease relapse, and delay disability progression.

NEDA-3 status has been an important clinical endpoint and treatment goal of high-efficacy MS therapies [20]. In this study, the proportions of patients achieving NEDA-3 status at 6 and 12 months after at least 12 months of teriflunomide treatment were 85.60% and 71.20%, respectively, and in the long-term teriflunomide use cohort (≥ 2-year completers), the proportions of patients achieving NEDA-3 status at 6, 12, and 24 months after treatment were 91.55%, 84.51%, and 73.24%, respectively. The results were similar to those of a previous single-center prospective real-world study

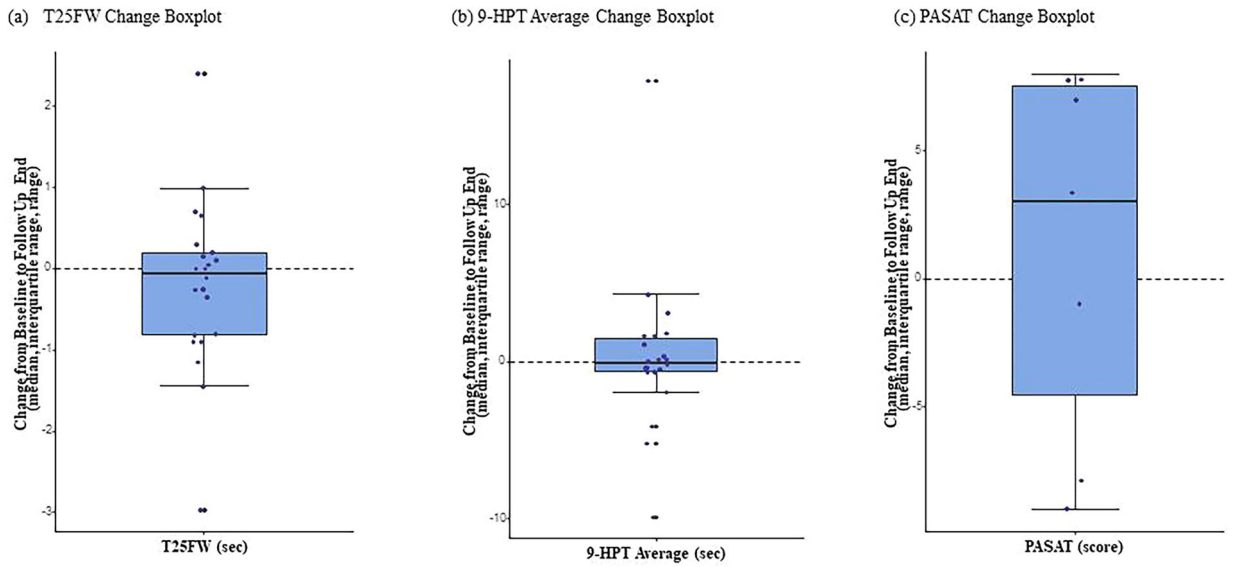

Fig. 2 Boxplots of effectiveness endpoints. Median change from baseline to follow-up end in **a** T25FW (s), **b** 9-HPT average score (s), and **c** PASAT score. *T25FW* timed 25-foot walk test, *9-HPT* nine-hole peg test, *PASAT* paced auditory serial addition test

(79.0% at 12 months) [21], with a proportion much higher than that observed in the Western population (Teri-RADAR: 46% at follow-up) [22], further confirming that teriflunomide may be more suitable for Chinese patients [10].

In the analysis of factors associated with the failure to achieve NEDA-3 status, we found that high EDSS before treatment was significantly associated with NEDA-3 failure, which is consistent with previous studies [21, 23]. We observed that SPMS, isolated optic nerve onset, and received immunosuppressive agent before teriflunomide initiation showed a potential association with NEDA-3 failure in univariate analysis. However, after conducting multivariate analysis, there was no significant correlation between them and NEDA-3 failure. This suggests that patients in these groups may have a higher baseline disability level.

It is important to note that while the EDSS is widely utilized to evaluate the progression of disability in patients with MS, it primarily focuses on quantifying the level of existing damage and does not directly provide insight into the underlying neurodegenerative and reparative processes happening within the disease [24]. To address this limitation, the T25FW and 9-HPT have been utilized to measure short-distance ambulatory and upper-extremity function, respectively [25]. It is worth noting that currently, there is insufficient data available regarding the specific impact of teriflunomide on the underlying neurodegenerative process in MS. However, this study showed that after at least 12 months of teriflunomide treatment, the T25FW and 9-HPT results remained relatively stable and even showed a slight decrease, although the differences were not statistically significant. This suggests that regular use of teriflunomide may not only delay the progression of existing disabilities but also potentially slow the neurodegenerative process to some extent.

Teriflunomide also plays an effective role in maintaining the stability of patients' cognitive impairment in MS. A post hoc analysis of the TEMSO study showed that teriflunomide significantly improved cognitive performance in patients with relapsing MS [26]. The real-world Teri-PRO study also confirmed the stability of cognitive impairment after teriflunomide treatment [27]. Herein, we observed that after at least 12 months of teriflunomide treatment, seven patients showed relative stability in their PASAT scores before and after treatment.

Table 7 Adverse effects in the overall population

Characteristics	Overall population
Patients, *n*	160
Adverse events, *n* (%)	61 (38.13)
Alopecia	44 (27.50)
Abnormal liver function test results	10 (6.25)
Leukopenia	6 (3.75)
Digestive symptoms	5 (3.13)
Skin rash	3 (1.88)
Frequent urination	2 (1.25)
Sleep disorders	2 (1.25)
Fatigue	2 (1.25)
Bowel and bladder dysfunction	1 (0.63)
Apathy	1 (0.63)
Sexual dysfunction	1 (0.63)
Tachycardia	1 (0.63)
Dizziness	1 (0.63)
Weakness	1 (0.63)
Chest tightness	1 (0.63)
Diarrhea	1 (0.63)
Chills	1 (0.63)
Exfoliation	1 (0.63)
Headache	1 (0.63)
Missing	3

However, because of the small sample size, this result needs further support from additional data.

Consistent with the safety results from a previous Chinese multicenter real-world study [10], the most common adverse effects reported in this study were alopecia (27.50%), abnormal liver function test results (6.25%), leukopenia (3.75%), digestive symptoms (3.13%), and skin rash (5.91%), all of which are known adverse effects of teriflunomide.

Table 8 Analysis of teriflunomide treatment discontinuation

Characteristics	Overall population
Patients, *n*	160
Treatment discontinuation, *n* (%)	64 (40.00)
Reasons of discontinuation, *n* (%)	
Relapse	33 (51.56)
Self-intention	9 (14.06)
Pregnant or plan to get pregnant	9 (14.06)
Financial reasons	4 (6.25)
Adverse drug reaction	4 (6.25)
Off-test	1 (1.56)
Missing	4

This study has some limitations. First, as a result of the low prevalence of MS in China, the sample size of this study was smaller than that of Western studies. The limited popularity of DMTs among Chinese patients with MS has also impacted the final sample size of the study. Second, as a result of the retrospective design, there were considerable missing assessments of patients' motor and cognitive functions, which affected the in-depth analysis of the impact of teriflunomide on motor and cognitive improvement, and some commonly used measures for cognitive function, such as the symbol digit modalities test (SDMT), were not used. It is hoped that in the future, with the standardization of the diagnosis and treatment of MS, there will be improvements in data collection for these aspects, and SDMT or other relevant cognitive function assessment scales will be incorporated. Third, as patients may have stopped teriflunomide treatment because of disease relapse, these patients may have done so before the 2-year mark and were therefore not included in the analysis of $\geq$ 2- year completers. As a result, we cannot ascertain whether the 100% of patients without disability progression includes these discontinuation cases. Furthermore, as for the limitation of a smaller subset of patients treated with teriflunomide for 3 or 4 years, we

did not perform specific analysis on the real-world effectiveness of teriflunomide with prolonged use over a considerable period (e.g., 3, 4, or $\geq$ 5 years) in the study; we will continue to conduct standardized follow-up to supplement this aspect in the future.

Taken together, these results suggested that medium- to long-term MS disease activity, as indicated by NEDA-3 status, is well controlled in patients treated with continuous teriflunomide treatment in real-world settings. The regular use of teriflunomide may slow motor and cognitive impairments in patients with RMS. Additionally, teriflunomide is generally well tolerated in this study.

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Declarations

Conflict of Interest. The authors declare that there are no conflicts of interest.

Ethical Approval. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Third Affiliated Hospital, Sun Yat-sen University (approval number [2007]33).

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