Efficacy and Safety of Teriflunomide in Chinese Patients with Relapsing Forms of Multiple Sclerosis: A Subgroup Analysis of the Phase 3 TOWER Study

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Abstract

Background: Disease-modifying therapy is the standard treatment for patients with multiple sclerosis (MS) in remission. The primary objective of the current analysis was to assess the efficacy and safety of two teriflunomide doses (7 mg and 14 mg) in the subgroup of Chinese patients with relapsing MS included in the TOWER study.
Methods: TOWER was a multicenter, multinational, randomized, double-blind, parallel-group (three groups), placebo-controlled study. This subgroup analysis includes 148 Chinese patients randomized to receive either teriflunomide 7 mg (n = 51), teriflunomide 14 mg (n = 43), or placebo (n = 54).
Results: Of the 148 patients in the intent-to-treat population, adjusted annualized relapse rates were 0.63 (95% confidence interval [*CI*]: 0.44, 0.92) in the placebo group, 0.48 (95% *CI*: 0.33, 0.70) in the teriflunomide 7 mg group, and 0.18 (95% *CI*: 0.09, 0.36)

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in the teriflunomide 14 mg group; this corresponded to a significant relative risk reduction in the teriflunomide 14 mg group versus placebo (−71.2%, $P = 0.0012$). Teriflunomide 14 mg also tended to reduce 12-week confirmed disability worsening by 68.1% compared with placebo (hazard ratio: 0.319, $P = 0.1194$). There were no differences across all treatment groups in the proportion of patients with treatment-emergent adverse events (TEAEs; 72.2% in the placebo group, 74.5% in the teriflunomide 7 mg group, and 69.8% in the teriflunomide 14 mg group); corresponding proportions for serious adverse events were 11.1%, 3.9%, and 11.6%, respectively. The most frequently reported TEAEs with teriflunomide versus placebo were neutropenia, increased alanine aminotransferase, and hair thinning.
Conclusions: Teriflunomide was as effective and safe in the Chinese subpopulation as it was in the overall population of patients in the TOWER trial. Teriflunomide has the potential to meet unmet medical needs for MS patients in China.
Trial Registration: ClinicalTrials.gov, NCT00751881; https://clinicaltrials.gov/ct2/show/NCT00751881?term=NCT00751881&rank=1

Key words: Chinese Patients; Efficacy; Phase 3; Relapsing Multiple Sclerosis; Safety; Teriflunomide; TOWER

Introduction

Multiple sclerosis (MS) is one of the most common neurological diseases in young adults and is the leading cause of nontraumatic disability in young and middle-aged adults.[1] The disease has a major physical, psychological, social, and financial impact on patients and their families and poses a substantial burden to health-care systems worldwide. In 2013, the global prevalence of MS was estimated as 33/100,000; the estimated median prevalence was greatest in North America (140/100,000) and Europe (108/100,000) and considerably lower in China (≤5/100,000).[2] It was defined as a rare disease in China in May 2018. However, with improving disease awareness and diagnostic techniques in China, the prevalence of MS is expected to increase markedly.

Clinically, MS manifests as neurological deficits in the central nervous system (CNS) that demonstrates dissemination in space and time. Diagnosis is made by clinical features and supportive magnetic resonance imaging (MRI), with the evaluation of cerebral spinal fluid according to the 2017 revised McDonald criteria.[3] "Relapsing MS" (RMS) encompasses all forms involving relapses, and these forms are the most frequent presentation.

Therapeutic goals in MS, as categorized according to the 2015 European guidelines for the development of drugs for MS,[4] include the following: (i) treatment of acute relapses to shorten the duration and/or severity of symptoms and/or prevent sequelae; (ii) modification of the natural history of the disease, by preventing or modifying relapses and/or by preventing or delaying disability accumulation through the use of disease-modifying therapies (DMTs); and (iii) improvement of an apparently stable residual disability.

Many DMTs are currently approved in various regions worldwide for the treatment of RMS. These DMTs include alemtuzumab, beta-interferons, dimethyl fumarate, fingolimod, glatiramer acetate, mitoxantrone, natalizumab, ocrelizumab, and teriflunomide. In most regions, beta-interferons and glatiramer acetate have been used widely, both of which can reduce the frequency of relapse by approximately 30% over 2–3 years.[5] However, beta-interferons and glatiramer acetate need to be administered by injection, which makes it difficult for some patients to tolerate. Moreover, missed dosages of interferon therapy are associated with disease progression. Most patients treated with beta-interferons and glatiramer acetate discontinued their treatment within the first 2 years due to a lack of efficacy or side effects such as flu-like symptoms and depression.[6] In addition, glatiramer acetate is not available commercially in China, and the availability of more convenient, noninjectable DMTs, with relatively favorable efficacy, safety, and tolerability profiles, would help to address the current unmet needs of Chinese patients with RMS.

Teriflunomide, an orally active DMT that inhibits lymphocyte proliferation, is approved in more than 70 countries for the treatment of relapsing-remitting MS. Teriflunomide selectively and reversibly inhibits dihydro-orotate dehydrogenase, an enzyme in the *de novo* synthesis pathway of pyrimidines,[7] resulting in reduced proliferation of peripheral T- and B-lymphocytes, and hence reduced numbers of lymphocytes crossing the blood–brain barrier and causing CNS damage. Teriflunomide appears to induce a shift from pro-inflammatory to regulatory T-cell subtypes, with no detrimental effect on cytokine and proliferative responses. Moreover, teriflunomide maintains the levels of CD4+ T-cell receptor clones in MS patients similar to levels noted in healthy individuals; this effect has not been demonstrated with other DMTs, such as dimethyl fumarate, interferon-β, or mitoxantrone.[8]

The selection of two doses of teriflunomide, 7 mg and 14 mg, for use in the current analysis was based on previous efficacy and safety data for these two doses from a phase 2, 36-week, double-blind, placebo-controlled study[9] and its long-term extension.[10] Importantly, data from the global, phase 3 Teriflunomide Oral in People with RMS (TOWER; ClinicalTrials.gov Identifier: NCT00751881) study of teriflunomide have been published previously and revealed statistically significant relative risk reductions for teriflunomide 14 mg versus placebo in annualized relapse rate (ARR; −36.3%, $P = 0.0001$) and 12-week confirmed disability worsening (CDW; −31.5%; $P = 0.0442$).[11] Importantly, the primary objective of the current analysis was to assess the efficacy and safety of two teriflunomide doses (7 mg and 14 mg) specifically in the subgroup of Chinese patients in the TOWER study.

Methods

Ethical approval

The study was approved by the relevant independent 32 Ethics Committees and Institutional Review Boards, 15 of which received ethical approval from the main center

(Beijing Hospital; approval number: 2009022), and 17 centers received ethical approval from their respective sub-centers, and all patients provided written informed consent before entry into the study. The study was done in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the *Declaration of Helsinki*.

Study design

The methodology of the overall TOWER trial has been described previously.[11] Briefly, TOWER was a multicenter, multinational, randomized, double-blind, parallel-group (three groups), placebo-controlled study. Patients were randomly assigned to receive either teriflunomide 7 mg, teriflunomide 14 mg, or placebo, in a ratio of 1:1:1.

Study participants

Inclusion and exclusion criteria for the overall TOWER study population have been described previously.[11] Briefly, eligible patients were aged 18–55 years and had RMS (meeting 2005 McDonald criteria)[12] and an Expanded Disability Status Scale (EDSS) score ≤5.5 at screening. Patients also had at least one relapse in 12 months before randomization or at least two relapses in 24 months before randomization.

Objectives

The primary objective of the current subgroup analysis was to assess the efficacy of both teriflunomide doses (7 mg and 14 mg), relative to placebo, on the frequency of MS relapses in Chinese patients with RMS. The key secondary objective was to assess the efficacy of both teriflunomide doses, relative to placebo, on CDW in Chinese patients with RMS. Other secondary objectives were to evaluate the effects of teriflunomide versus placebo on fatigue and health-related quality of life and to assess the safety and tolerability profiles of teriflunomide.

Study assessments

The primary efficacy variable for this study was the ARR, defined as the number of relapses per patient-year in patients with RMS. A relapse was defined as the appearance of a new clinical sign/symptom or clinical worsening of a previous sign/symptom (one that had been stable for at least 30 days) that persisted for a minimum of 24 h in the absence of fever.

Other endpoints included 12-week CDW, time to first relapse, proportion of patients free from relapses, proportion of patients free of CDW, and change from baseline in EDSS score. All study assessments and their evaluation time points have been defined previously.[11]

Statistical analysis

No specific sample size or power calculations were considered for patients enrolled in China alone, and sample size and power considerations for the overall TOWER study population have been described previously.[11] Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as number (percent). The modified intention-to-treat population (all randomly assigned patients who received at least one dose of study drug or placebo) was used for all efficacy analyses. All inferential statistical analyses were done at the two-sided 5% level of significance. A Poisson regression model with robust error variance, including factors for treatment and baseline EDSS scores (stratified by scores ≤3.5 or >3.5), was used to analyze ARR. Two-sided 95% confidence intervals (*CI*s) of the rate ratio as well as risk difference are provided for the comparisons of each active treatment versus placebo. The estimated relapse rate and its 2-sided 95% *CI*s and the gross estimate of ARR are provided for each treatment group. The primary endpoint

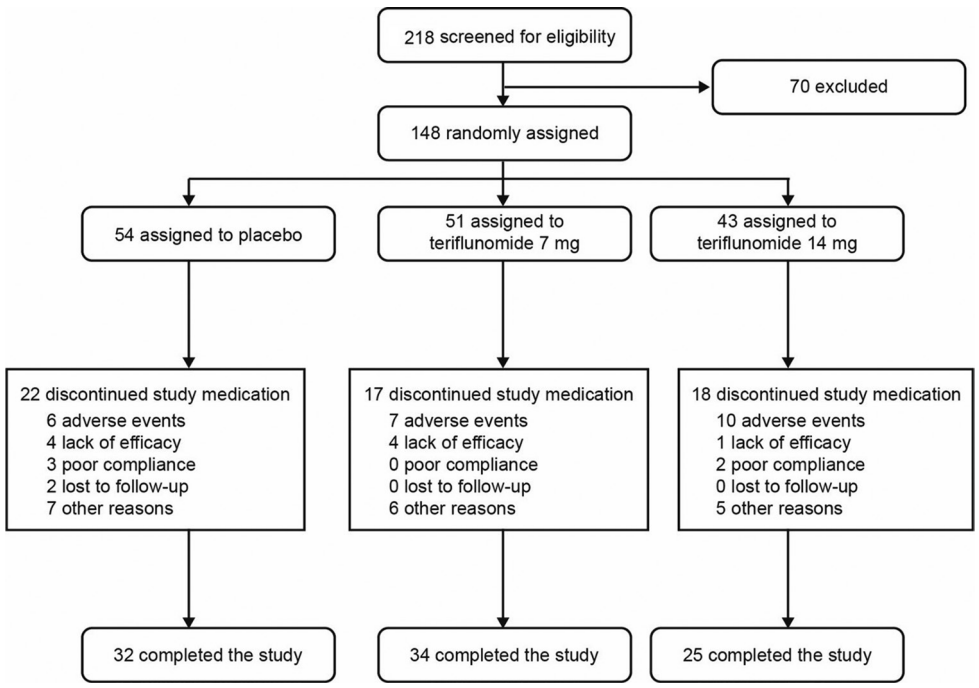

Figure 1: Trial profile of Chinese patients in TOWER study.

was analyzed using the generalized estimating equation (GEE) model instead of the regular Poisson model, since the GEE estimator was robust against violation of the correlation structure and the distributional assumptions. The time to disability progression was analyzed using the log-rank test with time to disability progression as the dependent variable, the treatment group as test variable, and baseline EDSS strata as stratification factors. The hazard ratio (*HR*) estimates for each teriflunomide treatment group versus placebo were estimated using a Cox regression model with treatment group and baseline EDSS strata as covariates. The Kaplan-Meier method was used to estimate the time to disability progression rate specific to each group, based on the ITT population. Kaplan-Meier graphs were generated and quartiles and point probabilities were calculated. Interval estimates were calculated using 95% point-wise *CI*s. All summaries and statistical analyses were carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 1165 patients included in the intent-to-treat (ITT) TOWER population, 148 (12.7%) were Chinese. In this subgroup, a total of 218 Chinese patients from 32 centers were screened and 148 were randomized: 54 to placebo, 51 to teriflunomide 7 mg, and 43 to teriflunomide 14 mg [Figure 1]. Among the randomized patients, 57 did not complete treatment. Discontinuation rates were similar among the three groups: placebo group 40.7%, teriflunomide 7 mg group 33.3%, and teriflunomide 14 mg group 41.9%. The most frequent cause for discontinuation was adverse events (AEs; 23 patients: 6 in the placebo group, 7 in the teriflunomide 7 mg group, and 10 in the teriflunomide 14 mg group), other (18 patients; many of these resulted from patient decision), and lack of efficacy (9 patients). No randomized patients were excluded from the ITT population. The median duration of study treatment was similar across all three groups: placebo, 469 (range 10–847) days; teriflunomide 7 mg, 506 (1–807) days; and teriflunomide 14 mg, 458 (7–762) days. Demographic and baseline characteristics of the Chinese population were comparable to the overall population [Table 1] with two exceptions: Chinese patients had a shorter time since first symptoms of MS compared

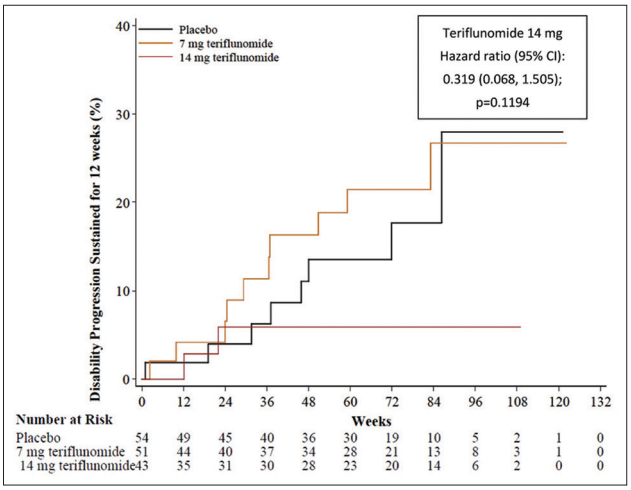

Figure 2: Kaplan-Meier plot of time to disability progression confirmed over 12 weeks in the intent-to-treat population. *CI*: Confidence interval.

Table 1: Baseline characteristics in the TOWER Chinese subgroup analysis and overall TOWER study population

Characteristics	TOWER Chinese subgroup				Overall TOWER study		
	Placebo (*n* = 54)	Teriflunomide 7 mg (*n* = 51)	Teriflunomide 14 mg (*n* = 43)	Overall (*n* = 148)	Placebo (*n* = 389)	Teriflunomide 7 mg (*n* = 408)	Teriflunomide 14 mg (*n* = 372)
Demographic characteristics							
Age (years)	37.3 ± 9.3	36.5 ± 9.6	37.8 ± 9.7	37.2 ± 9.5	38.1 ± 9.1	37.4 ± 9.4	38.2 ± 9.4
Female	37 (68.5)	35 (68.6)	26 (60.5)	98 (66.2)	273 (70.2)	300 (73.5)	258 (69.4)
Clinical characteristics							
Time from first MS symptom (years)	5.5 ± 6.1	4.0 ± 3.4	5.6 ± 5.7	5.0 ± 5.3	7.6 ± 6.7	8.2 ± 6.8	8.2 ± 6.7
Time since most recent relapse onset (months)	4.0 ± 2.6	5.0 ± 3.5	4.7 ± 3.6	4.6 ± 3.3	5.3 ± 3.4	5.2 ± 3.4	5.3 ± 3.3
Relapses per patient (number of times)							
Within previous year	1.6 ± 1.0	1.4 ± 0.7	1.3 ± 0.6	1.4 ± 0.8	1.4 ± 0.8	1.4 ± 0.7	1.4 ± 0.7
Within previous 2 years	2.2 ± 1.4	2.1 ± 1.1	2.1 ± 1.0	2.1 ± 1.2	2.1 ± 1.1	2.1 ± 1.1	2.1 ± 1.2
MS subtype*							
Relapsing-remitting	54 (100.0)	51 (100.0)	43 (100.0)	148 (100.0)	379 (97.4)	393 (96.3)	366 (98.9)
Secondary progressive	0 (0)	0 (0)	0 (0)	0 (0)	4 (1.0)	3 (0.7)	2 (0.5)
Progressive relapsing	0 (0)	0 (0)	0 (0)	0 (0)	6 (1.5)	12 (2.9)	2 (0.5)
Use of DMT in the previous 2 years	2 (3.7)	0 (0)	1 (2.3)	3 (2.0)	135 (34.7)	123 (30.1)	126 (33.9)
Baseline EDSS score	2.6 ± 1.4	2.7 ± 1.4	2.7 ± 1.4	2.6 ± 1.4	2.7 ± 1.4	2.7 ± 1.4	2.7 ± 1.4

Data are mean ± SD or *n* (%). *Data are not available for two patients in the teriflunomide 14 mg group. DMT: Disease-modifying therapy; EDSS: Expanded Disability Status Scale; MS: Multiple sclerosis; SD: Standard deviation.

Table 2: Clinical results in the TOWER Chinese subgroup analysis and overall TOWER study population

Items	TOWER Chinese subgroup		
	Placebo (*n* = 54)	Teriflunomide 7 mg (*n* = 51)	Teriflunomide 14 mg (*n* = 43)
Annualized relapse rate (primary endpoint)			
Adjusted annualized relapse rate (95% *CI*)*	0.63 (0.44, 0.92)	0.48 (0.33, 0.70)	0.18 (0.09, 0.36)
Relative risk (95% *CI*)	NA	0.76 (0.45, 1.29)	0.29 (0.14, 0.61)
Relative reduction versus placebo, % (95% *CI*)	NA	24.0 (–29.3, 55.4)	71.2 (38.8, 86.5)
P value versus placebo†	NA	0.3108	0.0012
Absolute reduction versus placebo (95% *CI*)	NA	–0.15 (–0.45, 0.15)	–0.45 (–0.71, –0.19)
P value versus placebo‡	NA	0.3172	0.0007
Time to sustained accumulation of disability (key secondary endpoint)			
HR versus placebo (95% *CI*)§	NA	1.26 (0.50, 3.19)	0.32 (0.07, 1.51)
P value versus placebo‖	NA	0.6580	0.1194
Other secondary endpoints			
Proportion free from protocol-defined relapse at 48 weeks, % (95% *CI*)¶	61.2 (47.8, 74.5)	59.1 (44.9, 73.4)	82.2 (69.2, 95.2)
Days to first relapse, 25% quartile (95% *CI*)	123 (84, 218)	152 (34, 334)	485 (211, NA)
HR versus placebo (95% *CI*)§	NA	0.98 (0.55, 1.77)	0.40 (0.18, 0.89)
P value versus placebo‖	NA	0.8878	0.0214
Proportion free from confirmed disability worsening, % (95% *CI*)¶			
24 weeks	96.0 (90.6, 100.0)	93.4 (86.2, 100.0)	94.1 (86.2, 100.0)
48 weeks	86.5 (76.3, 96.6)	83.7 (72.6, 94.8)	94.1 (86.2, 100.0)
108 weeks	72.1 (50.3, 93.8)	73.3 (58.0, 88.6)	94.1 (86.2, 100.0)
Items	**Overall TOWER study**		
	Placebo (*n* = 388)	**Teriflunomide 7 mg (*n* = 407)**	**Teriflunomide 14 mg (*n* = 370)**
Annualized relapse rate (primary endpoint)			
Adjusted annualized relapse rate (95% *CI*)*	0.50 (0.43, 0.58)	0.39 (0.33, 0.46)	0.32 (0.27, 0.38)
Relative risk (95% *CI*)	NA	0.78 (0.63, 0.96)	0.64 (0.51, 0.79)
Relative reduction versus placebo, % (95% *CI*)	NA	22.3 (4.2, 37.0)	36.3 (20.7, 48.8)
P value versus placebo†	NA	0.0183	0.0001
Absolute reduction versus placebo (95% *CI*)	NA	−0.11 (−0.20, −0.02)	−0.18 (−0.27, −0.09)
P value versus placebo‡	NA	0.0189	0.0001
Time to sustained accumulation of disability (key secondary endpoint)			
HR versus placebo (95% *CI*)§	NA	0.95 (0.68, 1.35)	0.68 (0.47, 1.00)
P value versus placebo‖	NA	0.7620	0.0442
Other secondary endpoints			
Proportion free from protocol-defined relapse at 48 weeks, % (95% *CI*)¶	60.6 (55.5, 65.6)	71.9 (67.3, 76.5)	76.3 (71.7, 81.0)
Days to first relapse, 25% quartile (95% *CI*)	188 (142, 249)	272 (201, 354)	369 (282, 485)
HR versus placebo (95% *CI*)§	NA	0.70 (0.56, 0.87)	0.63 (0.50, 0.79)
P value versus placebo‖	NA	0.0016	<0.0001
Proportion free from confirmed disability worsening, % (95% *CI*)¶			
24 weeks	92.0 (89.3, 94.8)	94.7 (92.4, 97.0)	97.3 (95.6, 99.1)
48 weeks	85.8 (82.1, 89.4)	87.9 (84.5, 91.3)	92.2 (89.2, 95.1)
108 weeks	80.3 (75.9, 84.8)	78.9 (73.9, 83.9)	84.2 (79.6, 88.8)

*Derived using the Poisson model with the total number of confirmed relapse onset between randomization date and last-dose date as the response variable; treatment and EDSS strata at baseline as covariates; and log-transformed treatment duration as an offset variable; †Chi-square test from estimation of rate ratios; ‡*Z*-test from estimating the risk difference; §Derived using Cox proportional hazards model with treatment and EDSS strata at baseline as covariates; ‖Derived from log-rank test with stratification of EDSS at baseline; ¶Derived from Kaplan-Meier estimates. *CI*: Confidence interval; EDSS: Expanded Disability Status Scale; *HR*: Hazard ratio; NA: Not applicable.

with the overall population and fewer Chinese patients had received another DMT therapy within the last 2 years compared with the overall population.

Of the 148 patients in the ITT population, adjusted ARRs using the Poisson regression model were 0.63 (95% confidence interval [*CI*]: 0.44, 0.92) in the placebo group, 0.48 (95% *CI*: 0.33, 0.70) in the teriflunomide 7 mg group, and 0.18 (95% *CI*: 0.09, 0.36) in the teriflunomide 14 mg group [Table 2]. These results revealed a significant reduction of relative risk in the teriflunomide 14 mg group (71.2%, $P = 0.0012$), while no statistically significant relative risk reduction was observed in the teriflunomide 7 mg group (24.0%, $P = 0.3108$). The effect of teriflunomide

14 mg on ARR was independent of the specific subgroups examined (i.e., gender, age <38 vs. ≥38 years, baseline EDSS score ≤3.5 vs. >3.5, and number of relapses in the last 1 or 2 years before randomization; data not shown).

The estimated percentages of patients free of 12-week CDW at week 48 using the Kaplan–Meier method were 86.5% in the placebo group, 83.7% in the teriflunomide 7 mg group, and 94.1% in the teriflunomide 14 mg group [Table 2]. Up to week 48, compared with placebo, the risk of 12-week CDW was reduced and the hazard ratio was 0.319 (95% *CI*: 0.068, 1.505) with teriflunomide 14 mg [Figure 2].

The proportion of patients with treatment-emergent AEs (TEAEs) was similar across all three groups (72.2% in the placebo group, 74.5% in the teriflunomide 7 mg group,

Table 3: Adverse events in the safety population of the TOWER Chinese subgroup*

Items	Placebo (n = 54)	Teriflunomide 7 mg (n = 51)	Teriflunomide 14 mg (n = 43)
All adverse events	39 (72.2)	38 (74.5)	30 (69.8)
Serious adverse events	6 (11.1)	2 (3.9)	5 (11.6)
Events leading to permanent treatment discontinuation	5 (9.3)	7 (13.7)	10 (23.3)
Death	1 (1.9)	0 (0)	1 (2.3)
Common adverse events†			
Neutropenia	2 (3.7)	6 (11.8)	9 (20.9)
ALT increased	4 (7.4)	8 (15.7)	6 (14.0)
Alopecia	0 (0)	2 (3.9)	6 (14.0)
Nasopharyngitis	11 (20.4)	3 (5.9)	6 (14.0)
Upper respiratory tract infection	5 (9.3)	4 (7.8)	5 (11.6)
Neutrophil count decreased	3 (5.6)	4 (7.8)	3 (7.0)
White blood cell count decreased	1 (1.9)	4 (7.8)	3 (7.0)
Urinary tract infection	4 (7.4)	3 (5.9)	2 (4.7)
Constipation	3 (5.6)	1 (2.0)	1 (2.3)
Headache	0 (0)	3 (5.9)	1 (2.3)
Pruritus	3 (5.6)	2 (3.9)	0 (0)
Infections and infestations			
Any event	20 (37.0)	11 (21.6)	10 (23.3)
Serious infections	3 (5.6)	0 (0)	1 (2.3)
Hepatic laboratory data			
ALT >1 × ULN	22 (40.7)	31 (62.0)	23 (53.5)
ALT >3 × ULN	4 (7.4)	4 (8.0)	6 (14.0)
ALT >5 × ULN	1 (1.9)	1 (2.0)	1 (2.3)
ALT >10 × ULN	0 (0)	0 (0)	0 (0)
ALT >20 × ULN	0 (0)	0 (0)	0 (0)
ALT >3 × ULN and total bilirubin >2 × ULN	0 (0)	0 (0)	0 (0)
AST >3 × ULN	2 (3.7)	1 (2.0)	1 (2.3)
GGT >2.5 × ULN	3 (5.6)	3 (6.0)	3 (7.0)
Hematological laboratory data			
Neutrophil counts ($\times 10^9$/L)			
<1.5	4 (7.4)	9 (18.0)	11 (25.6)
<0.5	0 (0)	1 (2.0)	0 (0)
Lymphocyte counts ($\times 10^9$/L)			
<0.8	11 (20.4)	13 (26.0)	10 (23.3)
<0.5	1 (1.9)	2 (4.0)	4 (9.3)
<0.2	0 (0)	0 (0)	0 (0)
Additional adverse events of interest			
Hypertension	0 (0)	0 (0)	0 (0)
Peripheral neuropathy	1 (1.9)	0 (0)	0 (0)
Adverse events leading to permanent treatment discontinuation‡			
ALT increased	1 (1.9)	1 (2.0)	2 (4.7)
AST increased	0 (0)	0 (0)	2 (4.7)
Neutropenia	0 (0)	0 (0)	2 (4.7)
Cholelithiasis	0 (0)	2 (3.9)	0 (0)

Data shown are n (%) patients with at least one treatment-emergent adverse event. *The safety population comprised all patients randomized and exposed to study medication; †Events with a crude incidence rate of >5% in any one group; ‡That occurred in >3% of patients in any one group. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT; γ-Glutamyltransferase; ULN: Upper limit of normal.

and 69.8% in the teriflunomide 14 mg group) [Table 3]. The incidence of treatment-emergent serious AEs was similar between the placebo and teriflunomide 14 mg groups (11.1% and 11.6%, respectively) but was lower in the teriflunomide 7 mg group (3.9%). TEAEs leading to permanent treatment discontinuation were reported with higher frequency in teriflunomide-treated patients than placebo recipients (13.7% in the teriflunomide 7 mg group, 23.3% in the teriflunomide 14 mg, and 9.3% in placebo group). Two patients died during the study: one patient in the placebo group died due to respiratory infection and one patient in the teriflunomide 14 mg group who had a 2-year history of depression died from suicide. However, neither of these events was considered related to study treatment. Frequencies of infections and infestations in both teriflunomide groups were similar to those in the placebo group. Raised alanine aminotransferase (ALT; >1 × the upper limit of normal [ULN]) occurred more often in the teriflunomide groups than in the placebo group, while the incidence of elevated ALT levels (>5 × ULN) was similar among the study groups. No patients met Hy's law criteria. None of the patients had hypertension, and only one patient (in the placebo group) developed peripheral neuropathy [Table 3].

As shown in Table 3, TEAEs (Medical Dictionary for Regulatory Activities version 15.0; preferred terms) were neutropenia (11.8% in the teriflunomide 7 mg group, 20.9% in the teriflunomide 14 mg group, and 3.7% in the placebo group), increased ALT (15.7% in the teriflunomide 7 mg group, 14.0% in the teriflunomide 14 mg group, and 7.4% in the placebo group), hair thinning (3.9% in the teriflunomide 7 mg group, 14.0% in the teriflunomide 14 mg group, and none in the placebo group), reduced white blood cell count (7.8% in the teriflunomide 7 mg group, 7.0% in the teriflunomide 14 mg group, and 1.9% in the placebo group), and headache (5.9% in the teriflunomide 7 mg group, 2.3% in the teriflunomide 14 mg group, and none in the placebo group). Conversely, nasopharyngitis, urinary tract infection, constipation, and pruritus were more common in the placebo group than in the teriflunomide groups [Table 3].

Discussion

To the best of our knowledge, the TOWER study was the first placebo-controlled, international confirmatory study of teriflunomide efficacy and safety in MS that included a Chinese subgroup.[11] The number of Chinese subgroup patients enabled meaningful analyses and data interpretation.

ARR is a more sensitive endpoint than CDW, for which lack of sensitivity is a well-recognized challenge in clinical trials. The demonstration of teriflunomide efficacy in our analysis is based primarily on ARR. Comparison of teriflunomide 14 mg with placebo for the Chinese subgroup revealed a statistically significant relative risk reduction in ARR of 71.2% ($P = 0.0012$), which is consistent with the findings for the overall TOWER population.[11] The high level of statistical significance reached for ARR in our analysis ($P = 0.0012$) confirms the marked extent of teriflunomide efficacy. Teriflunomide efficacy regarding secondary endpoints was also similar in the Chinese subpopulation and overall TOWER study population [Table 2].

For both ARR and disability worsening, effect sizes in the Chinese subpopulation were numerically greater than those for the overall TOWER population, that is, in the teriflunomide 14 mg versus placebo group, ARR was reduced by 71.2% in Chinese patients and by 36.3% in the overall population. One possible explanation for differences in the efficacy of teriflunomide between the Chinese subpopulation and the overall TOWER population may be due to differences in plasma teriflunomide concentrations. Based on a population pharmacokinetic analysis, with data pooled from Asian patients (90/121 were Chinese) and non-Asian patients ($n = 1687$), the model predicted a median value for the area under the plasma teriflunomide concentration versus time curve (0–24 h) in Chinese patients, which was 51.5% higher than that in non-Asian patients (data on file; Sanofi China). Polymorphisms in the breast cancer resistance protein gene (*BCRP*; also known as ATP-binding cassette subfamily G member 2 [*ABCG2*]) may contribute to moderately higher teriflunomide exposure in Asian patients. Indeed, Chinese patients have a higher frequency of the allelic gene *ABCG2* (single-nucleotide polymorphism rs2231142) than non-Asian patients, which results in a less active form of BCRP,[13] a protein that functions as an efflux transporter that may limit teriflunomide transport in the gastrointestinal tract, liver, and brain and that may also be involved in enterohepatic recycling. In addition, the differences in patients' characteristics between Chinese patients and the overall population may also have played a role in efficacy. Chinese patients had shorter disease duration compared to the overall population, which may suggest the benefits of earlier treatment.

Besides consistency with data from the overall TOWER trial,[11] findings from our analysis endorse results from the earlier phase 3 TEMSO trial,[14] in which teriflunomide 14 mg significantly reduced ARR and the risk of 12-week CDW; although teriflunomide 7 mg also significantly reduced ARR, it did not significantly influence disability progression. Interestingly, the study designs of the TEMSO and TOWER trials were relatively similar, such that pooled data analysis was possible: teriflunomide 14 mg significantly reduced ARR by 34% and significantly reduced the proportion of patients with sustained CDW at 108 weeks.[15] A recent meta-analysis of seven randomized controlled trials in patients with RMS reported that teriflunomide 14 mg versus placebo significantly reduced disability progression, and the ARR associated with investigator-assessed sequelae.[16]

Post hoc data from TEMSO also revealed that teriflunomide 14 mg versus placebo significantly reduced the annualized rate of neurologic sequelae (an increase in EDSS/Functional Status Score ≥30 days after relapse) by 36%. A dose-dependent decrease (teriflunomide vs. placebo) in the frequency of relapses requiring hospitalization

was also noted.[17] Extension trials following on from phase 2 and 3 evaluations of teriflunomide also demonstrated that long-term efficacy of the drug was maintained for up to 9 years.[10,18]

In our analysis, both doses of teriflunomide were well tolerated by Chinese patients and with a manageable safety profile which is consistent with that for the overall TOWER population. There were no new or specific safety concerns in the Chinese subpopulation, and the total incidence of TEAEs was slightly lower in Chinese patients (72.3%) than in the overall population (85.1%). The TEAE incidence was similar between the 7 mg group and 14 mg group in the Chinese and overall populations. For treatment-emergent serious AEs, the incidence was similar in the placebo and teriflunomide 14 mg groups in the Chinese population (11.1% and 11.6%, respectively) and overall population (12.0% and 12.0%, respectively); however, the incidence in the teriflunomide 7 mg group was lower in the Chinese subpopulation (3.9%) than in the overall population (13.0%). TEAEs leading to permanent treatment discontinuation showed a similar pattern in the Chinese and overall populations, with higher frequencies in the teriflunomide groups (13.0–23.3%) than the placebo group (6.0–9.3%).

Compared with the placebo group, the most frequently reported TEAEs with the higher incidence in the teriflunomide treatment groups were neutropenia, elevated ALT, and hair thinning. similar trends were evident in the overall population. Furthermore, in both the Chinese subpopulation and overall TOWER population, ALT elevations >2 × ULN and >3 × ULN were more common with teriflunomide 14 mg than in the placebo group. The incidence of ALT elevations >5 × ULN was well balanced between the three study groups in both the Chinese and overall populations. Clinically significant elevations in ALT >3 × ULN were generally reversible in all study groups, even during treatment, and there were no cases of Hy's law in the Chinese subpopulation. Altogether, the safety profile of teriflunomide in the Chinese subpopulation was similar to profiles in the overall TOWER population, in previous studies,[10,14] and in a large pooled analysis of safety and tolerability data collated over >12 years.[19]

TOWER did not include any MRI endpoints, which might be regarded as a limitation of the study. However, data from the phase 2 trial[9] and TEMSO trial[14] confirmed that teriflunomide significantly and dose dependently reduced MRI markers of disease activity and burden.[20] Brain volume loss was also reduced significantly in patients treated with teriflunomide in a reanalysis of the TEMSO MRI data set employing the Structural Image Evaluation using Normalisation of Atrophy method.[21] An additional limitation is the high discontinuation rate, although the rate was similar to that reported in other studies of oral DMTs in RMS.[22,23]

In conclusion, teriflunomide was as effective, safe, and tolerable in the Chinese subpopulation as it was in the overall population of patients with RMS in the TOWER trial. The best benefit–risk ratio was attained with teriflunomide at a dose of 14 mg once daily in both the Chinese subgroup and the overall population. Thus, teriflunomide has the potential to meet unmet medical needs for MS patients in China.

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Conflicts of interest

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特立氟胺用于中国复发型多发性硬化患者的有效性和安全性：III期TOWER研究亚组分析

摘要

背景：疾病修正治疗是多发性硬化患者缓解期的标准治疗。本研究旨在评估TOWER研究中特立氟胺（7 mg和14 mg）在复发型多发性硬化（RMS）中国患者中的有效性和安全性。

方法：TOWER研究是一项国际多中心、双盲、随机、平行组（3组）、安慰剂对照研究。该亚组分析包括148名中国患者，随机接受特立氟胺7 mg（*n*=51），特立氟胺14 mg（*n*=43）或安慰剂（*n*=54）。

结果： 在148例意向治疗人群中，调整后的ARR分别为安慰剂组0.63（95%可信区间[*CI*]：0.44, 0.92）、特立氟胺7 mg组0.48（95%*CI*：0.33，0.70）和特立氟胺14 mg组0.18（95%CI：0.09，0.36）；这相当于特立氟胺14 mg组与安慰剂组相比，相对风险显著降低（-71.2%，*P*=0.0012），至12周残疾进展风险有下降68.1%的趋势（风险比*HR*=0.319，*P*=0.1194），三组患者的治疗相关不良事件（TEAE）的发生率相似，安慰剂组、特立氟胺7 mg组和14 mg组分别为72.2%、74.5%和69.8%，严重TEAE发生率分别为11.1%、3.9%和11.6%。 与安慰剂相比，特立氟胺组最常见的TEAE为中性粒细胞减少、丙氨酸氨基转移酶升高和脱发。

结论：TOWER研究中国亚组中特立氟胺的有效性与安全性数据与研究总人群中的结果一致。特立氟胺有潜力满足中国多发性硬化患者的治疗需求。