MSJ Experimental Translational Clinical

Short report

Clinical efficacy of teriflunomide over a fixed 2-year duration in the TOWER study

Multiple Sclerosis Journal—Experimental, Translational and Clinical

April-June 2018, 1–5

DOI: 10.1177/2055217318775236

Mark S Freedman, Julia Morawski and Karthinathan Thangavelu

Abstract

Patients enrolled in the phase 3 TOWER study (NCT00751881) of teriflunomide had variable treatment durations (48–173 weeks). This has led to challenges when interpreting results in the context of other phase 3 trials of disease-modifying therapies for multiple sclerosis, which typically have a fixed 2-year duration. This communication reports clinical outcomes in TOWER over a fixed 2-year period. Reductions in annualised relapse rates and 12-week confirmed disability worsening associated with teriflunomide were comparable between overall intent-to-treat and fixed 2-year study populations in TOWER. Consistency in outcomes supports the inclusion of TOWER data in comparative analyses with other disease-modifying therapies.

ClinicalTrials.gov: NCT00751881.

Keywords: Teriflunomide, multiple sclerosis, clinical trial, phase 3, disease-modifying therapy, outcomes assessment

Date received: 5 January 2018; Revised received 21 March 2018; accepted: 12 April 2018

Introduction

Teriflunomide is a once-daily oral immunomodulator approved in 80 countries for the treatment of relapsing–remitting multiple sclerosis (MS). In two phase 3 studies in patients with relapsing forms of multiple sclerosis (RMS) – TEMSO[1] (NCT00134563) and TOWER[2] (NCT00751881) – teriflunomide 14 mg significantly reduced the annualised relapse rate (ARR) and risk of 12-week confirmed disability worsening (CDW), compared with placebo. Results from the phase 4 Teri-PRO study (NCT01895335) demonstrated high levels of patient satisfaction with teriflunomide treatment in both treatment-naïve patients and those switching from a prior disease-modifying therapy.[3] Teriflunomide has a well characterised safety and tolerability profile,[1,2] which remained consistent with long-term exposure.[4,5]

Patients in TOWER had variable treatment durations, ranging from 48 to 173 weeks,[1] with the trial ending 48 weeks after the last patient was randomised. Some health technology assessments and systematic reviews have excluded results from the TOWER dataset in meta-analyses of RMS studies, likely because, in contrast to most phase 3 trials, TOWER did not have a fixed 2-year treatment duration.[6–8] Therefore, we re-evaluated the TOWER dataset to determine whether clinical outcomes for a fixed 2-year duration and the full treatment period were consistent.

Methods

TOWER was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice[9] and the Declaration of Helsinki.[10] Study protocols were approved by central and local ethics committees and each site's institutional review board. All patients gave written consent prior to participation. Patients with RMS were randomised 1:1:1 to receive placebo or teriflunomide 7 mg or 14 mg (double-blind) for a minimum of 48 weeks; inclusion criteria for the study have previously been described.[1] The primary endpoint was ARR, and the key secondary

Correspondence to:
Mark S Freedman,
Multiple Sclerosis Research Clinic, University of Ottawa and the Ottawa Hospital Research Institute, 501 Smyth Road (Box #601), Ottawa, ON, K1H 8L6 Canada.
mfreedman@toh.ca

Mark S Freedman, Multiple Sclerosis Research Clinic, University of Ottawa and the Ottawa Hospital Research Institute, Canada

Julia Morawski, MS Global Health Economics and Value Assessment, Sanofi, USA

Karthinathan Thangavelu, Biostatistics, Sanofi, USA

endpoint was 12-week CDW (Expanded Disability Status Scale score increase of ≥1 point for baseline scores ≤5.5, or ≥0.5 points for baseline scores >5.5, sustained for a minimum of 12 weeks).

In this post hoc analysis, we compared ARR and 12-week CDW from the overall intent-to-treat (ITT) population with a study design that would fit a fixed 2-year study duration. The fixed-duration population included patients from the TOWER ITT population, based on their randomisation date, who could have received treatment for a minimum of 96 weeks. In the 2-year study analysis, data were censored at 96 weeks for patients whose treatment extended beyond this period. As the 14-mg dose of teriflunomide is the most widely approved and used dose in clinical practice, data presented here focus on outcomes in the 14-mg group only.

Results

Of the 758 patients in the ITT population (placebo and teriflunomide 14-mg groups only), 451 patients

Table 1. Demographics and baseline disease characteristics for patients receiving placebo and teriflunomide 14 mg in the overall ITT and fixed 2-year study populations.

	TOWER ITT population			TOWER 2-year study population		
	(*N*=758)[a]	Placebo (*n*=388)	Teriflunomide 14 mg (*n*=370)	(*N*=451)[b]	Placebo (*n*=228)	Teriflunomide 14 mg (*n*=223)
Age, years						
Mean (SD)	38.1 (9.3)	38.1 (9.1)	38.2 (9.5)	38.3 (9.3)	38.2 (9.2)	38.4 (9.4)
Women, *n* (%)	530 (69.9)	273 (70.4)	257 (69.5)	313 (69.4)	160 (70.2)	153 (68.6)
Race, *n* (%)						
White	629 (83.0)	317 (81.7)	312 (84.3)	405 (89.8)	207 (90.8)	198 (88.8)
Asian	108 (14.2)	60 (15.5)	48 (13.0)	32 (7.1)	15 (6.6)	17 (7.6)
Black	14 (1.8)	7 (1.8)	7 (1.9)	10 (2.2)	4 (1.8)	6 (2.7)
Other	7 (0.9)	4 (1.0)	3 (0.8)	4 (0.9)	2 (0.9)	2 (0.9)
Time since first symptoms of MS, years						
Mean (SD)	7.9 (6.7)[c]	7.6 (6.7)	8.2 (6.7)[d]	8.3 (6.9)	8.2 (7.3)	8.5 (6.6)[e]
Time since first diagnosis of MS, years						
Mean (SD)	5.1 (5.8)[c]	4.9 (5.7)	5.3 (5.9)[d]	5.3 (5.8)	5.1 (6.1)	5.6 (5.5)[e]
Number of relapses in past 1 year						
Mean (SD)	1.4 (0.7)[f]	1.4 (0.8)[g]	1.4 (0.7)[d]	1.4 (0.7)	1.4 (0.7)	1.5 (0.7)[e]
MS subtype, *n* (%)						
Relapsing–remitting	742 (98.1)[f]	378 (97.4)	364 (98.9)[h]	441 (98.0)[i]	222 (97.4)	219 (98.6)
Secondary progressive	6 (0.8)	4 (1.0)	2 (0.5)	4 (0.9)	3 (1.3)	1 (0.5)
Progressive relapsing	8 (1.1)	6 (1.5)	2 (0.5)	5 (1.1)	3 (1.3)	2 (0.9)
Baseline EDSS score						
Mean (SD)	2.7 (1.4)	2.7 (1.4)	2.7 (1.4)	2.6 (1.3)	2.7 (1.3)	2.6 (1.4)

[a]Overall ITT population includes all patients randomised to placebo or teriflunomide 14 mg in the core TOWER study who received at least one dose of study drug.
[b]Two-year study population includes patients treated for 96 weeks relative to individual randomisation dates and is extracted from the TOWER ITT population.
[c]*N*=757.
[d]*n*=369.
[c]*n*=222
[f]*N*=756.
[g]*n*=387.
[h]*n*=368.
[i]*N*=450.
EDSS: Expanded Disability Status Scale; ITT: intent-to-treat; MS: multiple sclerosis; SD: standard deviation.

met the criteria for inclusion in the fixed 2-year study, of whom 228 patients were randomised to the placebo group and 223 were randised to the teriflunomide 14-mg group. Patient demographics and baseline disease characteristics were similar between the overall ITT population and the fixed 2-year study population, and between the two treatment groups in both populations (Table 1); the only exception was a greater proportion of white patients in the 2-year placebo group versus the ITT population (P=0.0132). Patient disposition is reported in Supplementary Table 1.

Teriflunomide 14 mg significantly reduced ARR by 36.3% (P=0.0001) and 40.2% (P=0.0004) versus placebo in the overall ITT population and 2-year study population, respectively (Figure 1(a)). The risk of 12-week CDW was also significantly reduced in both populations versus placebo, by 31.5% (P=0.0442) and 38.7% (P=0.0479) in the overall ITT population and 2-year population, respectively (Figure 1(b)). Similarity between the overall ITT cohort and the 2-year subpopulation was also observed with respect to confirmed relapse, based on time-to-event analysis. Teriflunomide 14 mg reduced the risk of confirmed relapse by 36.9% for the ITT population versus placebo (P<0.0001, Figure 1(c)), and by 36.6% versus placebo for the 2-year study population (P=0.0027, Figure 1(d)).

Similar proportions of patients in each population reported adverse events (Supplementary Table 2).

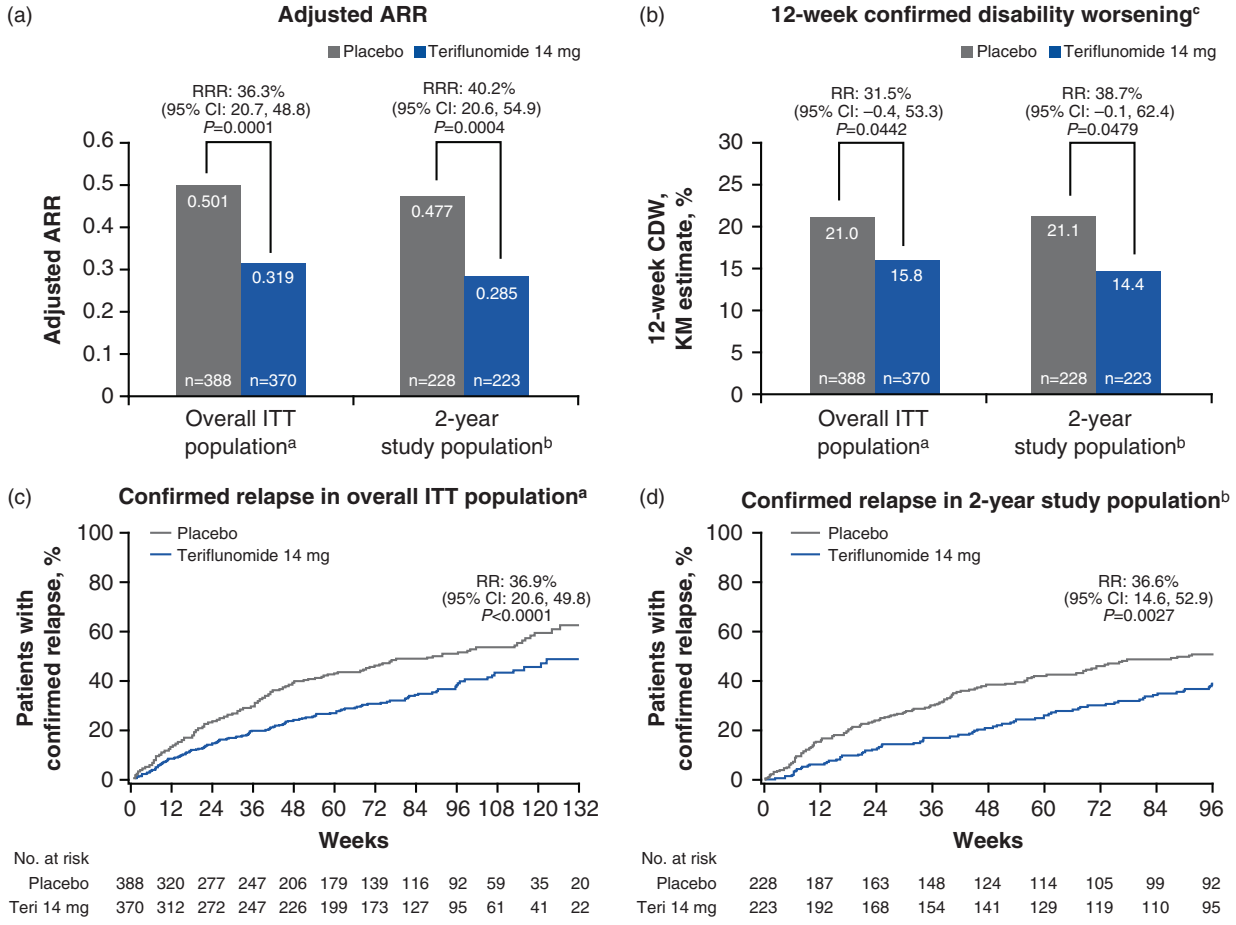

Figure 1. Efficacy results in the overall intent-to-treat (ITT) and 2-year study populations. [a]The overall ITT population includes all patients randomly assigned to placebo or teriflunomide 14 mg in the core TOWER study, who received at least one dose of study drug. [b]The 2-year study population includes patients treated for 96 weeks relative to individual randomisation dates and is extracted from the TOWER ITT population; the same statistical analysis was used as for the overall ITT population. [c]Observed number of patients (%) with 12-week confirmed disability worsening in placebo versus teriflunomide 14 mg groups: in ITT population, 65/388 (16.8%) versus 44/370 (11.9%); in 2-year study population, 42/228 (18.4%) versus 26/223 (11.7%). The 12-week confirmation of disability worsening should have occurred within the 2-year study period. ARR: annualised relapse rate; CI: confidence interval; RR: relative risk; RRR: relative risk reduction.

Discussion

The variable duration of treatment in TOWER presents a challenge when conducting comparative analyses with other clinical trials of disease-modifying therapies for MS. The main purpose of health technology assessments is to assimilate health and clinical data in order to inform policy decision-makers. These policies may result in allocation of funding to support new health interventions or to develop medical technologies. The exclusion of key results from a pivotal study could create bias in assessment conclusions, resulting in disadvantageous decisions for reimbursement for the treatment in question and potentially adversely impacting patient management.

This post hoc analysis demonstrates similar effects of teriflunomide between the fixed 2-year study population and the overall ITT population on the primary and key secondary outcomes of TOWER, which were also consistent with results from TEMSO, thereby supporting the inclusion of these results in future meta-analyses.

As in any clinical trial or post hoc analysis, there is the possibility of selection bias if patients with poor clinical outcomes discontinue. Nevertheless, in our analysis, the clinical outcomes were similar between the two populations studied. The consistency of results demonstrated between the two analysis populations may be of value when considering the design of future trials with respect to variable or fixed-duration treatment. Variable-duration trials may offer higher statistical power in detecting treatment differences compared with a fixed-duration treatment owing to the valuable additional follow-up time that contributes to analyses of ARR and the time to disability-worsening endpoints.

Conclusions

In the TOWER clinical trial of teriflunomide in patients with RMS, teriflunomide 14 mg significantly reduced ARR, and the risk of relapse and 12-week CDW compared with placebo, regardless of whether treatment duration was fixed or variable. The similarity of outcomes between the overall ITT population and the 2-year subpopulation in our report provides insight about the consistency of results of a clinical trial with variable treatment duration versus a fixed duration.

Acknowledgments

This study was supported by Sanofi. This paper was reviewed by Larisa Miller of Sanofi. Editorial assistance was provided by Louise Gildea of Fishawack Communications Ltd., also funded by Sanofi.

Conflict of interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MSF received research/educational grant support (Genzyme); honoraria/consulting fees (Actelion, Bayer HealthCare, Biogen Idec, Chugai, EMD Canada, Genzyme, Hoffman La-Roche, Novartis, Sanofi, Teva Canada Innovation); and is a member of company advisory boards/board of directors/other similar group (Bayer HealthCare, Biogen Idec, Chugai, Clene Nanomedicine, Merck, MedDay, Novartis, Sanofi, Teva Canada Innovation). JM is an employee of Sanofi. KT is an employee of Sanofi, with ownership interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by Sanofi.

Supplemental material

Supplementary material for this article is available online.

References

1. Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014; 13: 247–256.
2. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med* 2011; 365: 1293–1303.
3. Coyle PK, Khatri B, Edwards KE, et al. Patient-reported outcomes in relapsing forms of MS: real-world, global treatment experience with teriflunomide from the Teri-PRO study. *Mult Scler Relat Disord* 2017; 17: 107–115.
4. O'Connor P, Comi G, Freedman MS, et al. Long-term safety and efficacy of teriflunomide: nine-year follow-up of the randomized TEMSO study. *Neurology* 2016; 86: 920–930.
5. Comi G, Freedman MS, Kappos L, et al. Pooled safety and tolerability data from four placebo-controlled teriflunomide studies and extensions. *Mult Scler Relat Disord* 2016; 5: 97–104.
6. He D, Zhang C, Zhao X, et al. Teriflunomide for multiple sclerosis. *Cochrane Database Syst Rev* 2016; 3: CD009882.
7. Tramacere I, Del Giovane C, Salanti G, et al. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev* 2015; 18: Cd011381.

8. Couto E, Hamidi V, Ringerike T, et al. Medicines used for multiple sclerosis – a health technology assessment. *Interferon* 2015; 6: 1.
9. International Conference on Harmonisation Expert Working Group. *ICH harmonised tripartite guideline: guideline for good clinical practice E6(R1)*. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf (1996, accessed 13 March 2018).
10. World Medical Association. Declaration of Helsinki. *Bull WHO* 2001; 79: 373–374.