DX10

Clinical Outcomes in Patients With Faster Advancing MS Treated With Teriflunomide in TEMSO and TOWER

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OBJECTIVE

- **To investigate the clinical outcomes of teriflunomide-treated patients who had faster advancing MS (Multiple Sclerosis Severity Score [MSSS] >5) prior to treatment initiation in the TEMSO and TOWER studies**

INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for relapsing-remitting MS
- In 2 pivotal phase 3 trials in patients with relapsing forms of MS (RMS), teriflunomide 14 mg demonstrated consistent efficacy in reducing the risk of disability worsening confirmed for ≥12 weeks (TEMSO, NCT00134563, 29.8% hazard ratio reduction vs placebo, *P*=0.0279; TOWER, NCT00751881, 31.5% hazard ratio reduction vs placebo, *P*=0.0442) and in reducing the annualized relapse rate (ARR) (TEMSO, 31.5% relative risk reduction [RRR] vs placebo, *P*=0.0005; TOWER, 36.3% RRR vs placebo, *P*=0.0001)[1,2]
  - In TEMSO, teriflunomide 14 mg also demonstrated efficacy on magnetic resonance imaging (MRI) lesion activity in patients with RMS.[1] MRI was not performed in TOWER[2]
  - In both TEMSO and TOWER, teriflunomide 7 mg significantly reduced ARR, but not disability worsening[1,2]
- Teriflunomide has also been shown to significantly reduce brain volume loss vs placebo over 2 years (teriflunomide 7 mg, 27.6%, *P*=0.0019; teriflunomide 14 mg, 30.6%, *P*=0.0001) in a SIENA (structural image evaluation using normalization of atrophy) analysis of TEMSO MRI scans, consistent with its positive effects on disability worsening[3]
- The MSSS integrates disease duration and Expanded Disability Status Scale (EDSS) scores to provide an indication of disease severity, with higher scores reflecting faster advancing disease[4]
- In a post hoc analysis of pooled data from the TEMSO and TOWER studies, we evaluated clinical outcomes in a subgroup of patients with faster advancing MS, according to disease severity using a baseline MSSS of 5 as a cutoff

METHODS

Study Design

- TEMSO and TOWER were phase 3, multicenter, multinational, randomized, double-blind, parallel-arm, placebo-controlled studies[1,2]
  - In TEMSO and TOWER, patients with RMS were randomized 1:1:1 to placebo, teriflunomide 7 mg, or teriflunomide 14 mg. Patients received treatment for 2 years in TEMSO. In TOWER, study duration was variable, ending 48 weeks after the last patient was randomized
  - Inclusion criteria, and primary and secondary study endpoints for both studies, have been previously described[1,2]

Subgroup Analyses

- The efficacy of teriflunomide on ARR and disability worsening, confirmed for ≥12 weeks in a subgroup of patients with faster advancing MS, defined as patients with baseline MSSS >5, was evaluated in a post hoc analysis of the pooled TEMSO/TOWER dataset

Statistical Analysis

- Analysis of ARR was performed using a Poisson model, with the total number of confirmed relapses between the randomization date and date of last study medication intake defined as the response variable; treatment group, EDSS strata at baseline, and region defined as covariates; and log-transformed standardized study duration defined as an offset variable
- The risk of disability worsening confirmed for ≥12 weeks or ≥24 weeks was evaluated using a Cox proportional hazards model, and log-rank test with EDSS strata at baseline and region as covariates was used to make treatment group comparisons. The probability of disability worsening was derived from Kaplan–Meier estimates

RESULTS

Patients

- Demographics and baseline disease characteristics for all patients and patients with baseline MSSS >5 in the TEMSO/TOWER pool are shown in **Table 1**
- A total of 1184/2257 patients (52%) had MSSS >5 at baseline (**Table 1**)
  - Compared with the overall TEMSO/TOWER pool, patients with baseline MSSS >5 had higher EDSS scores and a shorter time since diagnosis and first symptoms, with a higher proportion having a progressive MS subtype with superimposed relapses

Annualized Relapse Rate

- Consistent with the significant effects of teriflunomide in the overall study population, ARR was significantly reduced by both doses of teriflunomide in the MSSS >5 subgroup (**Figure 1**)
- Time to first relapse was also reduced by both doses of teriflunomide in the MSSS >5 subgroup, with reductions in relapse risk of 43.2% (*P*<0.0001) and 28.8% (*P*=0.0014) for teriflunomide 14 mg and 7 mg vs placebo, respectively (**Figure 2**)

Disability Worsening

- In patients with baseline MSSS >5, teriflunomide 14 mg significantly reduced the risk of both ≥12-week and ≥24-week confirmed disability worsening (**Figures 3A** and **3B**), compared with placebo

CONCLUSIONS

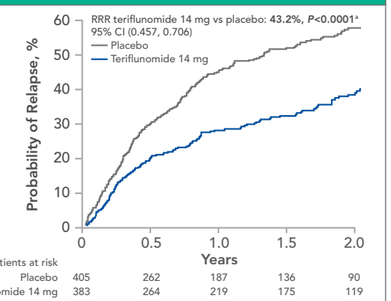
- **In a pooled subgroup analysis of patients in TEMSO and TOWER who had faster advancing disease, patients treated with teriflunomide had superior efficacy outcomes than patients treated with placebo**
  - **Teriflunomide 14 mg significantly reduced the risk of both ≥12-week and ≥24-week confirmed disability worsening**
  - **Both teriflunomide 7 mg and 14 mg significantly reduced ARR**
- **These data support the efficacy of teriflunomide in a broad spectrum of patients with RMS, including those with faster advancing disease, and are consistent with efficacy outcomes previously reported for both doses of teriflunomide in the individual studies and the TEMSO/TOWER pool[1,2]**

Table 1. Demographics and Baseline Disease Characteristics for Patients in the TEMSO/TOWER Pool

	All Patients[2]			Patients With Baseline MSSS >5		
	Placebo (n=752)	Teri 7 mg (n=774)	Teri 14 mg (n=731)	Placebo (n=405)	Teri 7 mg (n=396)	Teri 14 mg (n=383)
Age, mean (SD), y	38.2 (9.0)	37.4 (9.2)	38.0 (8.9)	38.6 (8.7)	37.9 (9.3)	38.0 (9.1)
Female, n (%)	548 (73)	555 (72)	513 (70)	288 (71.1)	280 (70.7)	262 (68.4)
Time since first symptoms, mean (SD), y	8.08 (6.93)	8.46 (6.79)	8.45 (6.74)[a]	6.54 (6.00)	7.15 (6.06)	6.54 (5.63)
Time since diagnosis, mean (SD), y	5.02 (5.63)	5.29 (5.40)[b]	5.42 (5.70)[a]	2.91 (3.04)	3.24 (3.32)	3.04 (3.01)
No. of relapses in previous year, median (min, max)	1.00 (0.0, 7.0)[c]	1.00 (0.0, 6.0)[d]	1.00 (0.0, 5.0)[e]	1.00 (0.0, 7.0)[f]	1.00 (0.0, 5.0)[g]	1.00 (0.0, 5.0)[h]
MS subtype, n (%)						
Relapsing-remitting	708 (94.1)	726 (93.8)	699 (95.9)[i]	369 (91.1)	361 (91.2)	361 (94.3)
Secondary progressive	26 (3.5)	20 (2.6)	14 (1.9)	22 (5.4)	13 (3.3)	11 (2.9)
Progressive relapsing	18 (2.4)	28 (3.6)	16 (2.2)	14 (3.5)	22 (5.6)	11 (2.9)
EDSS score						
Mean (SD)	2.69 (1.35)	2.70 (1.37)	2.69 (1.30)	3.39 (1.05)	3.47 (1.07)	3.34 (1.06)
Median (min, max)	2.50 (0.0, 6.0)	2.50 (0.0, 6.0)	2.50 (0.0, 6.5)	2.00 (2.0, 6.0)	1.50 (2.0, 6.0)	3.50 (2.0, 6.5)

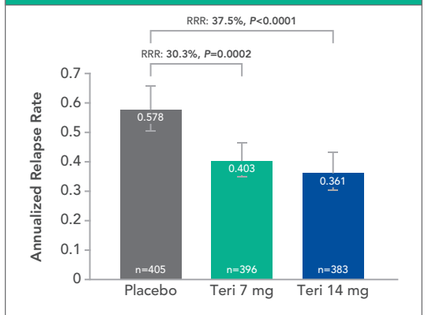
[a]n=730; [b]n=773; [c]n=665; [d]n=692; [e]n=643; [f]n=362; [g]n=357; [h]n=334; [i]n=729.
EDSS, Expanded Disability Status Scale; MSSS, Multiple Sclerosis Severity Score; SD, standard deviation.

Figure 2. Time to First Relapse in Patients With MSSS >5 at Baseline in the TEMSO/TOWER Pool



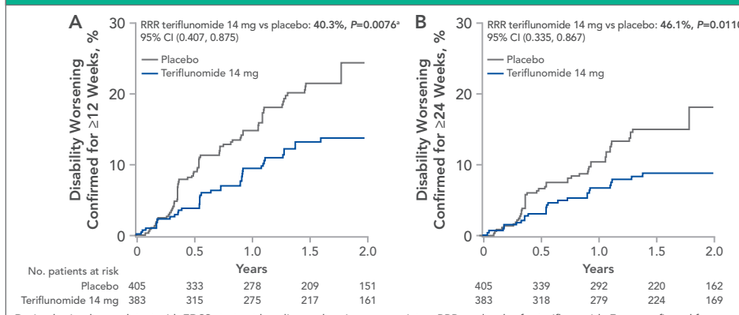
[a]Derived using log-rank test with EDSS strata at baseline and region as covariates. RRR vs placebo for teriflunomide 7 mg of time to first relapse, 28.8%, 95% CI (0.580, 0.872), *P*=0.0014.[a] CI, confidence interval; MSSS, Multiple Sclerosis Severity Score; RRR, relative risk reduction.

Figure 1. Annualized Relapse Rate in Patients With MSSS >5 at Baseline in the TEMSO/TOWER Pool



Error bars are 95% confidence intervals.
MSSS, Multiple Sclerosis Severity Score; RRR, relative risk reduction.

Figure 3. Risk of Disability Worsening Confirmed for (A) ≥12 Weeks or (B) ≥24 Weeks in Patients With MSSS >5 at Baseline in the TEMSO/TOWER Pool



[a]Derived using log-rank test with EDSS strata at baseline and region as covariates. RRR vs placebo for teriflunomide 7 mg confirmed for ≥12 weeks: 23.5%, 95% CI (0.536, 0.1092), *P*=0.1608[a]; confirmed for ≥24 weeks: 35.3%, 95% CI (0.414, 1.011), *P*=0.0706.[a]
CI, confidence interval; EDSS, Expanded Disability Status Scale; MSSS, Multiple Sclerosis Severity Score; RRR, relative risk reduction.

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Teriflunomide is approved in many countries, including the US and the European Union, for the treatment of relapsing multiple sclerosis or relapsing-remitting multiple sclerosis. This material may contain information that is outside of the approved labeling in some countries.

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