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Consistent Treatment Effect of Teriflunomide in Subgroups Based on Pre-trial Therapy: Pooled Analyses of TEMSO and TOWER

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BACKGROUND

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing–remitting MS (RRMS)
- Teriflunomide has been evaluated in two large phase 3 clinical studies with similar designs and patient populations:
  - TEMSO (**TE**riflunomide **MS O**ral, NCT00134563)[1]
  - TOWER (**T**eriflunomide **O**ral in people **W**ith relapsing multipl**E** scle**R**osis, NCT00751881)[2]
- A previous pooled analysis of TEMSO and TOWER key efficacy outcomes confirmed the consistent and robust effect of teriflunomide 14 mg on annualized relapse rate (ARR) and disability progression seen in the individual studies[1–3]
  - Teriflunomide 14 mg reduced ARR by 33.7% (P<0.001) and reduced the risk of sustained disability progression (confirmed for 12 weeks) by 30.5% (hazard rate reduction, P=0.003) compared with placebo
  - Teriflunomide 7 mg reduced ARR by 27.0% (P<0.001) and, although not significant, showed a reduction in disability progression (15.3%, P=0.139)
- Teriflunomide 14 mg and 7 mg had similar safety and tolerability profiles across studies and in pooled analyses
- Where studies of comparable size have similar enrollment criteria, interventions, and endpoints, pooled data analyses can provide additional valuable insight into treatment outcomes[4]
- Both TEMSO and TOWER included some patients who had received, and then discontinued treatment with, other disease-modifying therapies (DMTs) in the 2 years before study entry. These patients may be considered sub-optimal responders to their prior treatments and could be at higher risk of relapse or disease progression
- This poster presents pooled subgroup analyses from TEMSO and TOWER by pre-trial DMT use

OBJECTIVE

- To assess the consistency of the teriflunomide effect on ARR and disability progression across subgroups based on pre-trial MS therapy in the pooled TEMSO and TOWER dataset

METHODS

Study Designs

- TEMSO and TOWER were both phase 3, multicenter, multinational, randomized, double-blind, parallel-group, placebo-controlled studies[1,2]
  - Patients were randomized 1:1:1 to once-daily oral teriflunomide 14 mg or 7 mg, or placebo
  - In TEMSO, treatment was for a fixed duration of 108 weeks[1]
  - In TOWER, individual patients' treatment duration was based on time of enrollment. The study ended 48 weeks after the last patient was randomized. Mean treatment duration for TOWER was 78 weeks (minimum 48 weeks, maximum 152 weeks)[2]

Study Populations

- TEMSO and TOWER both enrolled patients aged 18–55 years with relapsing forms of MS meeting the McDonald diagnostic criteria (TEMSO, 2001 criteria[5]; TOWER, 2005 criteria[6]) and Expanded Disability Status Scale (EDSS) score ≤5.5[1,2]
  - ≥1 relapse in the 12 months before study entry or ≥2 relapses in the 24 months before study entry was also a requirement
- Patients were excluded from TEMSO/TOWER if they had received: natalizumab, any investigational drug in the last 6 months, interferon beta or glatiramer acetate in the last 4 (TEMSO) or 3 (TOWER) months, or intravenous immunoglobulins in the last 6 (TEMSO) or 3 (TOWER) months

Study Endpoints

- The primary endpoint for both TEMSO and TOWER was ARR[1,2]
- The key secondary outcome for both studies was sustained disability progression confirmed for 12 weeks
  - Defined as an increase from baseline of ≥1.0 EDSS point (or ≥0.5 points for a baseline EDSS score >5.5) for at least 12 weeks

Statistical Analysis

- Analyses were performed on the modified intent-to-treat population (mITT): all patients who were randomized and received ≥1 dose of study medication were analyzed in the treatment group to which they were randomized[1,2]
- Post hoc pooled analyses of ARR and 12-week confirmed disability progression were performed on subgroups defined by pre-trial therapy:
  - >1 prior DMT; 1 prior DMT; no prior DMT in the previous 2 years
- The consistency of treatment effects across subgroups (treatment-by-subgroup interaction) was assessed using a generalized estimating equation method for ARR and using a Cox regression model for disability progression. For both endpoints, models included terms for treatment, EDSS strata (≤3.5 or >3.5), region, and study in addition to subgroup and treatment-by-subgroup interaction
  - Subgroup analyses are designed to assess homogeneity of treatment effects across clinically relevant patient subgroups and not to test the treatment effect within each individual subgroup level

RESULTS

Analysis Population Characteristics

- A total of 2257 patients were randomized and 2251 are included in the mITT population and post hoc pooled analyses
- Baseline disease characteristics were generally well balanced between TEMSO and TOWER, as well as among treatment groups in the pooled dataset (**Table 1**)
  - The proportion of patients who had received prior DMT was higher in TOWER than in TEMSO
- Differences in some baseline characteristics among the post hoc analysis subgroups reflect the varying stages and severity of MS among enrolled patients
  - Patients with prior DMT use had longer times since first MS symptoms and first diagnosis than treatment-naïve patients

Efficacy Outcomes

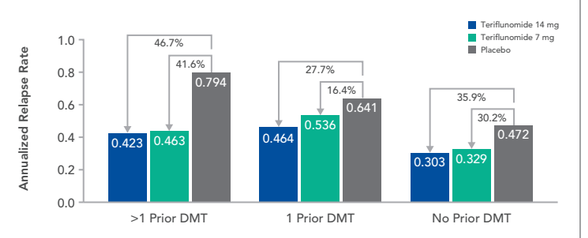
- In keeping with the premise that patients experiencing breakthrough, by meeting enrollment criteria for these studies despite prior treatment with one or more DMT, would be expected to have a poorer prognosis, the placebo rates of adjusted ARR and disability progression were higher for these subgroups compared with treatment-naïve patients (**Figure 1** and **Figure 2**)
- There were no significant between-subgroup differences in teriflunomide treatment effect
  - Reduction of ARR by teriflunomide 14 mg was consistent across subgroups defined by prior DMT use (**Figure 1**), and similar results were observed for teriflunomide 7 mg
  - Reduction of the risk of disability progression by teriflunomide 14 mg was also consistent across subgroups defined by prior DMT use (**Figure 2**)
  - The treatment effect of teriflunomide 14 mg on reducing the risk of disability progression was numerically greater in patients with >1 prior DMT (78.6%) compared with patients with 1 (46.6%) or no (17.4%) prior DMT

Table 1. Baseline Disease Characteristics by Prior Treatment in TEMSO and TOWER (mITT Population)

	TEMSO			TOWER			Pooled dataset (N=2251)		
	>1 Prior DMT	1 Prior DMT	No Prior DMT	>1 Prior DMT	1 Prior DMT	No prior DMT	>1 Prior DMT	1 Prior DMT	No Prior DMT
Patients, n	63	236	787	46	338	781	109	574	1568
Previous DMT in past 2 years, n (%)	63 (100)	236 (100)	0	46 (100)	338 (100)	0	109 (100)	574 (100)	0
Years since first diagnosis of MS, mean (SD)	7.54 (4.56)	7.42 (5.52)	4.53 (5.32)	7.07 (5.35)	6.78 (5.51)	4.34 (5.59)	7.34 (4.89)	7.04 (5.52)	4.44 (5.46)
Years since first symptoms of MS, mean (SD)	10.45 (6.29)	10.10 (6.19)	8.11 (7.07)	10.10 (6.11)	9.37 (6.38)	7.28 (6.81)	10.26 (6.19)	9.67 (6.31)	7.70 (6.95)
Months since most recent relapse onset, mean (SD)	6.68 (4.05)	6.61 (3.63)	6.25 (3.47)	6.00 (4.17)	5.74 (3.52)	5.03 (3.25)	6.39 (4.09)	6.10 (3.59)	5.64 (3.41)
Relapses in past year, median (range)	1.0 (0, 3)	1.0 (0, 6)	1.0 (0, 4)	1.0 (0, 4)	1.0 (0, 4)	1.0 (0, 7)	1.0 (0, 4)	1.0 (0, 6)	1.0 (0, 7)
Relapses in past 2 years, median (range)	2.0 (1, 9)	2.0 (1, 12)	2.0 (1, 7)	2.0 (1, 7)	2.0 (1, 9)	2.0 (1, 8)	2.0 (1, 9)	2.0 (1, 12)	2.0 (1, 8)
Relapsing–remitting, %	95.2	92.4	90.9	100	97.9	97.2	97.2	95.6	94.0
Baseline EDSS score, median (range)	2.5 (1.0, 5.5)	2.5 (0.0, 6.0)	2.5 (0.0, 6.0)	3.0 (0.0, 5.5)	2.5 (0.0, 5.5)	2.5 (0.0, 6.5)	2.5 (0.0, 5.5)	2.5 (0.0, 6.0)	2.5 (0.0, 6.5)

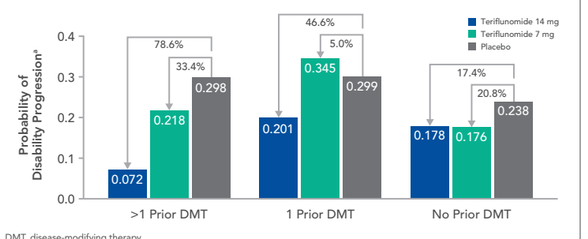
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; mITT, modified intent to treat; SD, standard deviation.

Figure 1. Adjusted Annualized Relapse Rate by Prior Treatment



DMT, disease-modifying therapy.
Overall P values for treatment-by-subgroup interaction: 14 mg, 0.4344; 7 mg, 0.3947; percentages represent relative risk reductions.

Figure 2. Disability Progression by Prior Treatment



DMT, disease-modifying therapy.
*Derived from Kaplan-Meier estimates at Week 132.
Overall P values for treatment-by-subgroup interaction: 14 mg, 0.0697; 7 mg, 0.6921; percentages represent relative reductions based on the hazard ratios.

CONCLUSIONS

- The placebo arms of the individual and pooled data sets show a higher ARR and risk of disability progression in patients experiencing one or more DMT prior to entering this study, confirming the suspicion that these patients are indeed at higher risk of disease activity
- Teriflunomide 14 mg showed a consistent treatment effect on relapse rate and disease progression across subgroups defined by pre-trial DMT use in analyses of pooled TEMSO and TOWER clinical trial data. Teriflunomide 7 mg showed a similar consistent effect on relapse rate
- The treatment effect of teriflunomide 14 mg appeared to be greatest in patients with experience of more than one prior DMT
- These findings support the beneficial effects of teriflunomide across a broad range of patients with RRMS, including robust activity in those patients who have previously used and discontinued other DMT

REFERENCES

1. O'Connor P, et al. *N Engl J Med.* 2011;365:1293-1303. 2. Confavreux C, et al. *Lancet Neurol.* 2014;13:247-256. 3. Kappos L, et al. Poster presented at: 29th Annual Congress of the ECTRIMS; October 2–5, 2013; Copenhagen, Denmark. P618. 4. Rothwell PM. *Lancet.* 2005;365:176-186. 5. McDonald WI, et al. *Ann Neurol.* 2001;50:121-127. 6. Polman CH, et al. *Ann Neurol.* 2005;58:840-846.

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