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Efficacy and Safety of Teriflunomide in Patients Switching From Other Disease-Modifying Therapies

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INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for relapsing-remitting MS
- In 2 pivotal phase 3 studies, TEMSO (NCT00134563)[1] and TOWER (NCT00751881),[2] teriflunomide 14 mg significantly reduced annualized relapse rate (ARR) and risk of disability progression confirmed for 12 weeks vs placebo
  - Teriflunomide 7 mg significantly reduced ARR compared with placebo[1,2]
  - For patients who had received other disease-modifying therapies (DMTs) before study entry, a minimum time interval between discontinuation of previous treatment and start of study treatment was required
  - Patients were excluded if they had ever received natalizumab, any investigational drug in the last 6 months, interferons or cytokine therapy in the last 4 (TEMSO) or 3 (TOWER) months, glatiramer acetate, or intravenous immunoglobulins in the last 6 (TEMSO) or 3 (TOWER) months
- In the phase 3 TENERE (NCT00883337) study, there was no difference between teriflunomide 14 mg and subcutaneous interferon beta-1a (sc IFNβ-1a) on either the primary endpoint of time to treatment failure (P=0.6), or the secondary endpoint of ARR (P=0.6). The study was designed as a teriflunomide superiority study[3]
  - In an open-label extension of TENERE, all patients, including those who previously received sc IFNβ-1a, received teriflunomide 14 mg without an intervening washout interval
- Patients who require a switch in treatment may potentially be considered suboptimal responders (due to safety/tolerability and/or efficacy reasons) and at higher risk of disease activity
  - Data from the pooled TEMSO/TOWER placebo-controlled studies, where a time interval between previous DMT use and study entry was required, together with data from patients switching directly from sc IFNβ-1a in the uncontrolled TENERE extension, provide complementary information that could clarify treatment effects in patients switching to teriflunomide from other DMTs

OBJECTIVE

- To assess efficacy and safety of teriflunomide in patients switching from other DMTs, either directly or after a time interval, using data from the TENERE open-label extension and pooled analysis of TEMSO and TOWER

METHODS

Study Design: TEMSO and TOWER

- Patients with relapsing forms of MS were randomized 1:1:1 to once-daily oral teriflunomide 14 mg or 7 mg, or placebo[1,2]
- Full details of study designs and inclusion/exclusion criteria have been published previously[1,2]
- Efficacy endpoints included ARR and disability progression

Study Design: TENERE

- In TENERE (a rater-blinded phase 3 study), patients with relapsing forms of MS were randomized 1:1:1 to teriflunomide 14 mg or 7 mg, or sc IFNβ-1a 44 μg
- Patients completing TENERE were eligible to participate in an open-label extension in which all patients received teriflunomide 14 mg, regardless of their previous treatment allocation
- Efficacy endpoints in the extension study included ARR
- Results presented here are based on an interim analysis of the extension with a cutoff date of October 2, 2014

Statistical Analysis

- For the pooled TEMSO and TOWER dataset, analyses were performed on the modified intent-to-treat population, defined as all patients who received ≥1 dose of study medication; data were analyzed in the treatment group to which patients were randomized[1,2]
  - Post hoc analyses of ARR and disability progression confirmed for 12 weeks were performed on subgroups defined by pretrial therapy: ≥2 prior DMTs, 1 prior DMT, or no prior DMT in the previous 2 years
  - Homogeneity of treatment effects across subgroups (treatment-by-subgroup interaction) and the rates of adjusted ARR and disability progression in the placebo arms of each subgroup were assessed using a generalized estimating equation method for ARR and a Cox regression model for disability progression. For both endpoints, models included terms for treatment, Expanded Disability Status Scale strata (≤3.5 or >3.5 points), region, and study, in addition to subgroup and treatment-by-subgroup interaction
- For the TENERE core study and extension, analyses were performed on the intent-to treat population[3]
  - Data are presented in 14-mg/14-mg, 7-mg/14-mg, and sc IFNβ-1a/14-mg treatment groups
  - Adjusted ARRs were derived using the Poisson model, with the total number of confirmed relapses with onset between inclusion date and last-dose date as the response variable; treatment, Expanded Disability Status Scale strata, and region as covariates; and log-transformed treatment duration as an offset variable

RESULTS

Patients

- Baseline disease characteristics for the TEMSO/TOWER modified intent-to-treat population (N=2251) are shown in **Table 1**. Disease duration was longer in the subgroup of patients who had used ≥2 prior DMTs vs those who had used ≤1 prior DMT
  - Patients who had used ≥1 prior DMT in the 2 years before study entry had received ≥1 of the following DMTs: glatiramer acetate, IFNβ, fingolimod, or natalizumab
- Of 249 patients who completed the TENERE study, 237 (95%) entered the extension
- Baseline characteristics (at core study entry) for the sc IFNβ-1a/14-mg group in the TENERE extension are shown in **Table 1** and were broadly similar across the 14-mg/14-mg, 7-mg/14-mg, and sc IFNβ-1a/14-mg treatment groups[4]

Annualized Relapse Rate

- In the patients randomized to receive placebo in TEMSO/TOWER, within each subgroup defined by prior DMT use, adjusted ARRs were higher for patients who had used ≥2 DMTs or 1 prior DMT vs treatment-naïve patients (**Figure 1**)
- Teriflunomide 14 mg consistently reduced ARR in all subgroups defined by prior DMT use vs placebo (**Figure 1**), with no significant treatment-by-subgroup interactions; reductions were significant in patients who had received 1 prior DMT (P=0.0142)
  - The comparison for reductions in ARR for teriflunomide 14 mg vs placebo in patients who had received ≥2 prior DMTs resulted in P=0.0569. The smaller number of patients in this subgroup could have resulted in lesser power for the comparison
  - Teriflunomide 7 mg numerically reduced ARR across all subgroups vs placebo (**Figure 1**)

Table 1. Baseline Disease Characteristics, Pooled TEMSO and TOWER Studies by Prior Treatments,[5] and Patients Switching From sc IFNβ-1a to Teriflunomide 14 mg in TENERE Extension Study[4]

	Pooled TEMSO and TOWER Studies[a]			TENERE Extension Study[b]
	≥2 Prior DMTs	1 Prior DMT	No Prior DMT	sc IFNβ-1a/14 mg
Patients, n	109	574	1568	59
Relapsing-remitting MS, %	97.2	95.6	94.0	100
Baseline EDSS score, median (min:max)	2.5 (0.0:5.5)	2.5 (0.0:6.0)	2.5 (0.0:6.5)	2.0 (0.0:5.5)
Relapses in past year, median (min:max)	1.0 (0:4)	1.0 (0:6)	1.0 (0:7)	1.0 (0:5)
Years since first symptoms of MS, mean (SD)	10.26 (6.19)	9.67 (6.31)	7.70 (6.95)	7.63 (7.57)
Months since most recent relapse onset, mean (SD)	6.39 (4.09)	6.10 (3.59)	5.64 (3.41)	11.53 (12.59)

[a]Modified intent-to-treat population; [b]intent-to-treat population.
Baseline characteristics in the TENERE extension are based on patients who entered the extension at core study entry and were broadly similar across the teriflunomide 14-mg/14-mg, teriflunomide 7-mg/14-mg, and sc IFNβ-1a/teriflunomide 14-mg treatment groups; however, only the sc IFNβ-1a/teriflunomide 14-mg group is shown.
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; sc IFNβ, subcutaneous interferon beta; SD, standard deviation.

- In the TENERE extension, the ARR in patients switching from sc IFNβ-1a to teriflunomide 14 mg was similar to that observed in this group at the end of the core study (**Figure 1**)
  - ARR remained low in all treatment groups: 0.239 in patients switching from IFNβ-1a, 0.181 in patients continuing teriflunomide 14 mg, and 0.223 in patients switching from teriflunomide 7 mg to 14 mg
  - No significant differences were seen between groups

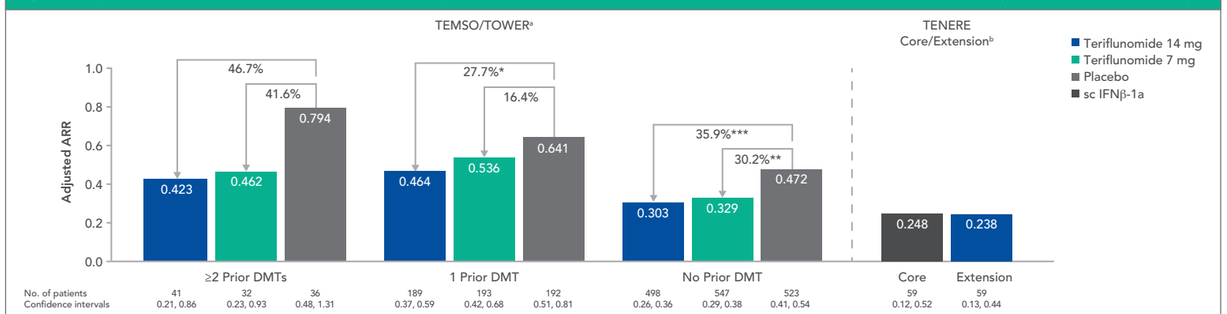
Disability Progression (Pooled TEMSO and TOWER Studies)

- In the placebo arms of each subgroup defined by prior DMT use, there was a greater risk of disability progression in patients who had received 1 prior DMT vs treatment-naïve patients. Although not statistically significant (possibly due to smaller sample size), this risk was also greater in patients who had used ≥2 prior DMTs (**Figure 2**)
- Teriflunomide 14 mg reduced the risk of disability progression in all subgroups defined by prior DMT use vs placebo (**Figure 2**), with no significant treatment-by-subgroup interactions; reductions were significant in patients who had received 1 prior DMT (P=0.0077) and P=0.0550 in patients who had received ≥2 prior DMTs

Safety

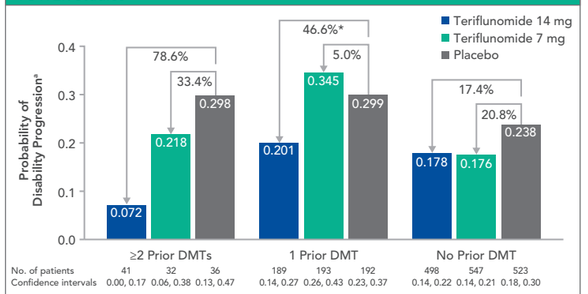
- TEMSO and TOWER demonstrated a consistent and manageable safety profile for teriflunomide, similar for the 14-mg and 7-mg doses[1,2]
- The incidence and nature of adverse events in the TENERE extension were similar in all groups[4] and consistent with previous studies
  - There were no new or unexpected adverse events associated with switching to teriflunomide

Figure 1. Adjusted ARR in Pooled TEMSO and TOWER Studies by Prior Treatments[5] and in Patients Switching From sc IFNβ-1a to Teriflunomide 14 mg in TENERE Extension Study[4]



[a]Modified intent-to-treat population; [b]intent-to-treat population; only sc IFNβ-1a/teriflunomide 14-mg group is shown. *, **, and *** denote P<0.05, P<0.001, and P<0.0001 vs placebo, respectively.
ARR, annualized relapse rate; DMT, disease-modifying therapy; sc IFNβ, subcutaneous interferon beta.

Figure 2. Disability Progression by Prior Treatment, Pooled TEMSO and TOWER Studies[5]



Modified intent-to treat population.
[a]Derived from Kaplan-Meier estimates at Week 132.
Percentages represent relative risk reductions based on the hazard ratios; * denotes P<0.05 vs placebo.
DMT, disease-modifying therapy.

CONCLUSIONS

- In the pooled TEMSO/TOWER dataset, teriflunomide 14 mg reduced ARR and disease progression across all subgroups defined by prior DMT use
- In the TENERE extension study, ARR remained low in patients switching from sc IFNβ-1a to teriflunomide 14 mg
- Analyses of the pooled TEMSO/TOWER studies and TENERE extension demonstrates efficacy for teriflunomide 14 mg, regardless of pretrial therapy
  - Efficacy, supported by statistically significant results as well as numerical trends in this post hoc analysis with small subgroups of patients, and consistent safety was observed in patients who had previously used and discontinued other DMTs (with or without a washout period) before commencing teriflunomide treatment

REFERENCES

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Disclaimer

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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