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Efficacy of Teriflunomide in MS Patients With a Primary Presentation of Optic Neuritis: A Subgroup Analysis of the Phase 3 TOPIC Study

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OBJECTIVE

- **To report clinical and magnetic resonance imaging (MRI) outcomes from a subgroup of patients with a primary presentation of optic neuritis (ON) in the TOPIC study**

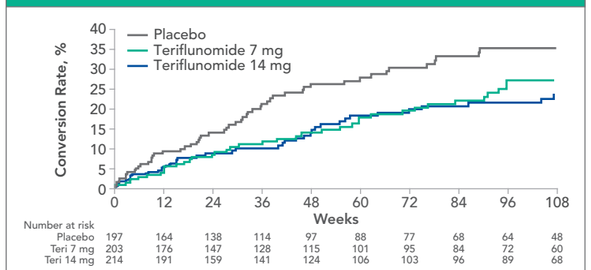
CONCLUSIONS

- **Treatment with teriflunomide 14 mg significantly reduced the risk of relapse determining conversion to CDMS in patients with a primary presentation of ON, including those with monofocal presentation**
- **Teriflunomide 14 mg also had a significant impact on MRI lesion activity, with more patients free of either Gd-enhancing lesions or UAL activity compared with placebo**
- **These findings extend the positive findings of teriflunomide, as an effective agent in treating patients with early MS, to include patients with ON**

INTRODUCTION

- In ~85% of patients with MS, disease onset is marked by an initial neurological event consistent with demyelination, known as clinically isolated syndrome[1]
- Presentations of clinically isolated syndrome can be either monofocal or multifocal, and typically affect the optic nerve, brainstem/cerebellum, spinal cord, or cerebral hemispheres[2]
  - ON is the presenting symptom in ~20% of patients with MS[1]
- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS
- TOPIC (NCT00622700) is a phase 3 study designed to evaluate the efficacy and safety of teriflunomide in patients with a first clinical episode suggestive of MS[3]
  - Teriflunomide significantly reduced the risk of relapse that determined conversion to clinically definite MS (CDMS; primary endpoint; **Figure 1**) and the occurrence of relapse or new MRI lesion vs placebo[3,4]
  - Safety results in the TOPIC trial were consistent with those from other clinical trials of teriflunomide[5,6]

Figure 1. Time to Relapse Determining Conversion to CDMS in All Patients[3]



Modified intent-to-treat population. CDMS, clinically definite MS.
Reprinted from *Lancet Neurol*, Vol 13, Miller AE, Wolinsky JS, Kappos L, Comi G, Freedman MS, Olsson TP, Bauer D, Benamor M, Truffinet P, O'Connor PW; for the TOPIC Study Group. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial, 977-986, Copyright (2014), with permission from Elsevier.

METHODS

- Patients were randomized (1:1:1) and treated with oral placebo, teriflunomide 7 mg, or teriflunomide 14 mg[3]
- Patients with a primary presentation of ON, and with an MRI scan demonstrating ≥2 T_2 lesions of ≥3 mm in diameter (ie, at least 1 lesion periventricular in location or ovoid in shape), were identified post hoc based on the description of symptoms by the investigators
- These patients were further stratified according to monofocal or multifocal ON presentation at baseline

RESULTS

Study Population

- Patient demographics and baseline disease characteristics of the overall TOPIC patient population and the patient subpopulation with ON are shown in **Table 1**
  - Of the 618 patients randomized and treated in TOPIC, 200 (32.4%) had a primary presentation of ON
  - Of those patients with ON, a greater proportion had monofocal (n=147) vs multifocal (n=53) presentation

Table 1. Demographics and Baseline Disease Characteristics of the Overall TOPIC Patient Population and the Optic Neuritis Patient Subpopulation

	All Randomized Patients (N=618)	Optic Neuritis (n=200)	Monofocal Optic Neuritis (n=147)	Multifocal Optic Neuritis (n=53)
Female, n (%)	419 (67.8)	145 (72.5)	106 (72.1)	39 (73.6)
Age, mean (SD), y	32.1 (8.5)	32.1 (8.7)	31.8 (8.7)	32.8 (8.9)
White, n (%)	594 (96.1)	195 (97.5)	145 (98.6)	50 (94.3)
Time since neurological event, mean (SD), mo	1.85 (0.55)	1.81 (0.56)	1.79 (0.55)	1.85 (0.57)
EDSS score Mean (SD) Median (min, max)	 1.67 (1.00) 1.50 (0.0, 6.0)	 1.55 (1.03) 1.50 (0.0, 5.5)	 1.32 (0.86) 1.50 (0.0, 3.5)	 2.20 (1.18) 2.00 (0.0, 5.5)
Number of Gd-enhancing lesions, mean (SD)[a] Placebo Teriflunomide 7 mg Teriflunomide 14 mg	 1.4 (4.1) 1.1 (3.0) 1.3 (3.7)	 0.6 (1.5) 1.3 (4.0) 0.6 (1.4)	 0.4 (1.0) 1.1 (2.3) 0.6 (1.5)	 1.6 (2.7) 1.6 (6.0) 0.3 (1.0)
Patients with ≥1 Gd-enhancing lesion, n (%)[a] Placebo Teriflunomide 7 mg Teriflunomide 14 mg	 58 (29.4) 66 (32.2) 70 (32.4)	 13 (22.8) 24 (31.6) 16 (23.9)	 9 (20.0) 16 (31.4) 14 (27.5)	 4 (33.3) 8 (32.0) 2 (12.5)

[a]Number of patients in the placebo/7-mg/14-mg groups: All randomized patients, 197/205/216; ON, 57/76/67; monofocal ON, 45/51/51; multifocal ON, 12/25/16, respectively.
EDSS, Expanded Disability Status Scale; Gd, gadolinium; mo, months; ON, optic neuritis; SD, standard deviation.

Clinical Outcomes

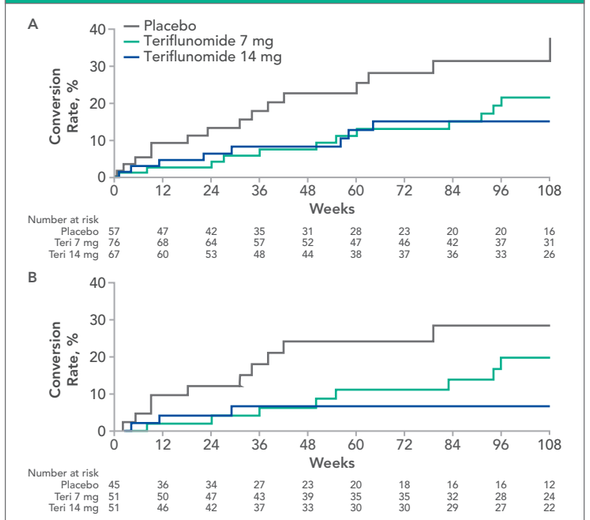
- Consistent with outcomes observed in the overall TOPIC population, treatment with teriflunomide 14 mg decreased the risk of relapse determining conversion to CDMS in patients with ON compared with placebo (58.4% reduction, *P*=0.0458) (**Table 2**, **Figure 2A**)
  - For teriflunomide 7 mg vs placebo, this risk was reduced by 49.9% (*P*=0.0755)
- Teriflunomide 14 mg reduced the risk of relapse determining conversion to CDMS in patients with a monofocal presentation of ON (n=147) compared with placebo (75.7% reduction, *P*=0.0325) (**Table 2**, **Figure 2B**)
  - For teriflunomide 7 mg vs placebo, this risk was reduced by 43.6% (*P*=0.2312)
- In patients with a multifocal presentation of ON (n=53), reductions were not significant for either dose of teriflunomide vs placebo, likely because of the small subgroup size (**Table 2**)

Table 2. Relapse Determining Conversion to CDMS in Patients With Optic Neuritis

	Teriflunomide 7 mg vs Placebo	Teriflunomide 14 mg vs Placebo
Patients with ON Hazard ratio (95% CI) Risk reduction, % *P* value	 0.501 (0.234, 1.074) 49.9 *P*=0.0755	 0.416 (0.176, 0.984) 58.4 *P*=0.0458
Patients with monofocal presentation of ON Hazard ratio (95% CI) Risk reduction, % *P* value	 0.564 (0.221, 1.441) 43.6 *P*=0.2312	 0.243 (0.067, 0.889) 75.7 *P*=0.0325
Patients with multifocal presentation of ON Hazard ratio (95% CI) Risk reduction, % *P* value	 0.495 (0.131, 1.877) 50.5 *P*=0.3012	 0.893 (0.254, 3.140) 10.7 *P*=0.8604

Modified intent-to-treat population.
CDMS, clinically definite MS; CI, confidence interval; ON, optic neuritis.

Figure 2. Time to Relapse Determining Conversion to CDMS in (A) All Patients With Optic Neuritis and (B) Patients With Monofocal Presentation of Optic Neuritis[4]

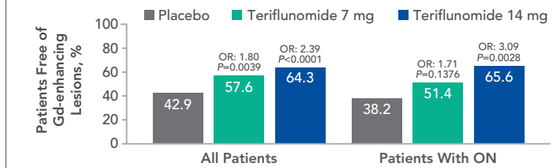


Modified intent-to-treat population.
CDMS, clinically definite MS.

MRI Outcomes

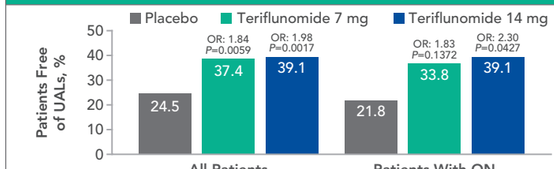
- At baseline, a similar proportion of patients with ON had gadolinium (Gd)-enhancing lesions in the placebo and teriflunomide groups (**Table 1**)
- Following treatment, a greater proportion of patients treated with teriflunomide 14 mg were free of Gd-enhancing lesions (ie, 0 Gd-enhancing lesions per MRI scan) compared with placebo-treated patients: odds ratio (OR) 3.09, 95% confidence interval (CI): 1.46, 6.54, *P*=0.0028 (**Figure 3**)
  - For teriflunomide 7 mg vs placebo, OR was 1.71 (95% CI: 0.84, 3.48), *P*=0.1376
- Following treatment, the proportion of patients with ≥4 Gd-enhancing lesions was smaller in both teriflunomide groups (14 mg, 7.8%; 7 mg 18.9%) vs the placebo group (34.5%)
  - For teriflunomide 14 mg vs placebo, OR was 6.23 (95% CI: 2.14, 18.13), *P*=0.0003; for teriflunomide 7 mg vs placebo, OR was 2.26 (95% CI: 1.01, 5.06), *P*=0.0442
- The impact of teriflunomide on Gd-enhancing lesions in patients with ON is similar to the impact of teriflunomide observed in the overall patient population (**Figure 3**)
- Following treatment with teriflunomide 14 mg, a greater proportion of patients were free of unique active lesions (UALs) compared with placebo-treated patients: OR was 2.30 (95% CI: 1.02, 5.18), *P*=0.0427 (**Figure 4**)
  - For teriflunomide 7 mg vs placebo, OR was 1.83 (95% CI: 0.82, 4.07), *P*=0.1372
- Following treatment, the proportion of patients with ≥4 UALs was also smaller in both teriflunomide groups (14 mg, 26.6%; 7 mg, 43.2%) vs the placebo group (54.5%)
  - For teriflunomide 14 mg vs placebo, OR was 3.32 (95% CI: 1.54, 7.15), *P*=0.0019; for teriflunomide 7 mg vs placebo, OR was 1.58 (95% CI: 0.78, 3.18), *P*=0.2039
- The impact of teriflunomide on UALs in the subgroup of patients with ON is similar to the impact of teriflunomide observed in the overall patient population (**Figure 4**)

Figure 3. Proportion of Patients in the Overall Population and Subgroup of Patients With ON Free of Gd-enhancing Lesions Following Treatment



Gd, gadolinium; ON, optic neuritis; OR, odds ratio (vs placebo).

Figure 4. Proportion of Patients in the Overall Population and Subgroup of Patients With ON Free of Unique Active Lesions Following Treatment



ON, optic neuritis; OR, odds ratio (vs placebo); UAL, unique active lesion.

References

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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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