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Review

# The efficacy and safety of teriflunomide based therapy in patients with relapsing multiple sclerosis: A meta-analysis of randomized controlled trials

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ABSTRACT

The aim of this study was to evaluate the efficacy and safety of teriflunomide in reducing the frequency of relapses and progression of physical disability in patients with relapsing multiple sclerosis (RMS). Literatures were searched in Pubmed, Medline and Embase to screen citations from January 1990 to April 2015. Studies of parallel group design comparing teriflunomide and placebo for RMS were screened. After independent review of 234 citations by two authors, seven studies were identified as meeting the inclusion criteria. The results showed teriflunomide (7 and 14 mg) could significantly reduce annualized relapse rate and teriflunomide at the higher dose could also decrease the disability progression (risk ratio (RR) = 0.69, 95% confidence interval (CI): 0.55–0.87). And teriflunomide significantly reduce annualized rates of relapses with sequelae-EDSS/FS, relapses leading to hospitalization, and relapses requiring IV corticosteroids. Patients treated with teriflunomide 14 mg have a lower annualized rate of relapses with sequelae-investigator (RR = 0.37, 95% CI: 0.26–0.52). Teriflunomide 7 mg has a higher incidence of diarrhea (RR = 1.73, 95% CI: 1.32–2.26) and hair thinning (RR = 1.99, 95% CI: 1.4–2.81), while teriflunomide 14 mg has a higher incidence of diarrhea (RR = 1.71, 95% CI: 1.34–2.18), hair thinning (RR = 2.81, 95% CI: 2.02–3.91) and nausea (RR = 1.65, 95% CI: 1.03–2.31) compared with placebo. The incidence of elevated alanine aminotransferase levels was also higher with teriflunomide than with placebo. However, the incidence of serious adverse events was similar across groups. In conclusion, teriflunomide significantly reduces annualized relapse rates and disability progression with a similar safety and tolerability profile to placebo.



## 1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease affecting central nervous system in which autoreactive $CD4^+$ and $CD8^+$ T lymphocytes, B lymphocytes, antibodies, macrophages and cytokines synergize in myelin sheath attack and injury of the underlying axons [1,2]. The overall incidence rate of MS in the world is 2.8 cases per 100,000 person-year and it affects 2.1 million people worldwide [3]. Relapse is one of the representative clinical features of MS. The symptoms of MS greatly affect the psychological and emotional state, and quality of life of patients with MS, resulting in a major financial burden on the patients, family and society [4]. The first-line treatment for relapsing forms of multiple sclerosis (RMS) is mainly injectable disease-modifying therapies including interferon beta and glatiramer acetate. However, these therapies always lead to injection-related adverse events.

Teriflunomide is a novel oral disease-modifying therapy (DMT) in development for the treatment of RMS [5]. As the principal active metabolite of leflunomide, teriflunomide has been approved for the treatment of rheumatoid arthritis [6,7]. Teriflunomide could selectively inhibit dihydroorotate dehydrogenase which is required by rapidly dividing B and T lymphocytes and limiting the immune responses. Thus, it is considered to inhibit MS disease activity [5,8].

Previous studies have indicated the efficacy and safety of teriflunomide in RMS therapy. However, the sample size of those studies was small. Therefore, we performed a meta-analysis including current double-blind randomized controlled trials (RCTs) to further evaluate the efficacy and safety of teriflunomide for RMS treatment.

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## 2. Methods

### 2.1. Search strategy and inclusion criteria

Databases (Embase, Medline, and Pubmed) were searched for RCTs from January 1990 to April 2015. The key words "teriflunomide" and "relapsing multiple sclerosis" were used in screening relevant citations. The inclusion criteria were: (1) the studies were RCTs; (2) the studies provided the data at least with one of main outcomes, including annualized relapse rate, disability progression, relapse outcomes, most common adverse events and serious adverse events; (3) the trials should be placebo controlled; (4) the dose of teriflunomide should be 7 mg or 14 mg.

### 2.2. Data extraction and quality assessment

Two reviewers extracted the data from included studies independently. The following information was extracted from each study: first author name; year of publication; number of patients; annualized relapse rate; disability progression; relapse outcomes; most common adverse events; serious adverse events. The Jadad score was used to assess the quality of included studies [9]. The studies with score no less than 3 were regarded as high quality RCTs, while the studies with score less than 3 were defined as low quality ones.

### 2.3. Assessment of efficacy and statistical analysis

Annualized relapse rate, disability progression and relapse outcomes were used to evaluate the efficacy in RMS. Data analysis was performed by using the Stata12 for each individual study, dichotomous data were reported as risk ratio (RR) with 95% confidence interval (CI). Heterogeneity between studies was assessed by Cochrane Q statistics and $I^2$ test. A significant level of no less than 50% for $I^2$ test was considered as evidence of heterogeneity. Fix effect model was used when there was no evidence of heterogeneity, otherwise random effect model was chosen. Publication bias was evaluated by Begg's test and $P > 0.05$ was regarded as no publication bias [10].

## 3. Results

### 3.1. Search results and characteristics

A total of 234 citations were obtained via database searches, and seven met the inclusion criteria for this study (Fig. 1). A total of 3054 patients have been involved, in which 1010 subjects were treated with placebo, 1040 subjects with 7 mg teriflunomide and 1004 subjects with 14 mg teriflunomide. The information in these citations is summarized in Table 1. All seven studies have been assessed by Jadad score system with score no less than 3 (Table 1). In the seven included studies, O'Connor [11,12] and Miller [13] reported the results of the Teriflunomide Multiple Sclerosis Oral (TEMSO) trials, Miller [14] reported the results of the TOPIC trial, and Confavreux [15] and Miller [16] reported the results of the Teriflunomide Oral in People With Relapsing Multiple Sclerosis (TOWER) trials.

### 3.2. Efficacy

#### 3.2.1. Annualized relapse rate

Annualized relapse rate was defined as the number of confirmed relapses per patient-year and was reported in four studies. The results of meta-analysis showed that teriflunomide significantly reduced the annualized relapse rate at either 7 mg (RR = 0.72, 95% CI: 0.64–0.81) or 14 mg (RR = 0.67, 95% CI: 0.59–0.76) compared with placebo. There was no heterogeneity present (Fig. 2).

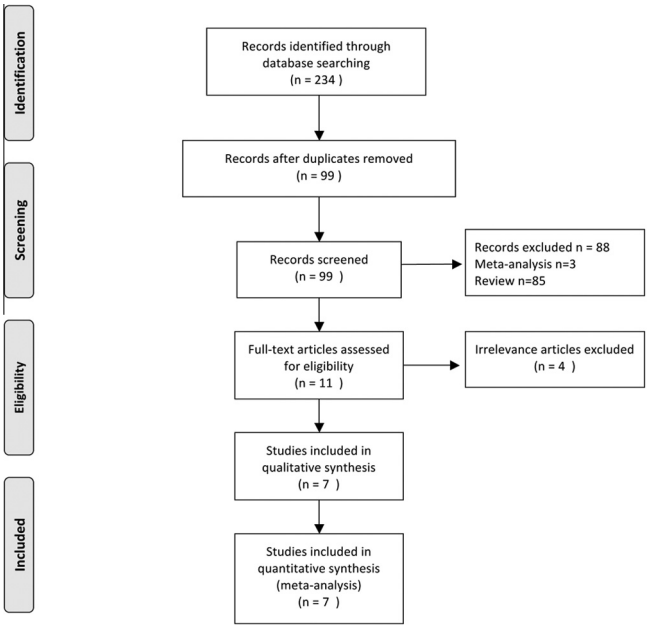


**Fig. 1.** Flow diagram of the studies identified.

#### 3.2.2. Disability progression

Disability progression was defined as an increase from baseline of at least 1.0 point in the EDSS score (or at least 0.5 point for patients with a baseline EDSS score greater than 5.5) that persisted for at least 12 weeks. Three trials have reported the disability progression. The results indicated that teriflunomide at the higher dose could significantly reduce disability progression compared with placebo (RR = 0.69, 95% CI: 0.55–0.87), while teriflunomide at the lower dose has a similar effect with placebo (RR = 0.86, 95% CI: 0.69–1.07). There was no heterogeneity present (Fig. 3).

#### 3.2.3. Effects of teriflunomide treatment on relapse outcomes

The annualized rate of relapse with sequelae, defined by EDSS/FS increase at 30 days post relapse was lower in both teriflunomide groups than in the placebo group (teriflunomide 7 mg vs. placebo, RR = 0.64, 95% CI: 0.49–0.82; teriflunomide 14 mg vs. placebo, RR = 0.59, 95% CI: 0.45–0.77). The annualized rate of relapse with sequelae, determined at the end of the relapse by the investigator, was lower in teriflunomide 14 mg group than in placebo group (RR = 0.37, 95% CI: 0.26–0.52). The annualized rate of relapses leading to hospitalization was lower in both teriflunomide groups than in the placebo group (teriflunomide 7 mg vs. placebo, RR = 0.7, 95% CI: 0.51–0.95; teriflunomide 14 mg vs. placebo, RR = 0.51, 95% CI: 0.41–0.64). The annualized rate of relapses requiring IV corticosteroids was lower in both teriflunomide groups than in the placebo group (teriflunomide 7 mg vs. placebo, RR = 0.63, 95% CI: 0.51–0.78; teriflunomide 14 mg vs. placebo, RR = 0.51, 95% CI: 0.41–0.64, Fig. 4).

### 3.3. Safety

#### 3.3.1. Common adverse events during treatment

Among the most common adverse events, teriflunomide at the lower dose has a higher incidence of diarrhea (RR = 1.73, 95% CI: 1.32–2.26) and hair thinning (RR = 1.99, 95% CI: 1.4–2.81), while teriflunomide at the higher dose has a higher incidence of diarrhea