Teriflunomide

Jiwon Oh, MD, FRCPC

Paul W. O'Connor, MD, MSc, FRCPC

Summary

Teriflunomide is a novel disease-modifying agent that was recently approved for use in the treatment of multiple sclerosis (MS). Teriflunomide has demonstrated clinical efficacy and safety in a number of large, multicenter, phase III clinical trials and is an attractive agent to add to the growing repertoire of available treatments for MS, as it has the benefit of oral administration. Furthermore, existing clinical experience with its parent drug, leflunomide, provides indirect long-term safety data. This review summarizes teriflunomide's pharmacologic properties, pivotal clinical trials, and safety profile, and ends with a discussion of the role of teriflunomide in the context of current and emerging MS treatment options.

Teriflunomide was recently approved for use in relapsing forms of multiple sclerosis (MS) in the United States. It is the second oral agent that has been approved for MS, and existing experience with its parent drug, leflunomide, gives teriflunomide the benefit of indirect long-term safety data. This review summarizes teriflunomide's pharmacologic properties, clinical efficacy, safety profile, and use in light of the expanding treatment options of relapsing-remitting MS (RRMS).

Mechanism of action

Teriflunomide is primarily an inhibitor of dihydroorotate-dehydrogenase (DHODH), a key mitochondrial enzyme involved in the *de novo* synthesis of pyrimidines in rapidly proliferating cells. In MS, teriflunomide reduces the activity of proliferating T-lymphocytes and B-lymphocytes, thereby diminishing the overall inflammatory response. Pyrimidines are involved in other cellular functions in addition to DNA/RNA synthesis, including protein and lipid glycosylation, phospholipid synthesis, and DNA repair, which lead to a variety of downstream immunomodulatory effects. Importantly, teriflunomide is a cytostatic rather than cytotoxic drug, as homeostatic hematopoietic cell lines are not affected by DHODH inhibition due to a DHODH-independent "salvage pathway" that can generate necessary cellular pools of pyrimidine.¹

Teriflunomide has additional effects independent of DHODH inhibition, which include inhibiting protein tyrosine-kinases, altering cytokine production, and modulating the expression

Department of Neurology (JO), Johns Hopkins University, Baltimore, MD; and Division of Neurology, Department of Medicine (JO, PWO), St. Michael's Hospital, University of Toronto, Toronto, Canada.

Correspondence to: oconnorp@smh.ca

In the absence of any definitive clinical data, strict contraception is recommended for female patients, and male patients are cautioned not to father a child while on teriflunomide.

of cell surface molecules, all which may contribute to its observed immunomodulatory effects (figure).^{2,3}

Teriflunomide's oral bioavailability is 100%, with peak plasma levels achieved within 1–2 hours of intake. Leflunomide is converted almost entirely into teriflunomide in the intestinal mucosa or plasma, making the pharmacokinetics of these drugs nearly identical. Food intake, age, sex, and hepatic impairment do not affect teriflunomide's pharmacokinetics, although concomitant food ingestion impairs initial absorption. Teriflunomide is almost entirely protein-bound in plasma (>99%), demonstrates linear pharmacokinetics at doses of 5–25 mg/day, has a mean plasma half-life of 10–18 days, and achieves steady-state levels within 20 weeks. Drug clearance is through both biliary and renal mechanisms.⁴ Teriflunomide has a number of drug interactions as it is a weak inhibitor of CYP2C8 and a weak inducer of CYP1A2. Thus, patients on drugs metabolized by CYP2C8 (repaglinide, pioglitazone, paclitaxel, among others) and CYP1A2 (duloxetine, theophylline, tizanidine, among others) should be monitored as drug levels can be affected by concomitant teriflunomide use. Teriflunomide is known to decrease the effect of warfarin, and increases peak concentrations of ethinylestradiol/levonorgestrol for patients on oral contraceptives.

Clinical trials

A number of phase II/III clinical trials have demonstrated the efficacy of teriflunomide at daily doses of 7 mg and 14 mg in relapsing MS (table 1).^{5,6} The first pivotal phase III trial, Teriflunomide Multiple Sclerosis Oral trial (TEMSo), followed 1,088 patients over 108

Figure Mechanism of action of teriflunomide

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Table 1 Pivotal clinical trials of teriflunomide in multiple sclerosis

Clinical trial name	Study phase/design	Study participants	Study arms	Treatment period	Primary/secondary outcomes	Study results
Safety and Efficacy of Teriflunomide in MS with Relapses (NCT01487096)	Phase II: multicenter, randomized, placebo-controlled, double-blind, parallel group	Relapsing MS, n = 179	Placebo; teriflunomide 7 mg; teriflunomide 14 mg	36 weeks	Primary: CUALs per MRI secondary: other MRI outcomes, relapse frequency, disability progression, safety, and tolerability	Decrease in CUALs in both Rx groups vs placebo (RRR = 61.1%, $p < 0.03$ in 7-mg; RRR = 61.3%, $p < 0.01$ in 14-mg group); decrease in other MRI outcomes in both Rx groups vs placebo (all $p < 0.04$); decrease in proportion of patients showing disability progression in 14-mg Rx group vs placebo (7.4% vs 21.3% respectively, $p < 0.04$)
Pilot Study of Teriflunomide as Adjunctive Therapy to IFN-β in Subjects with MS (NCT00489489)	Phase II: multicenter, randomized, placebo-controlled, double-blind, parallel group	Relapsing MS on stable dose of IFN- β (>26 weeks), n = 118	IFN- β + placebo; IFN- β + teriflunomide 7 mg; IFN- β + teriflunomide 14 mg	24 weeks	Primary: no. of patients with adverse events, clinically significant abnormalities; secondary: ARR, MRI outcomes	Decrease in number of T1-Gd lesions both Rx groups vs IFN- β alone (RRR = 84.6%, $p = 0.0005$ in 7-mg; RRR = 82.8%, $p < 0.0001$ in 14-mg group); decrease in T1-Gd lesion volume in 14-mg Rx group vs IFN- β alone (RRR = 70.6%, $p = 0.02$); trend toward decreased ARR in 14-mg Rx group vs IFN- β alone (RRR = 57.9%, $p = 0.10$)
Study of Teriflunomide in Reducing the Frequency of Relapses and Accumulation of Disability in Patients with MS (TEMSO) (NCT00134563)	Phase III: multicenter, randomized, placebo-controlled, double-blind, parallel group	Relapsing MS, n = 1,088	Placebo; teriflunomide 7 mg; teriflunomide 14 mg	108 weeks	Primary: ARR; secondary: disability progression, fatigue, MRI outcomes	Decreased ARR in both Rx groups vs placebo (RRR = 31.2% in 7-mg, 31.5% in 14-mg group, both $p < 0.001$); trend toward decreased proportion of patients with disability progression in 7-mg Rx group vs placebo (21.7% in 7-mg, 27.3% in placebo, $p = 0.08$); decreased proportion of patients with disability progression in 14-mg Rx group vs placebo (20.2% in 14-mg, 27.3% in placebo, $p = 0.03$); improved MRI outcomes in both Rx groups (possible dose-effect) vs placebo ($p < 0.001$)
An Efficacy Study of Teriflunomide in Patients With Relapsing MS (TOWER) (NCT00751881)	Phase III: multicenter, randomized, placebo-controlled, double-blind, parallel group	Relapsing MS, n = 1,110 (estimated)	Placebo; teriflunomide 7 mg; teriflunomide 14 mg	48-202 weeks	Primary: ARR; secondary: time to disability progression, change in fatigue, change in health status	Decreased ARR in both Rx groups vs placebo (RRR = 22.3%, $p = 0.02$ in 7-mg; RRR = 36.3%, $p < 0.0001$ in 14-mg group); decreased disability progression in 14-mg Rx group vs placebo (RRR = 31.5%, $p = 0.04$); further results TBA
A Study Comparing the Effectiveness and Safety of Teriflunomide and IFN-β-1a in Patients with Relapsing MS (TENERE) (NCT00883337)	Phase III: multicenter, randomized, rater-blinded, parallel group	Relapsing MS, n = 300 (estimated)	IFN- β -1a 44 mcg sc TIW; teriflunomide 7 mg; teriflunomide 14 mg	48-174 weeks	Primary: time to failure (relapse or treatment discontinuation); secondary: ARR, fatigue, subject satisfaction	Preliminary results: no statistical superiority of Rebif over either Rx group in time to failure (proportion of patients with failure: 48.6%, 37.8%, and 42.3% in 7-mg, 14-mg, and IFN- β -1a, respectively); ARR not different in 14-mg Rx group and IFN- β -1a group (0.259 vs 0.216); higher ARR in 7-mg Rx group vs Rebif (0.410 vs 0.216); further results TBA

Abbreviations: ARR = annualized relapse rate; CUAL = combined unique active lesion; IFN = interferon; MS = multiple sclerosis; RRR = relative risk reduction; Rx = teriflunomide treatment; TBA = to be announced.

In comparison to other emerging oral DMAs, teriflunomide and BG-12 have the benefit of indirect long-term safety data from their use in rheumatologic disorders.

weeks. Patients in each teriflunomide group had diminished annualized relapse rates (ARR) vs placebo (0.37 in each teriflunomide arm, 0.54 for placebo; $p < 0.001$). Furthermore, both treatment arms had reduced proportions of patients with confirmed disability progression (27.3%, 21.7%, 20.2% for placebo, teriflunomide 7 mg [$p = 0.08$], and 14 mg [$p = 0.03$]), and improved MRI-related measures of disease activity in comparison to placebo ($p < 0.001$).⁵ Teriflunomide Oral in people With relapsing-remitting MS (TOWER), the second phase III trial, followed 1,169 patients over 48 weeks. There was a significant decrease in ARR in both teriflunomide treatment arms vs placebo (0.50, 0.39, 0.32 in placebo, 7 mg, 14 mg teriflunomide; $p = 0.02$ and $p < 0.0001$, respectively). There was a reduction in sustained disability accumulation in the 14 mg teriflunomide arm vs placebo (15.8% vs 22.2%, $p = 0.04$), while there was no difference in the 7-mg arm.⁶

Teriflunomide as add-on treatment to interferon β agents demonstrated improvement in MRI measures of disease in a phase II clinical trial.⁷

Safety

Teriflunomide is generally a well-tolerated drug, with predominately mild to moderate treatment-emergent adverse events (TEAEs), and only rare serious adverse events (SAEs). In TEMSO, the incidence of adverse events (AEs) (87.5–90.8%), SAEs (12.8–15.9%), and AEs leading to study discontinuation were similar across treatment arms (8.1%, 9.8%, 10.9% in placebo, 7 mg, 14 mg teriflunomide). AEs observed more frequently with teriflunomide and associated with a dose effect included nausea, diarrhea, hair thinning/decreased hair density, and elevated alanine aminotransferase (ALT) levels. Reductions in neutrophil and lymphocyte counts were small in magnitude, and typically stabilized within 3 months. In rare patients with significant neutropenia, stabilization occurred spontaneously or with treatment discontinuation. Small increases in blood pressure were seen more commonly in both teriflunomide treatment arms in comparison to placebo (+3 mm Hg systolic in teriflunomide arms vs –1 mm Hg in placebo). There were no deaths or serious opportunistic infections reported.⁵

AEs observed in TOWER were consistent with those reported in previous trials. Headache, ALT increase, hair thinning/alopecia, diarrhea, nausea, and neutropenia were reported more frequently in the teriflunomide arms. There were 4 reported deaths: 3 in the teriflunomide arms due to suicide, a motor vehicle accident, and sepsis; and 1 in the placebo arm due to respiratory infection.⁶

In the open-label extension of the phase II trial that followed patients for a median of 7.1 years, there were no serious opportunistic infections, and the incidence of malignancy was similar to population-based estimates. There was a single death from a sudden cardiac disorder when a patient died within hours of admission for malaise, anxiety, hypotension, and tachycardia. An extensive safety evaluation concluded that concomitant conditions and medications likely contributed.⁸

Existing experience with leflunomide can further supplement teriflunomide's safety profile. Leflunomide has been used in rheumatoid arthritis for over 14 years, and postmarketing surveillance suggests that its safety profile is acceptable. However, there have been rare SAEs, including hepatotoxicity, hypertension, pneumonitis, cytopenia, and 2 cases of progressive

Table 2 Teriflunomide safety monitoring guidelines

Baseline	<ul style="list-style-type: none"> • CBC and LFTs within 6 months before initiation of teriflunomide • Measure blood pressure • Screen for latent tuberculosis with tuberculin skin test
Periodic monitoring	<ul style="list-style-type: none"> • Monthly LFTs for the first 6 months, then periodically thereafter at prescribing physician's discretion • CBC should be monitored if signs/symptoms of hematologic toxicity • Monitor blood pressure periodically
Contraindications to teriflunomide use	<ul style="list-style-type: none"> • Severe hepatic impairment • Pregnancy • Current treatment with leflunomide
Abbreviations: CBC = complete blood count, LFT = liver function test.	

multifocal leukoencephalopathy in patients previously treated with other forms of immunosuppression, which underscores the importance of clinical vigilance when monitoring patients on teriflunomide.^{9–11}

Although the teratogenic potential of teriflunomide has not been evaluated in humans, given leflunomide's known teratogenicity in animals, pregnancy is a contraindication to teriflunomide use. It is somewhat reassuring that an analysis of all 65 pregnancies reported in clinical trials of teriflunomide found no structural or functional deficits in any newborns with prenatal teriflunomide exposure following elimination.¹² In the absence of any definitive clinical data, strict contraception is recommended for female patients, and male patients are cautioned not to father a child while on teriflunomide. Female patients who become pregnant while on teriflunomide should undergo a cholestyramine or activated charcoal-based washout procedure after treatment discontinuation, and confirm that the plasma level is <0.02 g/L.¹³

Contraindications to teriflunomide use and safety monitoring recommendations are presented in table 2.

Teriflunomide in clinical practice

Teriflunomide is an efficacious and relatively safe agent approved for use in the treatment of relapsing MS as monotherapy at doses of 7 mg and 14 mg, with some evidence suggesting that teriflunomide at 14 mg is more efficacious than 7 mg. The convenience of oral administration makes teriflunomide an attractive agent to add to the available treatment armamentarium for RRMS.

Although comparative clinical trials with existing therapies will provide more definitive evidence of teriflunomide's relative efficacy in comparison to other existing disease-modifying agents (DMAs) in MS, currently available data suggest that teriflunomide has similar efficacy to existing first-line DMAs.^{5,6,14} Teriflunomide has also demonstrated safety and efficacy as an add-on agent to interferon β drugs.⁷ In clinical practice, teriflunomide will likely be used as a first-line monotherapy DMA in relapsing forms of MS. In comparison to other emerging oral DMAs, teriflunomide and BG-12 have the benefit of indirect long-term safety data from their use in rheumatologic disorders. Although theoretically, teriflunomide might be used as add-on therapy in patients with suboptimal responses to the first-line injectable DMAs, cost would be a significant, if not prohibitive issue in this setting.

As with any novel pharmacologic agent, postmarketing surveillance will be essential to more definitively characterize the long-term safety and efficacy of teriflunomide in the treatment of RRMS.

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