

Oral teriflunomide or placebo added to interferon beta for 6 months in patients with relapsing multiple sclerosis: safety and efficacy results

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ABSTRACT

Background: Teriflunomide has anti-proliferative and immunomodulatory properties. In a previous study¹ in patients with relapsing MS, treatment with either oral teriflunomide 7 or 14 mg/day significantly reduced MRI activity >61% relative to placebo (PBO) and was well tolerated. Several large clinical efficacy and safety studies including patients with relapsing MS or patients with a first clinical episode are ongoing.

Objective: To report the safety and efficacy results of the study where teriflunomide was added to ongoing treatment with IFN.

Methods: In 29 sites, MS patients concurrently on a stable dose of IFN Beta were randomised for a 24-week double-blind treatment period to receive a daily dose of either PBO (n=41), 7 mg (n=37) or 14 mg (n=38) teriflunomide. Safety was evaluated from Treatment Emergent Adverse Event (TEAE), physical examination and laboratory data (e.g. Liver Function Tests, every 2–8 weeks), ECG and pancreatic ultrasound (24 weeks). MRI activity, including T1-gadolinium (T1-Gd) with central reading, as well as relapses and EDSS were recorded every 8 weeks.

Results: Demographic and disease baseline characteristics were comparable among treatment groups. Mean age was 40 years, and 70% of patients were female. Mean EDSS score was 2.5. 40% of patients had no relapse in the previous year. A third of patients were on low-dose IFN (IFN beta-1a 30 mcg im qw or 22 mcg sc tiw), whereas two thirds were taking high-dose, high-frequency IFN (IFN beta-1a 44 mcg sc tiw or IFN beta-1b 250 mcg sc eod).

Safety: Approximately 90% of patients completed the 24-week treatment period in each group. Treatment was prematurely discontinued for TEAE in one patient in each group. The proportion of patients with TEAE due to increased ALT was higher on 14 mg (28.9%) than on 7 mg (13.5%) or PBO (12.2%). Among them, the proportion of patients with ALT greater than 3xULN was low (4.8% in PBO; 0% in 7 mg; 5.2% in 14 mg) with one treatment discontinuation from PBO and one from 14 mg. No cases had associated bilirubin increase. The proportion of patients with TEAE potentially related to immunosuppression (including white blood cell counts, infections and infestations) was higher in the teriflunomide groups (PBO: 32%, 7 mg: 49%, 14 mg: 47%). Among these events upper respiratory tract infections (nasopharyngitis, sinusitis) appeared to be more frequent at 14 mg (23.7%) than PBO (14.6%) and 7 mg (10.8%). None of these events led to treatment discontinuation.

Efficacy: The number of T1-Gd lesions was significantly reduced in both teriflunomide arms, relative to PBO (7 mg: 56% and 14 mg: 81%; all p<0.001). The proportion of patients free of T1-Gd lesions was higher in both teriflunomide arms (placebo: 58%, 7 mg: 70%, 14 mg: 82%). Few relapses were reported during the 24-week period (5 on PBO, 5 on 7 mg and 2 on 14 mg).

Conclusion: In this trial, addition of teriflunomide to stable-dosed IFN Beta significantly improved disease control beyond IFN alone, as evaluated by T1-Gd MRI activity, with acceptable safety and tolerability over 24 weeks of treatment. Further data are required to establish clinical benefit.

METHODS

Patients

- Eligible patients were males or females aged 18 to 55 years who met McDonald's criteria for definite MS diagnosis and were classified as ambulatory (Expanded Disability Status Scale [EDSS] ≤5.5).
- In addition, eligible patients:
 - exhibited a relapsing clinical course, with and without progression
 - had received a stable dose of IFN-β (employing the dosing regimen of the specific IFN-β used) for at least 26 weeks prior to screening
 - had no relapse in the preceding 8 weeks and were clinically stable for 4 weeks prior to randomisation.
- Patients were ineligible if they had:
 - impaired bone marrow function (anaemia, leucopenia or thrombocytopenia), history of cancer, acute tuberculosis, persistent infection, HIV, pancreatitis or hepatitis
 - developed clinically relevant cardiovascular, hepatic or endocrine disorders, or severe depressive disorder and/or suicidality
 - received glatiramer acetate or immunosuppressive treatment at any time (e.g. natalizumab, cladribine, mitoxantrone, methotrexate, azathioprine, cyclophosphamide, mycophenolate, cytokine therapy, intravenous immunoglobulin), or any investigational drug in the preceding 24 weeks.

Study design

- The study design is shown in Figure 1. Patients were evenly randomised to one of three treatment groups (IFN-β plus either placebo [PBO], teriflunomide 7 mg/day, or teriflunomide 14 mg/day).
- Randomisation was stratified by the country in which patients received treatment and according to whether the baseline IFN-β regimen was low or high dose.
 - Low dose: interferon beta-1a 30 µg once-a-week intramuscularly; interferon beta-1a 22 µg three-times-per-week subcutaneously.
 - High dose: interferon beta-1a 44 µg three-times-per-week subcutaneously; interferon beta-1b 0.25 mg every-other-day subcutaneously.

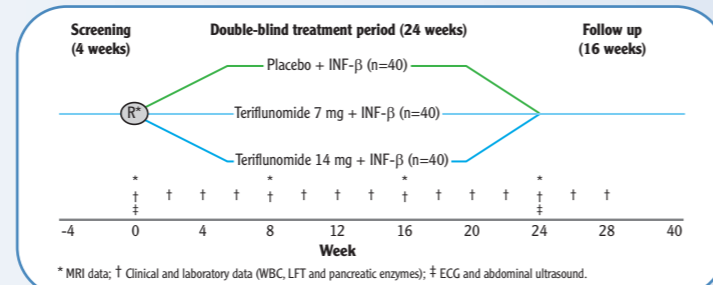


Figure 1. Study design. At the end of the study, patients were eligible to continue treatment for a further 6 months.

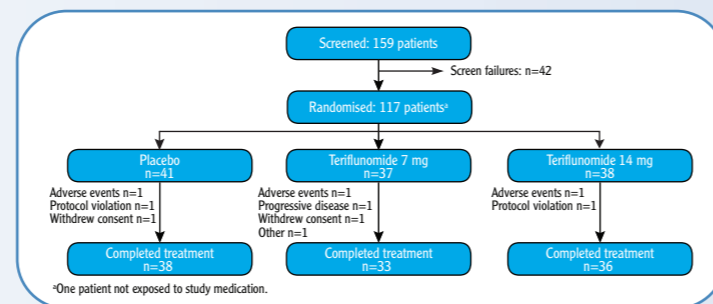


Figure 2. Patient flow.

Tolerability, safety and efficacy evaluations

- Tolerability and safety evaluations included monitoring of treatment-emergent adverse events (TEAEs), physical examination (every 8 weeks), ECG and abdominal ultrasound (at 24 weeks) and laboratory data (including WBC, liver function tests and pancreatic enzymes every 2 weeks).
- Efficacy evaluations included serial brain MRI assessment (with and without Gd enhancement) and relapse.

RESULTS

Approximately 40 patients were randomised to each treatment group and around 90% of patients completed the 24-week study treatment (PBO: 92.7%, 7 mg: 89.2%, 14 mg: 94.7%) (Figure 2).

Baseline demographics and disease characteristics (Table 1)

- Baseline demographics and disease characteristics were well balanced among the treatment groups.
 - Mean age was 40.1 years, 69.8% of patients were female, and mean time since first MS diagnosis was about 8 years. As expected for a safety study without criteria to include patients with very active disease, 40% had no relapse in the previous year.
 - Approximately one-third of patients in each group were treated with low-dose IFN-β and the remainder were on high dose.
 - The proportion of patients with T1-Gd lesions was around 22% in all treatment groups.
 - The proportion of patients with IFN-neutralising antibodies was similar across treatment groups.

	Placebo + IFN-β (n=41)	Teriflunomide 7 MG + IFN-β (n=37)	Teriflunomide 14 MG + IFN-β (n=38)
Demographics			
Mean age, years (SD)	39.2 (9.0)	41.4 (6.8)	39.6 (8.1)
Female, n (%)	31 (75.6)	25 (67.6)	25 (65.8)
Clinical characteristics			
Mean time since first symptoms of MS, years (SD)	11.6 (6.2)	11.2 (7.7)	10.1 (8.1)
Mean time since onset of most recent relapse, months (SD)	27.7 (38.5)	29.0 (34.1)	24.7 (36.0)
Number of relapses in previous 12 months, median (range)	1.0 (0–4)	0.0 (0–3)	1.0 (0–4)
MS subtype, n (%)	38 (92.7)	30 (81.1)	34 (89.5)
Relapsing-remitting	2 (4.9)	2 (5.4)	3 (7.9)
Secondary progressive	1 (2.4)	5 (13.5)	1 (2.6)
Progressive relapsing	2.5	2.0	2.5
Baseline EDSS, median (range)	(0.0–5.5)	(0.0–5.5)	(0.0–5.5)
Baseline IFN-β dose at randomisation, n (%)			
High dose	28 (68.3)	25 (67.6)	25 (65.8)
Low dose	13 (31.7)	12 (32.4)	13 (34.2)
Interferon-neutralising antibodies			
Missing data n (%)	4 (5 (13.5))	7 (19.4)	4 (12.5)
MRI characteristics (n)	40	37	38
Gd-enhancing T1 lesions, n (%)			
0	31 (77.5)	29 (78.4)	30 (78.9)
≥1	9 (22.5)	8 (21.6)	8 (21.1)
Burden of disease, mean (SD) [†]	17.8 (17.9)	18.6 (21.2)	12.7 (11.0)

Table 1. Demographics and clinical and MRI characteristics of the study population at baseline.

Tolerability and safety

- Tolerance and safety of both doses combined with IFN-β were acceptable during the 24-week study, with a similar frequency of TEAEs between groups, and a low and well-balanced incidence of TEAEs leading to treatment discontinuation (a single case in each group: transaminase increases in placebo and 14 mg, and one hair loss in 7 mg). There were three serious TEAEs (one transaminase increase in placebo and 7 mg, and one deep vein thrombosis in 7 mg [Table 2]). No fatality was reported.

	Placebo + IFN-β (n=41)	Teriflunomide 7 MG + IFN-β (n=37)	Teriflunomide 14 MG + IFN-β (n=38)
Any TEAE, n (%)	35 (85.4)	33 (89.2)	32 (84.2)
Serious TEAEs, n (%) [*]	1 (2.4)	2 (5.4)	0
TEAEs leading to treatment discontinuation, n (%) [*]	1 (2.4)	1 (2.7)	1 (2.6)
TEAEs, n (%)[*]			
Infections and infestations	12 (29.3)	13 (35.1)	13 (34.2)
Upper respiratory tract infections	6 (14.6)	4 (10.8)	9 (21.7)
Nasopharyngitis	2 (4.9)	3 (8.1)	5 (13.2)
Sinusitis	0	0	2 (5.3)
Urinary tract infections	4 (9.8)	3 (8.1)	2 (5.3)
Neurological symptoms	7 (17.1)	6 (16.2)	12 (31.6)
MS-related symptoms	2 (4.9)	3 (8.1)	5 (13.2)
Headaches/migraines	3 (7.3)	2 (5.4)	5 (13.2)
Skin (e.g. dry skin/skin lesion/psoriasis)	2 (4.9)	7 (18.9)	5 (13.2)
Alopecia	0	2 (5.4)	2 (5.3)
Musculoskeletal (e.g. arthralgia/joint swelling/osteoarthritis)	4 (9.8)	6 (16.2)	6 (15.8)
Muscle spasms/weakness	3 (7.3)	0	0
Back pain/stiffness/pain extremity	0	5 (13.5)	4 (10.5)
Respiratory disorder	6 (14.6)	3 (8.1)	4 (10.5)
Cough	3 (7.3)	0	2 (5.3)
Gastrointestinal	7 (17.1)	4 (10.8)	7 (18.4)
Dyspepsia/nausea/vomiting	4 (9.8)	1 (2.7)	5 (13.2)
Diarrhoea	4 (9.8)	3 (8.1)	3 (7.9)
General disorders	5 (12.2)	4 (10.8)	4 (10.5)
Asthemia/fatigue	2 (4.9)	1 (2.7)	2 (5.3)
Psychiatry (e.g. anxiety/sleep disorder)	0	3 (8.1)	2 (5.3)

Table 2. Treatment-emergent adverse events (TEAEs).

- The proportion of patients with ALT > 3xULN was low and similar across treatment groups. However, the proportion of patients with a reported TEAE of increased ALT was higher in the 14 mg group (28.9%) than in the 7 mg (13.5%) and placebo (12.2%) groups. No case of concomitant increase in total bilirubin was observed.
- TEAEs potentially related to immunosuppression (including infections and infestations, WBCs) were slightly more frequent in the two teriflunomide groups (PBO: 32%, 7 mg: 49%, 14 mg: 47%). Among these events upper respiratory tract infections (mainly nasopharyngitis and sinusitis) were more frequent with teriflunomide 14 mg than placebo or teriflunomide 7 mg (Table 2). There was an apparent dose effect in patients with leucocyte counts below 3 Giga/L (placebo: 4.9%, 7 mg: 13.5%, 14 mg: 23.7%) and in neutrophil counts below 1.5 Giga/L (placebo: 9.8%, 7 mg: 8.9%, 14 mg: 36.8%). One TEAE of neutropenia in the 14 mg group recovered under treatment. There was no serious event or event leading to treatment discontinuation.
- Among other notable TEAEs were: four patients with hair loss (one patient in 7 mg recovered 1 month after study discontinuation, two patients in 14 mg recovered under treatment and one in 7 mg recovered two months after normal end of treatment); respiratory symptoms, including cough, were more frequent in the placebo group. In particular, there was no signal of pulmonary interstitial disease (Table 2).
- There was no significant ECG and pancreatic enzymes/abdominal ultrasound abnormalities.

Efficacy

- The number of Gd-enhancing T1 lesions was significantly reduced in both teriflunomide groups, compared with placebo (all p<0.001) (Figure 3A). Relative to placebo, a 56% and 81% reduction in the number of these lesions was observed with teriflunomide 7 mg and 14 mg, respectively. The proportion of patients free of Gd-enhancing T1 lesions was higher in both teriflunomide groups (Figure 3B).
- Few relapses were reported during the 24-week period (5 on PBO, 5 on 7 mg and 2 on 14 mg). Annualised relapse rates for the study population were 0.279, 0.305 and 0.116 for placebo, teriflunomide 7 mg and teriflunomide 14 mg, respectively.

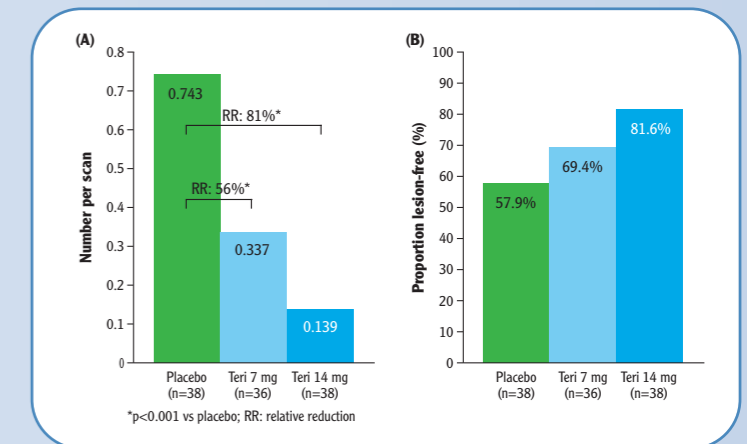


Figure 3. MRI assessment of (A) the number of gadolinium-enhancing (Gd-enhancing) T1 lesions per scan and (B) the proportion of patients free of Gd-enhancing T1 lesions.

CONCLUSIONS

- Both doses of teriflunomide demonstrated acceptable tolerability and safety when combined with stable-dose IFN-β. The safety profile was similar to what has been previously reported for teriflunomide.
- Addition of teriflunomide to stable-dose IFN-β improved disease control beyond that achieved with IFN-β alone, with dose-dependent effects of teriflunomide in reducing the number of Gd-enhancing T1 lesions.
- Additional data will help to fully determine the clinical benefit of this new combination treatment approach.

Acknowledgements

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References

1. O'Connor PW, et al. *Neurology* 2006; 66: 894–900.

INTRODUCTION AND PURPOSE

- Although interferon-beta (IFN-β) has been shown to be an effective therapy in multiple sclerosis (MS), not all patients have full disease control and the use of additional therapy in conjunction with IFN-β might offer further benefit to patients.
- Teriflunomide is a *de novo* pyrimidine synthesis inhibitor with antiproliferative activity.
- In a previous randomised, double-blind, placebo-controlled study, oral teriflunomide (7 mg/day and 14 mg/day) was well tolerated and effective in reducing brain MRI activity in patients with relapsing MS.¹ Over a 32-week treatment period, the median number of combined unique active lesions per MRI scan was 0.5, 0.2 and 0.3 for placebo, teriflunomide 7 mg (p<0.03 vs placebo), and teriflunomide 14 mg (p<0.01 vs placebo), respectively.
- Several large phase III clinical studies of teriflunomide are ongoing. Here we report the findings of a randomised, multinational, double-blind, placebo-controlled study of teriflunomide in patients with relapsing MS treated with a stable dose of IFN-β.
- The primary objective of the study was to assess the tolerability and safety of oral teriflunomide (7 mg and 14 mg once daily for 24 weeks) compared with placebo, in patients with relapsing MS on a stable dose of IFN-β.
- The efficacy of teriflunomide was also evaluated using MRI T1-gadolinium (Gd) activity.