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Original Research Paper

Characterizing lymphocyte counts and infection rates with long-term teriflunomide treatment: Pooled analysis of clinical trials

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Abstract

Background: In Phase 3 studies, teriflunomide reduced relapse rates and disability progression compared with placebo; however, decreases in lymphocyte counts were also observed.

Objective: To describe the effect of long-term teriflunomide treatment on lymphocyte counts and infection rates among patients in pooled analyses of Phase 3 core and extension studies.

Methods: Four randomized trials (TEMSO, TOWER, TENERE, and TOPIC) compared teriflunomide 7 mg or 14 mg treatment with either placebo and/or subcutaneous interferon (IFN) β-1a 44 µg in patients with relapsing forms of multiple sclerosis (MS) (or first clinical episode suggestive of MS in TOPIC).

Results: In 1895, patients ever exposed to teriflunomide, mean (standard deviation) absolute lymphocyte counts declined from Week 0 (1.89 (0.59)) to Week 24 (1.67 (0.52)) and then remained stable thereafter. In the core plus extension studies (up to 10.7 years), 7.3% and 2.2% experienced Grade 1 and Grade 2 lymphopenia, respectively. Infections were reported in 56.9% of patients without lymphopenia, 60.9% with Grade 1 lymphopenia, and 54.8% with Grade 2 lymphopenia. Serious infections occurred in 3.7%, 4.3%, and 7.1%, respectively.

Conclusion: Long-term risk of lymphopenia and infections in patients who continue to receive teriflunomide is low, demonstrating a limited impact on adaptive and innate immunity.

Keywords: Teriflunomide, multiple sclerosis, lymphocyte counts, infection rates, pooled analysis

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Introduction

Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing forms of MS or relapsing remitting MS, depending on the local label, in over 80 countries, including the United States and countries of the European Union.[1,2] As of August 2018, over 93,000 patients were being treated with teriflunomide, with a total real-world exposure of approximately 237,400 patient-years as of September 2018.

Teriflunomide selectively and reversibly inhibits dihydro-orotate dehydrogenase (DHODH), a mitochondrial enzyme essential for *de novo* pyrimidine synthesis in rapidly dividing lymphocytes.[3] As a result, the proliferation and function of activated T- and B-cells (thought to contribute to the damaging inflammatory processes in MS) are reduced, while the resting cells of the adaptive immune system are spared.[3] In addition to a reduction of T- and B-cell proliferation via DHODH inhibition, teriflunomide may also act by reducing cytokine expression and release via a DHODH-independent mechanism.[4–6] Because disease-modifying drugs are administered on a long-term basis and target the immune system, it is important to track lymphocyte counts as the reduction in lymphocyte production may potentially lead to complications such as lymphopenia and an increased risk of infections.[7]

In the Phase 3 TEMSO (NCT00134563), TOWER (NCT00751881), and TOPIC (NCT00622700) studies, teriflunomide reduced relapse rates and disability

progression compared with placebo.[8–10] However, decreases in white blood cell counts (mean: <15% from baseline levels) were observed in placebo-controlled trials with teriflunomide, although a greater decrease was observed in some patients. This reduction in lymphocytes occurred during the first 6 weeks of treatment, then stabilized over time at a level <15% from baseline. Effects on red blood cell counts (mean decrease from baseline <2%) and platelet counts (mean decrease from baseline <10%) were less pronounced.[2]

The aim of this analysis was to describe the effect of long-term teriflunomide treatment on lymphocyte counts and infection rates among patients in the pooled TEMSO, TOWER, TOPIC, and TENERE (NCT00883337; a Phase 3 trial comparing daily oral teriflunomide with subcutaneous interferon (IFN) β-1a 44 μg three times weekly)[11] core and extension studies.

Methods

Study design

Details of the TEMSO, TOWER, TOPIC, and TENERE patient populations and study designs have been published previously.[8–11] In TEMSO, TOWER, and TENERE, patients were included if they had a diagnosis of relapsing forms of multiple sclerosis (RMS), including patients with secondary progressive MS or progressive RMS[8,9,11] In TOPIC, patients were included if they had only experienced a first clinical episode suggestive of MS.[10] Individual patient data from the clinical trials were pooled for this analysis.

In TEMSO, TOWER, and TOPIC, patients were randomized 1:1:1 to placebo or teriflunomide 7 mg or 14 mg;[8–10] in TENERE, patients were randomized 1:1:1 to subcutaneous IFN β-1a 44 μg, teriflunomide 7 mg, or teriflunomide 14 mg.[11] TEMSO and TOPIC had a fixed duration of 108 weeks, although TOPIC was terminated early due to revisions to diagnostic criteria, enabling earlier diagnosis of MS. Patients who completed the study were given the option of entering the extension phase at the time of termination. Patients who had a relapse defined as clinically definite multiple sclerosis, and had been treated for at least 24 weeks, could also enter the extension study.[8,10] In TOWER and TENERE, study duration was variable, ending 48 weeks after the last patient was randomized.[9,11] In the TEMSO and TOPIC extension studies (5.1 and 2.3 years duration (median), respectively), teriflunomide-treated patients continued on their original dose; patients in the placebo group were re-randomized 1:1 to teriflunomide 7 mg or 14 mg.[8,10] In the TOWER and TENERE extension studies (4.3 and 3.4 years duration (median), respectively), all patients received teriflunomide 14 mg.[9,11]

Assessment schedule

In the TEMSO, TOWER, TENERE, and TOPIC core studies, lymphocyte counts were obtained at baseline, every 2 weeks until Week 24, and every 6 weeks thereafter until study completion. In the TOPIC extension study, lymphocyte counts were obtained every 12 weeks until the end of the extension period.

Lymphopenia and infections

Lymphopenia was defined as two consecutive assessments of lymphocyte counts below the lower limit of normal (LLN, 1.0×10^9/L). Two consecutive assessments below the LLN were used in order to confirm that the first assessment was not an anomaly in the data. According to the Common Terminology Criteria for Adverse Events Version 4.0, lymphocyte counts higher than 1.0×10^9/L were considered non-lymphopenic (Grade 0); counts $<1.0 \times 10^9$/L to 0.8×10^9/L were scored as Grade 1; counts $<0.8 \times 10^9$/L to 0.5×10^9/L were scored as Grade 2; counts $<0.5 \times 10^9$/L to 0.2×10^9/L were scored as Grade 3; and counts $<0.2 \times 10^9$/L were scored as Grade 4. Infections and serious infections (defined as any infection requiring hospitalization) were identified per protocol according to the Medical Dictionary for Regulatory Activities®.

Statistical analyses

Data from the pooled core studies are reported for patients treated with placebo, IFNβ-1a, or teriflunomide 14 mg, while results from the pooled core and extension studies are reported for patients ever exposed to teriflunomide 14 mg. Lymphocyte counts and incidences of lymphopenia and infections are reported using descriptive statistics.

Results

Patient demographics and disease characteristics

Demographic and baseline disease characteristics are presented in Table 1 for patients who were treated with teriflunomide 14 mg ($n = 1055$), IFN β-1a ($n = 101$), and placebo ($n = 936$) in the core studies, and teriflunomide 14 mg ($n = 1895$) in the core plus extension studies. Demographics and baseline disease characteristics were similar across the core and core plus extension groups as well as between

Table 1. Baseline demographics and disease characteristics for the randomized population.

	Core			Core + extension
	Placebo ($n=936$)	IFNβ-1a[a] ($n=101$)	Teriflunomide ($n=1055$)	Teriflunomide ($n=1895$)
Age, mean (SD), years	37.0 (9.3)	37.1 (10.6)	36.8 (9.1)	37.8 (9.2)
Female, *n* (%)	675 (72.1)	69 (68.3)	742 (70.3)	1346 (71.0)
White, *n* (%)	849 (90.8)[b]	101 (100)	977 (92.7)[c]	1731 (91.4)[d]
Time since diagnosis of MS[e], mean (SD), years	5.0 (5.6)[f]	3.9 (5.8)	5.2 (5.8)[g]	5.8 (5.6)[h]
Time since first symptoms of MS[e], mean (SD), years	8.1 (6.9)[f]	7.9 (7.7)	8.2 (6.9)[g]	8.9 (6.8)[h]
Number of relapses within past 2 years, mean[e] (SD)	2.2 (1.1)	1.7 (1.2)	2.1 (1.1)[i]	1.4 (1.3)[ij]
Baseline EDSS score, mean (SD)	2.5 (1.4)[k]	2.1 (1.2)	2.5 (1.3)[c]	2.5 (1.4)[j]
Prior DMT use, mean (SD)	227 (30.5)	25 (24.8)	244 (29.1)	763 (47.3)

IFN: interferon; MS: multiple sclerosis; EDSS: Expanded Disability Status Scale; SD: standard deviation; RMS: relapsing multiple sclerosis; CIS: clinically isolated syndrome; DMT: disease-modifying therapy.
All patients had a diagnosis of RMS, with or without progression, or CIS (TOPIC only).
[a]TENERE only.
[b]$n=935$.
[c]$n=1054$.
[d]$n=1893$.
[e]TENERE, TOWER, and TEMSO only.
[f]$n=745$.
[g]$n=838$.
[h]$n=1612$.
[i]$n=1611$.
[j]$n=1894$.
[k]$n=837$.

placebo-, IFNβ-1a-, and teriflunomide-treated patients in the core studies. Across all treatment groups, the majority of patients were female (68.3–72.1%), with a mean age of approximately 37 years.

Lymphocyte counts

Overall, in patients ever exposed to teriflunomide in the core and extension studies, mean (SD) absolute lymphocyte counts declined from Week 0 (1.89 (0.59)) to Week 24 (1.67 (0.52)) then remained stable thereafter. When stratified by status of lymphopenia, a similar pattern was observed for patients with no lymphopenia and for patients who experienced ⩾1 occurrence of Grade 1 lymphopenia (Figure 1). In patients who experienced ⩾1 occurrence of Grade 2 lymphopenia, mean counts decreased between Week 0 and Week 48, then remained relatively stable thereafter. Mean counts generally remained within the normal range, however, Grades 1 and 2 lymphopenia occurred in 7.3% and 2.2% of patients, respectively (Figure 2).

Lymphopenia

In the pooled core studies, Grade 1 lymphopenia was experienced by 1.8% of placebo-treated patients, 7.9% of IFNβ-1a-treated patients, and 6.7% of teriflunomide-treated patients. Percentages of patients experiencing Grade 2 lymphopenia were 0.4%, 6.9%, and 1.3%, respectively (Figure 2). The overall numbers of patients with lymphopenia treated with placebo, IFNβ-1a, and teriflunomide were 21 (2.2%), 15 (14.9%), and 85 (8.1%), respectively. No cases of Grade 3 or Grade 4 lymphopenia were reported. The total number of teriflunomide-treated patients with lymphopenia overall was 180 (9.5%).

In patients with lymphopenia, the median duration of treatment with teriflunomide prior to the development of lymphopenia in the core period was 17.9 weeks for Grade 1 and 20.4 weeks for Grade 2 (Table 2). The corresponding values were 10.6 and 13.1 weeks in placebo-treated patients and 14.0 and 16.1 weeks in IFN β-1a-treated patients.

The prevalence of Grade 1 or Grade 2 lymphopenia declined over time (up to 10.7 years of follow-up) with continuing teriflunomide treatment (Figure 3). Most events occurred in Year 1 of therapy, and fewer cases were reported after Year 3, although a slight rise in incidence of Grade 1 lymphopenia was apparent at Years 6, 7, and 8. No lymphopenia was seen in any patient after Year 8, although this observation may

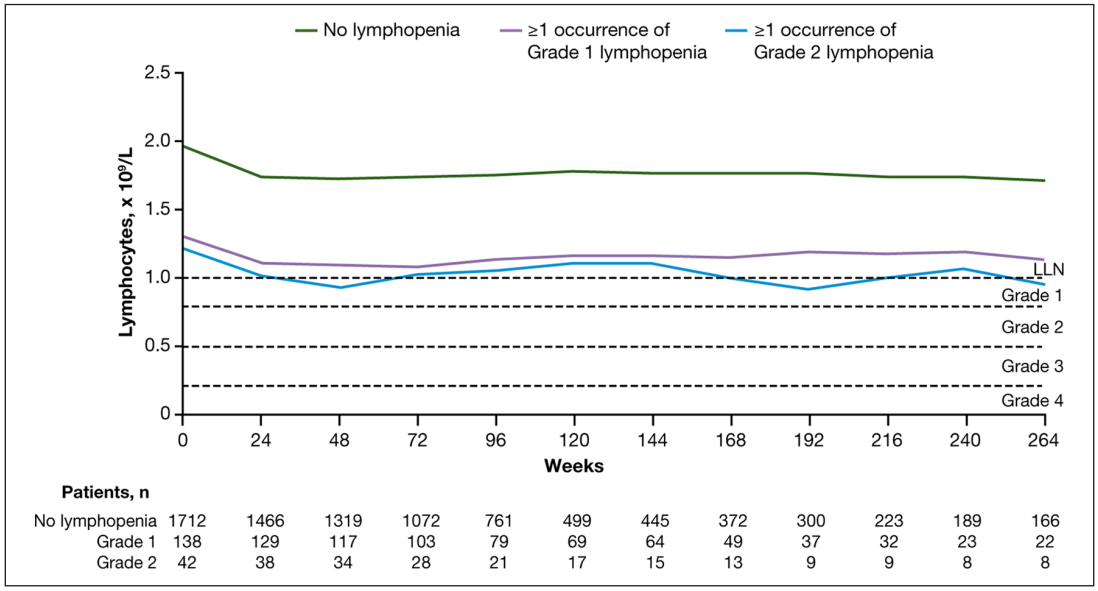

Figure 1. Mean absolute lymphocyte counts over time in patients ever exposed to teriflunomide 14 mg in the pooled TEMSO, TOWER, TOPIC, and TENERE core and extension studies. No Grade 3 or 4 lymphopenia was reported. Data reported for time points with at least five patients per lymphopenia group for up to 5 years of follow-up (Week 264).
LLN: lower limit of normal (1×10^9/L).

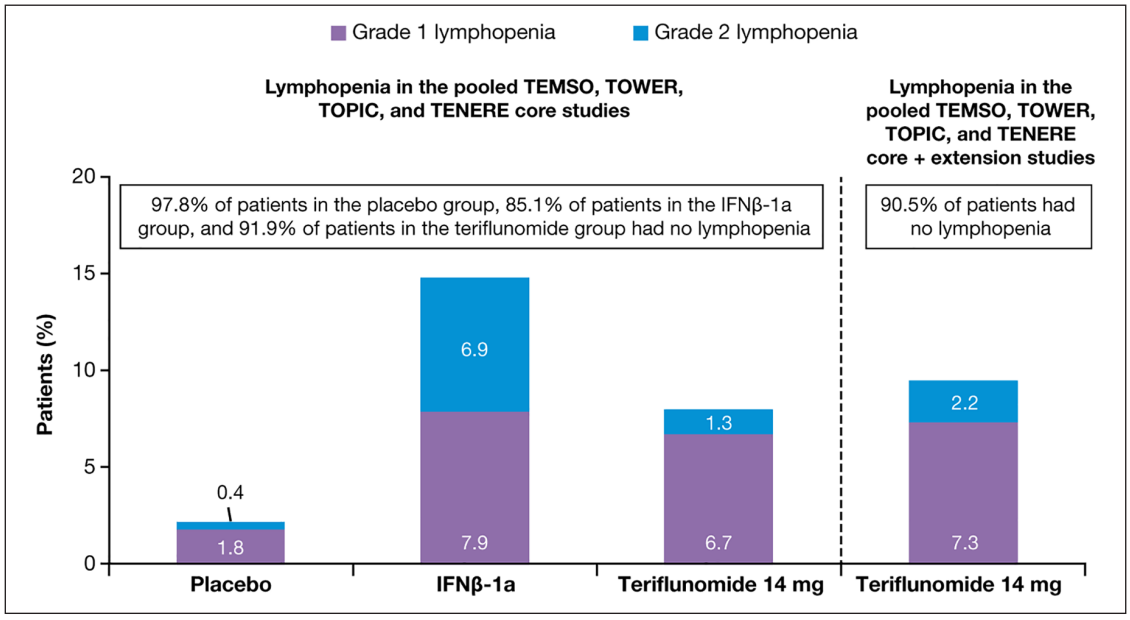

Figure 2. Incidence of lymphopenia in the pooled TEMSO, TOWER, TOPIC, and TENERE core and extension studies. No Grade 3 or 4 lymphopenia was reported.
IFN: interferon.

have been influenced by the relatively smaller number of patients remaining in the combined study population at these later time points. The pooled overall median duration of treatment exposure (Q1:Q3) in the core studies for teriflunomide 14 mg, IFN β-1a, and placebo were 672 (338:757), 421 (324:542), and 684 (374:757) days, respectively. In the core plus extension studies, median treatment exposure to teriflunomide 14 mg was 152.4 (79:229.6) weeks. The median and maximum duration of exposure to teriflunomide in the core and extension studies are also shown in Figure 3.

Table 2. Time (weeks) on treatment prior to development of Grades 1 and 2 lymphopenia in the pooled TEMSO, TOWER, TOPIC, and TENERE core and extension studies.

	Core			Core + extension
	Placebo (n=936)	IFNβ-1a[a] (n=101)	Teriflunomide (n=1055)	Teriflunomide (n=1895)
Time to first instance of Grade 1 lymphopenia[b]				
Median (Q1:Q3)	10.6 (6.0:30.3)	14.0 (5.4:39.3)	17.9 (6.1:36.1)	19.6 (10.1:60.0)
Number of patients	17	8	71	138
Time to first instance of Grade 2 lymphopenia[c]				
Median (Q1:Q3)	13.1 (7.1:52.2)	16.1 (6.0:24.1)	20.4 (12.0:66.1)	23.1 (12.1:93.1)
Number of patients	4	7	14	42
Time to first instance of Grade 1 or 2 lymphopenia[d]				
Median (Q1:Q3)	7.1 (2.1:42.6)	6.1 (4.0:16.4)	9.7 (6.1:14.1)	9.0 (4.1:21.1)
Number of patients	4	7	14	42

IFN: interferon; Q1: first quartile; Q3: third quartile.
[a]TENERE only.
[b]Time to Grade 1 lymphopenia was the time to the patient first meeting the criteria for Grade 1 lymphopenia.
[c]Time to Grade 2 lymphopenia was the time to the patient first meeting the Grade 2 criteria.
[d]Among patients with Grade 2 lymphopenia, time to Grade 1 or 2 lymphopenia was the time to the patient first meeting either the Grade 1 or Grade 2 criteria.

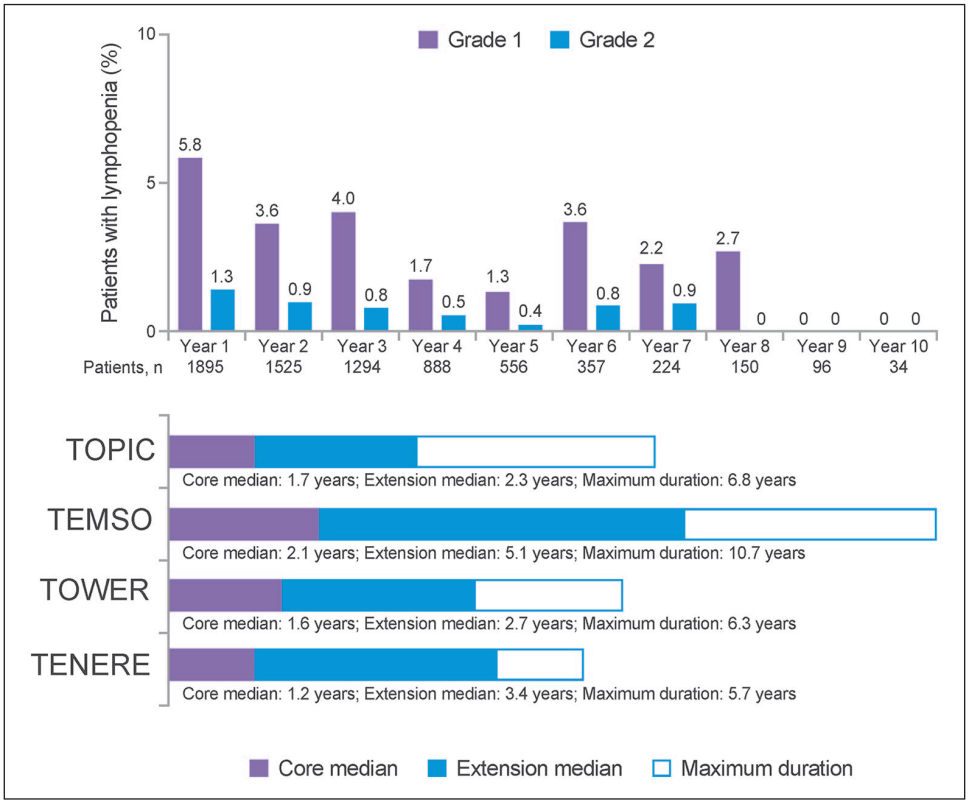

Figure 3. Percentage of patients with lymphopenia by year in the pooled TEMSO, TOWER, TOPIC, and TENERE core studies and extensions. The lower part of figure displays median duration of exposure to teriflunomide 14 mg in the core and extension studies and maximum duration in the core plus extension studies. No Grade 3 or 4 lymphopenia was reported. A patient could have had multiple instances of lymphopenia; multiple instances of lymphopenia occurring in the same year were only counted once. Multiple instances in different years were counted in each year that they occurred.

Table 3. Time (weeks) to recovery from lymphopenia in the pooled TEMSO, TOWER, TOPIC, and TENERE core and extension studies.

	Core			Core + extension
	Placebo (n=936)	IFNβ-1a[a] (n=101)	Teriflunomide (n=1055)	Teriflunomide (n=1895)
Time to recovery or last observation for patients with lymphopenia				
Patients with Grade 1 lymphopenia who achieved recovery				
Median (Q1:Q3)	10.0 (4.6:17.1)	7.1 (4.3:12.3)	11.1 (4.4:16.3)	10.6 (6.2:17.4)
Number of patients	16	6	50	100
Patients with Grade 2 lymphopenia who achieved recovery				
Median (Q1:Q3)	22.3 (4.3:40.3)	37.6 (24.3:49.6)	49.9 (24.1:65.4)	16.6 (9.1:51.1)
Number of patients	2	4	5	18
All patients with Grade 1 lymphopenia[b]				
Median (Q1:Q3)	11.9 (5.0:18.0)	7.1 (3.9:12.3)	10.3 (4.3:20.3)	12.1 (6.3:24.1)
Number of patients	17[c]	8[d]	71[e]	138[f]
All patients with Grade 2 lymphopenia[b]				
Median (Q1:Q3)	8.7 (3.1:26.7)	33.1 (23.1:43.9)	24.1 (7.1:55.1)	25.0 (11.1:64.1)
Number of patients	4[g]	7[h]	14[i]	42[j]

IFN: interferon; Q1: first quartile; Q3: third quartile.
Recovery from lymphopenia was defined as lymphocyte levels in two consecutive blood tests that are greater than or equal to the lower limit of normal.
[a]TENERE only.
[b]Includes patients without recovery during available follow-up (data censored at last available timepoint).
[c]One patient (5.9%) was censored before recovery.
[d]Two patients (25.0%) were censored before recovery.
[e]21 patients (29.6%) were censored before recovery.
[f]38 patients (27.5%) were censored before recovery.
[g]Two patients (50.0%) were censored before recovery.
[h]Three patients (42.9%) were censored before recovery.
[i]Nine patients (64.3%) were censored before recovery.
[j]24 patients (57.1%) were censored before recovery.

Duration of lymphopenia

Persistent lymphopenia was defined as lymphopenia lasting longer than 6 months. In the core studies, persistent Grade 1 lymphopenia was reported in 0.2% of placebo-treated patients, 5.9% of IFN β-1a-treated patients, and 1.5% of patients treated with teriflunomide; no persistent Grade 2 lymphopenia was reported.

In the core plus extension studies, 44 (2.3%) patients ever-exposed to teriflunomide had persistent Grade 1 lymphopenia; no persistent Grade 2 lymphopenia was reported.

Recovery from lymphopenia

In the core period, for those who recovered from Grade 1 lymphopenia, median time to recovery was 10.0 weeks (placebo), 7.1 weeks (IFN β-1a), and 11.1 weeks (teriflunomide) (Table 3). For patients with Grade 2 lymphopenia, the corresponding values were 22.3 weeks, 37.6 weeks, and 49.9 weeks, respectively. In the core plus extension period, the median time to recovery from Grade 1 and Grade 2 lymphopenia in patients treated with teriflunomide was 10.6 weeks and 16.6 weeks, respectively.

Adherence to and discontinuation from treatment

No patients in the core or extension studies discontinued treatment due to lymphopenia. The number of patients with lymphopenia treated with teriflunomide (n=180) who did not recover but completed the studies was 31 (17.2%), compared with 22 (12.2%) patients with lymphopenia who discontinued before the end of the study for other reasons.

Infections

In the core studies, infections in patients without lymphopenia were reported in 53.4% (489/915) of patients treated with placebo, 45.3% (39/86) with IFNβ-1a, and 52.8% (512/970) with teriflunomide (Table 4). Serious infections occurring in patients treated with placebo, IFNβ-1a, and teriflunomide

Table 4. Rates of infections and serious infections by grade of lymphopenia in the pooled TEMSO, TOWER, TOPIC, and TENERE core and extension studies.

	Core			Core + extension
	Placebo ($n=936$)	IFNβ-1a[a] ($n=101$)	Teriflunomide ($n=1055$)	Teriflunomide ($n=1895$)
No lymphopenia, *n*	915	86	970	1715
All infections, *n* (%)	489 (53.4)	39 (45.3)	512 (52.8)	975 (56.9)
Serious infections, *n* (%)	20 (2.2)	1 (1.2)	29 (3.0)	63 (3.7)
Grade 1 lymphopenia, *n*	17	8	71	138
All infections, *n* (%)	7 (41.2)	4 (50.0)	33 (46.5)	84 (60.9)
Serious infections, *n* (%)	0	0	0	6 (4.3)
Grade 2 lymphopenia, *n*	4	7	14	42
All infections, *n* (%)	3 (75.0)	4 (57.1)	5 (35.7)	23 (54.8)
Serious infections, *n* (%)	1 (25.0)	0	0	3 (7.1)

IFN: interferon; LLN: lower limit of normal (1×10^9/L).
Normal range for lymphocytes: 1.0–3.0×10^9/L. Grades of lymphopenia: No lymphopenia (≥LLN); Grade 1 (<LLN to ≥0.8×10^9/L); Grade 2 (<0.8×10^9/L to ≥0.5×10^9/L); Grade 3 (<0.5×10^9/L to ≥0.2×10^9/L); Grade 4 (<0.2×10^9/L).
No Grade 3 or 4 lymphopenia was reported.
[a]TENERE only.

were 2.2%, 1.2%, and 3.0%, respectively. Most common infections included nasopharyngitis, upper respiratory tract infections, urinary tract infections, and influenza (Supplementary Material).

In the core studies, infections in patients with Grade 1 lymphopenia were reported in 41.2% (7/17) of patients treated with placebo, 50.0% (4/8) with IFN β-1a, and 46.5% (33/71) with teriflunomide; no serious infections were reported. Infections in patients with Grade 2 lymphopenia were reported in 75.0% (3/4) patients treated with placebo, 57.1% (4/7) with IFN β-1a, and 35.7% (5/14) with teriflunomide. Serious infections were reported only in placebo-treated patients (25.0%). The median time to all infections in patients without lymphopenia for placebo, IFN β-1a, and teriflunomide was 18.1, 19.4, and 15.1 weeks, respectively; the median time for patients with lymphopenia was 13.8, 8.7, and 9.3 weeks in the core studies (Table 5).

In the core plus extension studies, infections while receiving teriflunomide were reported in 56.9% (975/1715) of patients without lymphopenia, 60.9% (84/138) of patients with Grade 1 lymphopenia, and 54.8% (23/42) of patients with Grade 2 lymphopenia. Serious infections occurred in 3.7% (63/1715) of patients without lymphopenia, 4.3% (6/138) with Grade 1 lymphopenia, and 7.1% (3/42) with Grade 2 lymphopenia. Contrary to the core study period, the median time to all infections in patients without lymphopenia was 21.7 weeks; for patients with lymphopenia, the median time to all infections was 37.3 weeks in the core plus extension studies (Table 5).

Discussion

This analysis investigated the effect of long-term treatment with teriflunomide on lymphocyte counts and infection rates in the TEMSO, TOWER, TOPIC, and TENERE core and extension studies; a combined treated population of up to 1895 patients. Low-grade (Grade 1 or Grade 2) lymphopenia was infrequent in the core and extension studies across all treatment groups, with no reports of high-grade (Grade 3 or Grade 4) lymphopenia.

Patients treated with teriflunomide who had Grade 1 lymphopenia experienced a reduction in lymphocyte counts from Week 0 to Week 24, after which lymphocyte counts stabilized. In patients treated with teriflunomide who experienced Grade 2 lymphopenia, lymphocyte counts reduced between Week 0 and Week 48, after which lymphocyte counts stabilized. These results are consistent with those from the Phase 4, real-world Teri-PRO study (NCT01895335).[12] Decreases in lymphocyte counts over 1 year in the Teri-PRO study were small, similar to those observed in the teriflunomide Phase 3 clinical program, with mean lymphocyte counts at Year 1 above the LLN in all studies.

A small percentage of patients (2.3%) had persistent lymphopenia. Taken together, these findings suggest

Table 5. Time to infections and serious infections for patients with and without lymphopenia in the pooled TEMSO, TOWER, TOPIC, and TENERE core and extension studies.

	Core			Core + extension
	Placebo	IFNβ-1a	Teriflunomide	Teriflunomide
Time to all infections (weeks) in patients without lymphopenia				
Median (Q1:Q3)	18.1 (7.1:43.7)	19.4 (12.1:41.4)	15.1 (5.9:37.7)	21.7 (7.7:59.6)
Number of patients	489	39	512	975
Time to all infections (weeks) in patients with lymphopenia				
Median (Q1:Q3)	13.8 (8.0:36.4)	8.7 (7.4:41.6)	9.3 (3.6:45.6)	37.3 (7.1:85.6)
Number of patients with infections	10	8	38	107
Time to serious infections (weeks) in patients without lymphopenia				
Median (Q1:Q3)	47.7 (26.4:70.1)	23.9 (N/A)	32.3 (8.9:61.6)	80.1 (32.3:154.9)
Number of patients	20	1	29	63
Time to serious infections (weeks) in patients with lymphopenia				
Median (Q1:Q3)	16.1 (N/A)	–	–	112.7 (49.1:268.1)
Number of patients	1	0	0	9

IFN: interferon; Q1: first quartile; Q3: third quartile; LLN: lower limit of normal (1×10^9/L).
Normal range for lymphocytes: 1.0×10^9/L to 3.0×10^9/L. All grades of lymphopenia were combined due to few patients in the Grade 2 lymphopenia population.

that the long-term risk of lymphopenia in patients who continue to receive treatment is low.

Rates of infections and serious infections were consistent across placebo-, IFN β-1a-, and teriflunomide-treated patients without lymphopenia; rates across groups with lymphopenia were similar but less consistent, likely due to the smaller patient numbers in these groups. Overall rates of infection with teriflunomide were slightly lower (31.9%) in the real-world Teri-PRO study compared with the individual TEMSO, TOWER, and TOPIC studies (36.1–50.0%) and were lower than placebo (40.5–43.1%). The types of infections observed were also broadly similar across trials, and mild to moderate in severity.[12] This suggests that teriflunomide-treated patients with lymphopenia do not have an increased risk of infection.

Since immunosuppression is often associated with an increased risk of infection, these results support the proposed mechanism of action of teriflunomide, exerting a selective, modulatory effect on the immune system, without compromising mechanisms of adaptive immunity.[8,13] Results from vaccination studies evaluating immune responses to recall antigens or neoantigens also indicate that the cytostatic effects of teriflunomide on activated T- and B-cells do not adversely impact protective immunity.[14,15] This could be of great importance to patients with MS, who are likely to require lifelong treatment, enabling them to continue with teriflunomide without risk of damage to protective immunity, particularly as they age and may become more susceptible to opportunistic infection.

A general limitation of pooled analyses is that data included from many sources may obscure subtle effects in individual studies. The studies included in this pooled analysis had varying designs and mixed patients (secondary progressive MS or progressive RMS in TEMSO, TOWER, and TENERE, and those with a first clinical episode suggestive of MS in TOPIC). The pooled analysis also included varying study durations; however, having a wider range of patients may be considered advantageous due to the large heterogenous sample providing a more accurate representation of real-world populations. Monitoring of lymphocyte counts in the TOPIC trial was infrequent (every 12 weeks) compared with the other trials (every 2 weeks until Week 24, and every 6 weeks thereafter). The infrequent monitoring between lymphocyte assessments could have led to an underestimate of lymphopenia in TOPIC as well as an overestimate in time to lymphopenia.

Furthermore, the data were obtained through a *post hoc* analysis of clinical trials which have strict inclusion and exclusion criteria, and therefore may not be representative of the general MS population. Notably, this *post hoc* analysis of pooled studies has shown consistency with the results of the individual studies, demonstrating robustness. However, there were some differences in the methods used to

ascertain lymphopenia across the core trials and the pooled analysis. In the original studies, patients were considered lymphopenic if their lymphocyte counts dropped below the LLN on just one occasion; in the pooled analysis, lymphopenia was defined by levels below the LLN on two consecutive visits.

Approximately 90% of the study subjects were Caucasian, which may reduce the generalizability of the results in other ethnic populations. All studies included largely treatment-naïve patients: placebo, 69.5%; IFN β-1a, 75.2%; and teriflunomide 14 mg, 79.9% in core studies. Those switching from a prior disease-modifying therapy (DMT) to teriflunomide may have switched from a treatment that is associated with lymphopenia. However, results from the real-world Teri-PRO study which evaluated mean lymphocyte counts in treatment-naïve patients and those who received prior DMT treatment (IFN β-1a, glatiramer acetate, dimethyl fumarate, fingolimod, and natalizumab) concluded that reductions in lymphocyte counts were comparable between treatment-naïve patients and patients switching from another DMT to teriflunomide.[12]

Conclusion

In this pooled analysis of teriflunomide-treated patients in TEMSO, TOWER, TOPIC, and TENERE, low-grade (Grade 1 or Grade 2) lymphopenia was infrequent in both the core and extension studies and no high-grade (Grade 3 or Grade 4) lymphopenia was reported, which suggests that the long-term risk of lymphopenia in patients who continue to receive teriflunomide is low. Infection rates in patients treated with teriflunomide were also similar in populations with and without low grade lymphopenia, indicating that patients with lymphopenia are not subject to a higher risk of infection.

These results reinforce the view that teriflunomide selectively and reversibly targets activated T- and B-lymphocytes, without compromising mechanisms of adaptive immunity.[8,13] The comparable incidence of infections observed with teriflunomide and placebo/IFN β-1a across the TOWER, TOPIC, TEMSO, and TENERE studies also indicates that teriflunomide preserves immunocompetence. Therefore, teriflunomide can be considered an effective immunotherapy for the treatment of RMS, while demonstrating limited impact on adaptive and innate immunity.

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