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Original Research Paper

Effects of teriflunomide treatment on cognitive performance and brain volume in patients with relapsing multiple sclerosis: Post hoc analysis of the TEMSO core and extension studies

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Abstract

Background: In post hoc analyses of Teriflunomide Multiple Sclerosis Oral study (TEMSO; NCT00134563), teriflunomide 14 mg significantly reduced brain volume loss (BVL) versus placebo in patients with relapsing multiple sclerosis (MS).

Objective: In this post hoc analysis of TEMSO and its long-term extension (NCT00803049), we examined the relationship between teriflunomide's effects on BVL and cognition.

Methods: We analyzed data from 709 patients who received teriflunomide 14 mg in TEMSO or its extension. The change in cognitive performance, assessed using the Paced Auditory Serial Addition Test 3 (PASAT-3), was measured in subgroups stratified by BVL over 2 years (least BVL: ⩽0.52%; intermediate BVL: >0.52%–2.18%; most BVL: >2.18%). BVL, MRI lesions, and relapses over 2 years were evaluated as potential mediators of the effect of teriflunomide on cognition.

Results: Teriflunomide 14 mg significantly improved PASAT-3 *Z*-scores versus placebo through year 2. In the least- and intermediate-BVL groups, significant improvements in PASAT-3 *Z*-score were demonstrated versus the most-BVL group over 3 years in the extension. According to the mediation analysis, 44% of the teriflunomide effect on cognition was due to effects on BVL at year 2.

Conclusion: Teriflunomide improves cognition largely through its effects on BVL. Accelerated BVL earlier in the disease course may predict cognitive outcomes.

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Keywords: Teriflunomide, multiple sclerosis, brain volume loss, cognition, TEMSO

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Introduction

Accelerated brain volume loss (BVL) is a hallmark of multiple sclerosis (MS) and an increasingly important biomarker.[1] BVL begins early and may underlie clinical manifestations of MS, including cognitive decline and other aspects of disability.[2–5] Cognitive impairment affects 40%–65% of patients with MS.[6,7] The impact of disease-modifying therapies on BVL may partially explain their impact on cognitive outcomes, but there is a dearth of studies examining those relationships.

Teriflunomide, a once-daily oral immunomodulator, is approved for the treatment of relapsing forms of MS or relapsing–remitting MS, depending on the local label. Similar to data on other disease-modifying therapies, data on relationship between teriflunomide's effects on BVL and cognitive outcomes are sparse. A recent small, single-center, observational study from Italy ($N=30$) suggested a correlation between a slower neurological damage and improvements in memory performance in patients treated with teriflunomide versus controls.[8]

Post hoc analyses of the phase 3 Teriflunomide Multiple Sclerosis Oral study (TEMSO; NCT00134563) suggest that the 14 mg dose was associated with a relative BVL reduction versus placebo of 37% after

1 year and 31% after 2 years of treatment.[9] Mediation analyses indicated that this effect on BVL reduction accounted for 51% of teriflunomide's effect on the reduction of disability worsening versus placebo.[10]

In this post hoc analysis of the TEMSO study and its long-term extension (NCT00803049), we investigated the association between treatment effects of 14 mg teriflunomide on BVL and cognitive performance, as assessed using PASAT.

Methods

Study design and patients

TEMSO was a multinational, multicenter, randomized, placebo-controlled, double-blind, parallel-group phase 3 study in patients with relapsing forms of MS. Details of the TEMSO core and long-term extension studies have been published previously.[11,12] Briefly, eligible patients were aged 18–55 years, had an Expanded Disability Status Scale (EDSS) score of 0–5.5, and had ⩾2 clinical relapses in the previous 2 years or 1 relapse during the previous year. In the core study, 1086 patients received once-daily oral teriflunomide 7 mg ($n=365$) or 14 mg ($n=358$) or placebo ($n=363$), for 108 weeks. Upon core study completion, patients could enter the long-term, double-blind extension and remain on teriflunomide 7 mg or 14 mg or be rerandomized (1:1) to teriflunomide 7 mg or 14 mg if treated previously with placebo (Figure 1(a)). Both studies were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocols were approved by central and local ethics committees and each site's institutional review board. Patients gave written informed consent before entering the study.

Analyses of the association between BVL and cognition include all participants with available data, whereas analyses of treatment effects of teriflunomide focus on patients who were initially treated with teriflunomide 14 mg (the only dose approved in Europe) or placebo in the core study and continued or initiated treatment with the 14 mg dose in the extension; results for patients treated with teriflunomide 7 mg are presented in the Supplementary Appendix.

Cognitive assessment: PASAT-3

PASAT-3 measures attention and information processing speed by giving patients a new single-digit number every 3 seconds and asking them to add the new number to the previous number.[13,14] In patients with MS, poor performance on PASAT may be caused primarily by problems with information processing speed.[15] Score increases from baseline indicate improved performance. This analysis includes PASAT-3 scores measured at weeks 0 (baseline), 24, 48, 72, 96, 108 (end of core study/extension baseline), 132, 156, 180, 204, 228, and 252.

SIENA analysis

Blinded SIENA analysis was carried out post hoc using magnetic resonance imaging data collected at baseline, week 48 (year 1) and week 108 (year 2). The applied methodology for SIENA has been described in detail previously.[9] SIENA was applied to axial T1-weighted images without contrast (slice thickness 3 mm, no gap), of a 70 mm section of central brain area (Montreal Neurological Institute z-coordinates −10 to +60 mm), an area selected for optimal reproducibility and comparability to previous trials of other oral disease-modifying therapies.[16–19] Magnetic resonance imaging of two time points was co-registered and surface changes were determined using SIENA to estimate BVL. Details of the MRI analysis are provided in the Supplementary Appendix. For statistical analysis, BVL from baseline to year 2 was annualized.

Statistical analysis

Teriflunomide effect on cognition. Raw PASAT-3 scores (number of questions correctly answered out of 60)[20] were transformed into Z-scores for analysis[14] using the intent-to-treat (ITT) population (or other subgroup of interest for each analysis) as the reference population. Changes from baseline in PASAT-3 Z-scores over the core period were calculated using an analysis of covariance model adjusted for baseline PASAT-3 Z-score and treatment arm. Least-squares (LS) mean difference between teriflunomide 14 mg and placebo was evaluated. The baseline for long-term PASAT-3 change was the time point at which teriflunomide 14 mg was initiated.

Association between BVL and PASAT-3 scores. Patients were stratified into three groups using the interquartile range of change in BVL from baseline to year 2 in placebo-treated patients to better reflect natural history, as described previously.[10] To focus on patients with extremes of high and low BVL, the middle two quartiles were combined into a single group. Groups were defined as least BVL (⩽0.52%), intermediate BVL (>0.52%–2.18%), and most BVL (>2.18%). Change in PASAT-3 Z-scores according to BVL group was analyzed using an analysis of

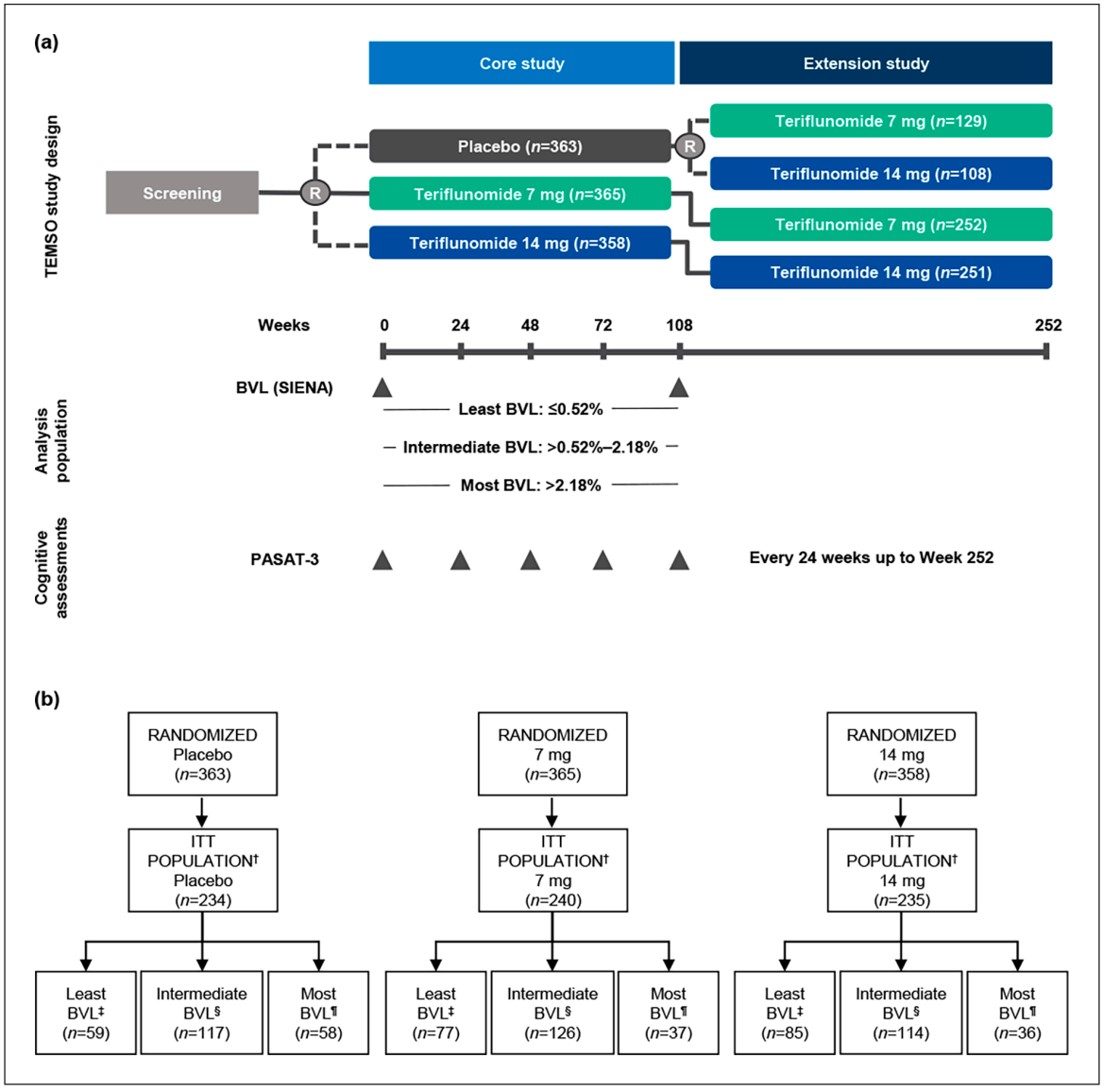

Figure 1. TEMSO core and extension study design (a), and flow diagram based on treatment group and the number of patients from each treatment group in each BVL subgroup after stratification (b).
BVL: brain volume loss; ITT: intent to treat; PASAT-3: Paced Auditory Serial Addition Test 3; R: randomization; SIENA: structural image evaluation using normalization of atrophy.
†ITT population with valid scans at baseline and year 2.
‡Least BVL from core study baseline to week 108: ⩽0.52%.
§Intermediate BVL from core study baseline to week 108: >0.52%–2.18%.
¶Most BVL from core study baseline to week 108: >2.18%.

covariance model adjusted for age, baseline PASAT-3 *Z*-score, baseline EDSS strata (⩽3.5 vs >3.5), treatment arm, and baseline contrast-enhancing lesion (CEL) status (yes/no). The EDSS cut-off value was selected as >3.5 as this is considered a disability milestone.[21] Sensitivity analyses were carried out for change in PASAT-3 *Z*-scores over time by BVL group adjusting for normalized brain volume at baseline or for normalized brain volume, number of CELs, and T2w lesion volume at baseline.

Mediation analysis. The Prentice criteria[22] were used to identify potential mediators of the relationship between treatment and clinical outcome. Criterion 1 requires the potential surrogate/mediator to be significantly associated with treatment. Criterion 2 requires the clinical outcome (i.e. cognition) to be associated with treatment. Criterion 3 requires the clinical outcome to be associated with the potential surrogate/mediator. Criterion 4 requires, for an ideal surrogate, that the association of treatment with the clinical

outcome be fully attenuated when adjusting for the potential surrogate. In addition to BVL, relapses through year 2 and the number of new/enlarging T2w lesions at week 108 were considered as potential surrogates based on prior evidence that they mediate the teriflunomide treatment effect on disability progression.[10] The number of CELs was also included as a potential surrogate as it is significantly associated with treatment (Criterion 1). This analysis was conducted with and without exclusion of the most extreme values, defined as patient data with studentized residual > 3, in absolute value, in the first iteration.

The proportion of treatment effect on cognition that was explained by the surrogates was estimated as the percent attenuation in the adjusted (Criterion 4) versus unadjusted (Criterion 2) association between treatment and cognition.

Results

Patients

In the least-, intermediate-, and most-BVL groups, 59, 117, and 58 received placebo, respectively, and 85, 114, and 36 patients received teriflunomide 14 mg (Figure 1(b)). Compared with their placebo-treated counterparts, patients treated with teriflunomide had 68% higher odds of being in the group with the least BVL than in the group with intermediate/most BVL (odds ratio 1.68 (95% confidence interval, 1.28–2.08), $p = 0.010$) and 82% higher odds of being in the group with least/intermediate BVL than in the group with most BVL (odds ratio 1.82 (95% confidence interval, 1.36–2.28), $p = 0.010$). Patient characteristics at baseline were generally similar across BVL groups (Table 1); however, the least- and intermediate-BVL groups had slightly lower mean EDSS scores than the most-BVL group.

Patients with the least BVL had significantly higher normalized brain volume ($p < 0.001$) and higher PASAT-3 *Z*-scores ($p = 0.01$) at baseline than those with the most BVL. Patients with the most BVL over 2 years had the highest number of CELs and T2w lesion load. Baseline characteristics by core study treatment group are provided in Table S1 and by treatment group and BVL quartile in Table S2.

Teriflunomide effect on cognition

In the core study, PASAT-3 *Z*-scores were significantly improved with teriflunomide 14 mg versus placebo over 2 years ($p = 0.015$; Figure 2(a)). In a pooled analysis of patients who received teriflunomide 14 mg in the core study and/or the extension, PASAT-3 *Z*-scores increased through week 252 post teriflunomide initiation (Figure 2(b)).

Patients who received teriflunomide 14 mg in the core study and extension had higher PASAT-3 *Z*-scores through week 252 compared with those who switched to teriflunomide 14 mg at the start of the extension (Figure S1).

Association between BVL and PASAT-3 scores

At week 48, PASAT-3 score changes from core study baseline were significantly greater in the least-BVL ($p = 0.0185$) and intermediate-BVL ($p = 0.0015$) groups versus the most-BVL group. Significantly improved scores in both the least-BVL ($p = 0.019$) and intermediate-BVL ($p < 0.001$) groups continued through week 96 of the core study. Across the extension, changes in LS means from core study baseline PASAT-3 scores were significantly improved in the least- and intermediate-BVL groups versus the most-BVL group (Figure 3).

Similar changes were observed across BVL subgroups when analyses were adjusted for normalized brain volume at baseline, T2w lesion volume and CELs at baseline (Figure S2). To evaluate potential confounding by core study treatment, the association between BVL and cognition was determined separately for patients who received teriflunomide 14 mg and those who received placebo (Figure S3). Notably, early teriflunomide treatment had a stabilizing effect on cognition in patients with the most BVL during the core period.

Mediation analysis of teriflunomide treatment effect on cognition

Significant reductions across the surrogate markers of relapse, new/enlarging T2w lesions, CELs, and BVL were observed with teriflunomide 14 mg versus placebo (Prentice Criterion 1)[11] along with improved cognition in teriflunomide-treated patients (Prentice Criterion 2).[23] BVL, CELs, and new/enlarging T2w lesions were significantly associated with change in PASAT-3 *Z*-score at year 2, which was not the case with relapses (Prentice Criterion 3; Figure S4). Upon removal of outlier values in a sensitivity analysis, the overall direction of the relationships did not change, and a significant association with changes in PASAT-3 *Z*-scores was shown for relapses, new/enlarging T2w

Table 1. Patient demographics and baseline clinical characteristics according to BVL group.[a,b]

	Least-BVL group (≤0.52% reduction) *n*=221	Intermediate-BVL group (>0.52%–2.18% reduction) *n*=357	Most-BVL group (>2.18% reduction) *n*=131
Age, years	38.4 (8.0)	37.8 (8.8)	36.1 (9.3)
Female, *n* (%)	152 (68.8)	272 (76.2)	99 (75.6)
Time since MS diagnosis, years	5.2 (5.8)	5.3 (5.5)[c]	4.3 (4.8)
Time since first MS symptoms, years	8.6 (7.2)	8.9 (7.0)	7.7 (6.5)
Time since most recent relapse, months	6.6 (3.4)	6.8 (3.7)	6.8 (4.0)
Number of relapses			
In previous year	1.3 (0.7)[d]	1.3 (0.7)[e]	1.4 (0.7)[f]
In previous 2 years	2.1 (0.9)	2.2 (0.9)	2.3 (1.0)
MS subtype, *n* (%)			
Relapsing-remitting	204 (92.3)	336 (94.1)	122 (93.1)
Previous DMT use, *n* (%)	47 (21.3)	83 (23.2)	35 (26.7)
EDSS score	2.4 (1.2)	2.5 (1.3)	2.8 (1.3)
Number of CELs	0.5 (1.2)[g]	1.2 (2.8)	4.0 (7.9)
Normalized brain volume, cm^3	1514.6 (74.8)	1509.5 (77.7)	1476.3 (85.1)
T2w lesion volume, mL	10.1 (11.1)	14.8 (14.8)	25.5 (17.7)
PASAT-3 *Z*-score	−0.03 (1.05)[h]	0.14 (0.89)[i]	−0.33 (1.13)[j]

BVL: brain volume loss; CEL: contrast-enhancing lesion; DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; ITT: intent to treat; MS: multiple sclerosis; PASAT-3: Paced Auditory Serial Addition Test 3; SD: standard deviation; T2w: T2 weighted.
Values are mean (SD) unless indicated otherwise.
[a]ITT population with valid scans at baseline and year 2.
[b]The ITT population represents pooled data from placebo and active-treatment groups.
[c]*n*=356.
[d]*n*=172.
[e]*n*=277.
[f]*n*=103.
[g]*n*=220.
[h]*n*=221.
[i]*n*=354.
[j]*n*=130.

lesions, and CELs, but not for BVL. The improvement in PASAT-3 performance with teriflunomide 14 mg versus placebo was no longer statistically significant after adjusting for either BVL (LS mean difference ± standard error (SE): 0.06 ± 0.05, $p=0.24$), CELs (0.09 ± 0.05, $p=0.08$) or new/enlarging T2w lesions (0.09 ± 0.05, $p=0.07$), but was significant after adjusting for relapses (0.11 ± 0.05, $p=0.023$; Prentice Criterion 4).

Assessment of individual surrogate markers indicated that BVL, CELs, new/enlarging T2w lesions, and relapses contributed 44%, 20%, 17%, and 7%, respectively, toward the teriflunomide 14 mg treatment effect on cognitive improvement (Figure 4).

To account for the potential correlation between the surrogates, we performed an analysis combining all four parameters. Combined contributions of BVL, new/enlarging T2w lesions, CELs, and relapses amounted to 47% of the treatment effect. Because the combined surrogates did not increase the contribution to teriflunomide treatment effect compared with BVL alone, the data suggest BVL was the predominant parameter affecting cognitive performance.

Mediation analyses of the teriflunomide 7 mg treatment effect on cognition yielded results similar to analyses of teriflunomide 14 mg. BVL, CELs, new/enlarging T2w lesions, and relapses contributed 78%, 35%, 30%, and 6%, respectively, toward the treatment effect on cognition (see Supplementary Appendix).

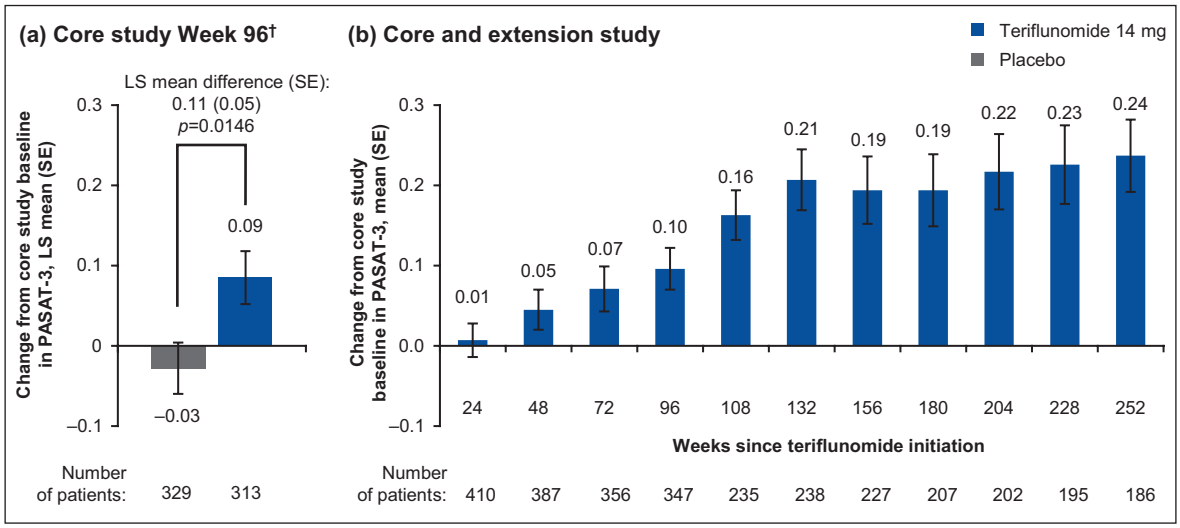

Figure 2. Change in PASAT-3 *Z*-score through the TEMSO core study in placebo and teriflunomide 14 mg patients (a), and through the TEMSO core study and its extension period in pooled teriflunomide 14 mg patients (b).
CEL: contrast-enhancing lesion; EDSS: Expanded Disability Status Scale; LS: least squares; PASAT-3: Paced Auditory Serial Addition Test 3; SE: standard error.
†Last visit of core study, up to week 96. *p*-Values were generated using analysis of covariance adjusted for age, baseline *Z*-score, baseline EDSS strata, baseline CEL status, treatment, and quartile category. Panel A analytic sample is all participants in the randomized population (randomized to placebo or teriflunomide 14 mg) with PASAT scores available at baseline and week 96. Panel B analytic sample is all participants after teriflunomide 14 mg initiation (either at baseline or in the extension) with PASAT scores available at the specific week reported.

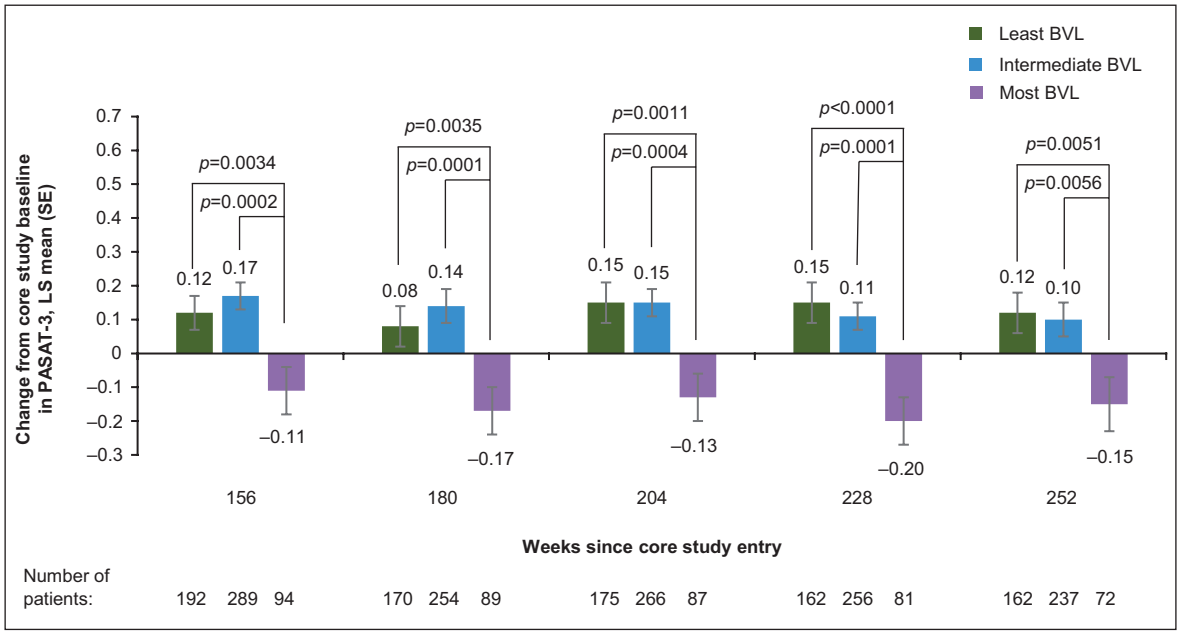

Figure 3. Change in PASAT-3 *Z*-score by BVL group through the TEMSO extension period.
BVL: brain volume loss; CEL: contrast-enhancing lesion; EDSS: Expanded Disability Status Scale; LS: least squares; PASAT-3: Paced Auditory Serial Addition Test 3; SE: standard error.
Least BVL: ⩽0.52%; intermediate BVL: >0.52%–2.18%; most BVL: >2.18%. *p*-Values were generated using analysis of covariance adjusted for age, baseline *Z*-score, baseline EDSS strata, baseline CEL status (yes/no), treatment, and quartile category. The analytic sample is all patients (placebo and both teriflunomide groups) with valid MRIs at baseline and week 108 (for categorizing BVL) who have PASAT scores at baseline and the specific week reported.

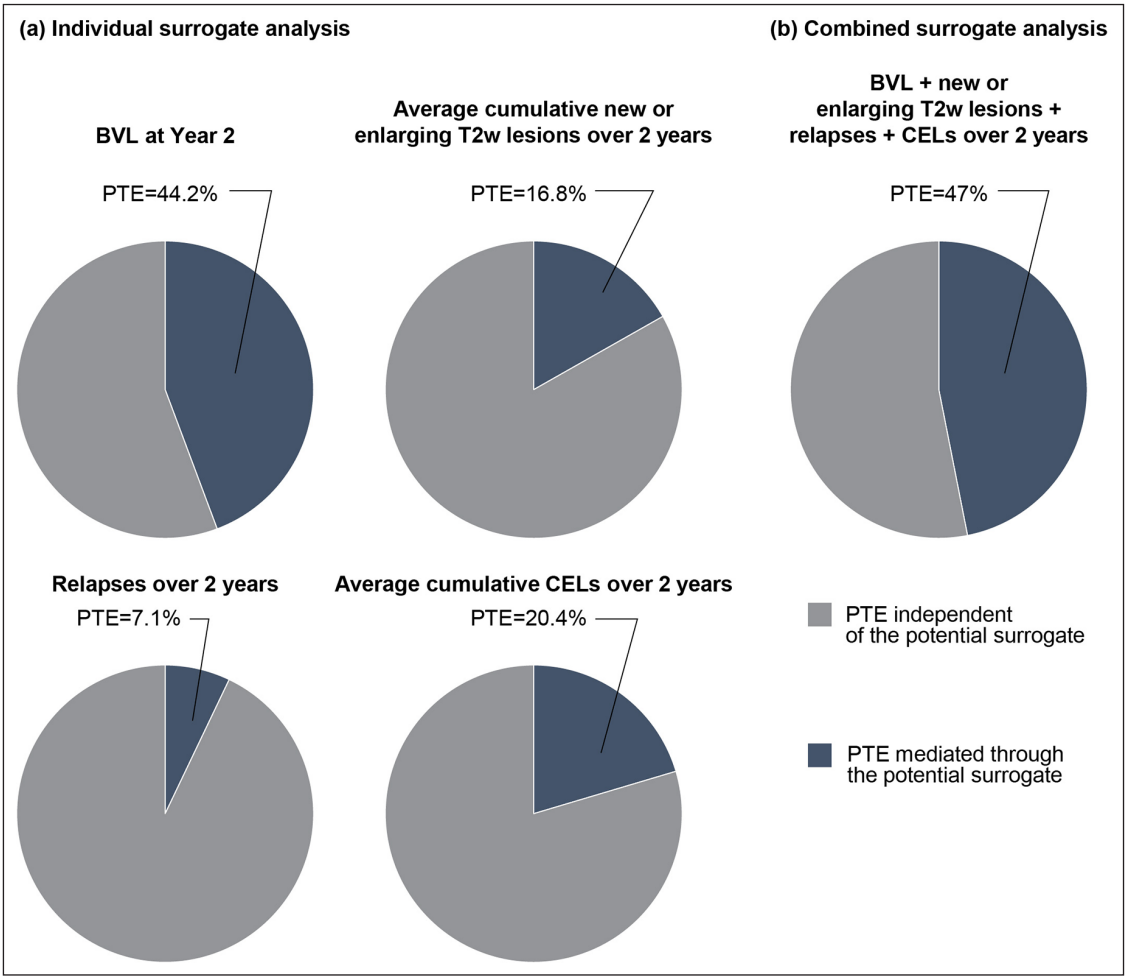

Figure 4. Percentage of relative contributions of each surrogate individually (a) and combined (b).
BVL: brain volume loss; CEL: contrast-enhancing lesion; PTE: proportion of treatment effect; T2w: T2 weighted.
The analytic sample is patients with valid MRIs at baseline and week 108.

Discussion

In patients with MS, identification of factors that drive deficits in daily functioning can be used to define and monitor a meaningful therapeutic response. In the present analysis, patients who received teriflunomide 14 mg in the 2-year core study experienced, compared with placebo-treated patients, significant improvements in cognition (most likely processing speed), with the benefits extending for up to 5 years. Cognitive performance in the extension study was better among patients with least BVL in the core study than in those who experienced the most BVL, suggesting that BVL can be a predictor of cognitive impairment.

These results are in agreement with previous studies indicating that BVL is associated with cognitive impairment.[7,24] Mediation analysis of both the 7 and the 14 mg dose supports the view that the treatment effect on cognition was generally driven by slowing of BVL at year 2, rather than by effects on CELs, new/enlarging T2w lesions, or relapses. BVL reflects both focal and diffuse disease mechanisms affecting white and gray matter.[4] Cognition is similarly thought to be impacted by focal inflammatory lesions and diffuse pathologic changes in the gray matter and normal-appearing white matter.[25] Cognition and brain volume thus may be parallel components of overall brain health in MS.

In the subset with the greatest BVL in the core study, patients initially randomized to receive 14 mg teriflunomide had a better cognitive performance in the extension study than those who were randomized to receive placebo. This observation suggests that an earlier intervention with teriflunomide would convey greater long-term cognitive benefits than a later intervention, particularly in patients with a higher BVL during the first 2 years of treatment.

Results of this study are consistent with a previous analysis, which showed that BVL at year 2 accounted for the largest proportion (51%) of the teriflunomide treatment effect on disability, as measured using the EDSS.[10] Although cognition is an important aspect of disability, it is not well captured by the EDSS. The present results therefore show meaningful extension of the prior analysis, demonstrating the importance of BVL in both physical and cognitive impairment in MS.

Key limitations of this analysis are its post hoc nature and the fact that it was not adequately powered. Furthermore, the imbalance in baseline patient characteristics across BVL strata may have introduced confounding. One possible consequence of this imbalance is the potential for patients with more lesions to have more inflammatory disease and therefore experience more pseudoatrophy following treatment initiation. We did adjust our models for the factors that were imbalanced between BVL groups at baseline, but there may have been other potential confounders that were not captured. Another limitation is that PASAT-3 reflects only certain aspects of cognitive function, primarily information processing speed; in addition, it is prone to significant practice effects.[26] (However, it should be noted that, in patients with MS, practice effect has been shown predominantly in PASAT versions with a delay of <2.6 s between numbers,[27] which suggests that our data may have been less affected by this phenomenon.). Finally, although significant, the magnitude of the observed *Z*-score increase is relatively small and there are no established cut-points in the PASAT-3 for defining clinically meaningful change.

Overall, these findings support the positive short- and long-term effect of teriflunomide on cognitive performance in patients with relapsing MS, and suggest that this effect may be caused, at least in part, by slowing of BVL. These data also suggest that earlier intervention with teriflunomide would mitigate cognitive decline in patients with relapsing MS more than a later intervention. Finally, this is one of the first studies to assess the relationship between disease-modifying therapies, BVL, and cognitive performance in MS. More inquiries into this relationship are needed.

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Data accessibility statement

Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and data set specifications. Patient-level data will be anonymized and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com.

Declaration of conflicting interests

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Previous presentation of the data

Some of the data included in this manuscript were presented previously at the 12th World Congress on Controversies in Neurology (CONy), 22–25 March 2018, Warsaw, Poland (Sprenger et al.); the 70th Annual Meeting of the American Academy of Neurology (AAN), 21–27 April 2018, Los Angeles, CA, USA (Sprenger et al., P372); the Australian and New Zealand Association of Neurologists (ANZAN) Annual Meeting, 28 May–1 June 2018, Darwin, Australia (Sprenger et al., P715); the 14th International Congress of Neuroimmunology (ISNI) Annual Meeting, 27–31 August 2018, Brisbane, Australia (Lechner-Scott et al., P92); the Pan-Asian Committee on Treatment and Research in Multiple Sclerosis (PACTRIMS), 1–3 November 2018, Sydney, Australia (Lechner-Scott et al., P93); and the 71st AAN, 4–10 May 2019, Philadelphia, USA (Wuerfel et al., P2-058).

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Supplemental material

Supplemental material for this article is available online.

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