Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

Original article

Fatigue in teriflunomide-treated patients with relapsing remitting multiple sclerosis in the real-world Teri-FAST study

Jérôme de Sèze [a,*], Richard Devy [b], Evelyne Planque [c], Jean Philippe Delabrousse-Mayoux [d], Olivier Vandhuick [e], Marmar Kabir [f], Amel Gherib [g]

[a] Strasbourg University, Hôpital Civil, Strasbourg, France
[b] Polyclinique Bordeaux Caudéran, France
[c] SCP Doctors, Épinal, France
[d] Neurology Practice, Bergerac, France
[e] Meridian Center, Rouen, France
[f] Sanofi, Chilly-Mazarin, France
[g] Sanofi, Gentilly, France

ARTICLE INFO

ABSTRACT

Background: Fatigue is a frequent and disabling symptom of multiple sclerosis (MS) often associated with impaired quality of life (QoL) in patients. Teriflunomide is a once-daily oral immunomodulator used for the treatment of relapsing remitting forms of MS. However, its effect on fatigue is not well known in real life practice. We evaluated the impact of teriflunomide on fatigue in patients with relapsing remitting MS (RRMS) after 2 years of treatment in the real-world Teri-FAST study.
Methods: Teri-FAST was a 2-year, prospective, observational study conducted in France in RRMS patients treated with teriflunomide 14 mg. Fatigue was assessed using the French version of the modified fatigue impact scale (EMIF-SEP). The primary endpoint was the change from baseline in EMIF-SEP score after 2 years of treatment. Secondary endpoints included evaluation of depression (Beck Depression Inventory [BDI]), health-related QoL (Two-Life Scale TLS-QoL 10), self-reported physical activity, and adverse events.
Results: 210 eligible patients were included in the study with a mean age of 45.4 years and a mean $\pm$ SD Expanded Disability Status Scale score of 1.76 ± 1.43 at baseline. About half (52.4%) of patients had no previous treatment for MS. In the 163 patients who completed at least 1 follow-up visit, the mean change in EMIF-SEP score at Year 2 was –1.54 (95% CI: –4.02, 0.94) indicating that fatigue remained stable. Similarly, there were no changes in depression level and QoL after 2 years of treatment. Physical activity slightly improved with 57% of patients reporting being physically active after 2 years as compared to 46% at baseline. The safety profile of teriflunomide was consistent with that seen during clinical development, and compliance with treatment was high.
Conclusion: Fatigue scores remained stable in RRMS patients treated with teriflunomide 14 mg over 2 years in real-life setting. Teriflunomide did not negatively impact depression or QoL.

1. Introduction

Fatigue is a frequently reported symptom of multiple sclerosis (MS) and is one of the most burdensome experienced by patients (Ayache and Chalah, 2017). It can affect 50% to 90% of MS patients according to studies and can occur at all stages of the disease including as a prodrome (Penner and Paul, 2017; Yusuf et al., 2020). In a study in 85 patients with MS, most patients reported fatigue as either their worst (14%) or one of their worst (55%) symptoms (Fisk et al., 1994). Similarly, in the global versus MS survey conducted in 1075 participants with MS, 76% of patients reported that their daily activities were limited by fatigue (18% severely) (Bass et al., 2019).

While fatigue is a frequent symptom in MS patients, it is also highly subjective and lacks a universally accepted definition. It may take many forms such as a feeling of exhaustion or tiredness at the physical and/or cognitive level, and has been commonly defined as "a subjective lack of

---

physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activity" (Braley and Chervin, 2010; Multiple Sclerosis Clinical Practice Guidelines, 1998). Fatigue is particularly disabling for MS patients and is often associated with impaired quality of life (QoL) by negatively impacting daily professional, physical and social activities (Gullo et al., 2019; Janardhan and Bakshi, 2002; Nourbakhsh et al., 2016). Altogether, the pathophysiology of fatigue in MS is still poorly understood and may result from multiple underlying causes, making it very challenging to manage (Chalah et al., 2015). Possible contributing factors include damage to the nervous system caused by MS, neuroendocrine dysfunction, inflammation, or side effects of MS therapy (Ayache and Chalah, 2017).

Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing remitting forms of multiple sclerosis (RRMS) (European Medicines Agency, 2013). Teriflunomide has been demonstrated to have efficacy on clinical and magnetic resonance imaging (MRI) outcomes in two large, placebo-controlled phase 3 studies, TEMSO (NCT00134563) and TOWER (NCT00751881) (Confavreux et al., 2014; O'Connor et al., 2011). In both studies, teriflunomide 14 mg once daily significantly reduced the risk of relapse and disability worsening in patients with relapsing forms of MS compared with placebo. Efficacy of teriflunomide was maintained in the long term in the TEMSO extension study (O'Connor et al., 2016).

The effect of teriflunomide on fatigue in MS patients, particularly in real life settings, has not been thoroughly investigated. We set up the Teri-FAST observational study to evaluate fatigue in patients with RRMS treated with teriflunomide 14 mg in real-world practice in France. Fatigue was self-assessed by patients using a routine and clinically validated tool, the Modified Fatigue Impact Scale (MFIS; EMIF-SEP in its French version). Patients were followed up for a total of 2 years.

2. Material and methods

2.1. Study design

Teri-FAST was a 2-year, prospective, open-label, observational study conducted to assess fatigue in patients with RRMS treated with teriflunomide 14 mg in real-life practice. Patients were recruited between January 2015 and June 2016 by 50 neurologists in private or mixed public-private practices evenly distributed throughout metropolitan France.

The study was carried out in accordance with the ethical principles of the declaration of Helsinki (1964 and revisions), the Recommendations on Ethics and Good Practice in Epidemiology (2007), and the local regulations in force.

2.2. Patients

Eligible patients were aged 18–65 years, with a diagnosis of RRMS, Expanded Disability Status Scale (EDSS) score ≤5.5, free of relapse for the last 60 days, and either no previous treatment for MS or previous treatment with interferon-β or glatiramer acetate for at least 6 months. Patients presenting a condition that could interfere with fatigue evaluations (such as severe depression) were not included in the study.

The decision to prescribe teriflunomide had to be made independently of the entry of the patient into the study and had to be in accordance with the recommendations outlined in the drug labelling (assessment of blood pressure, hepatic enzymes and complete blood cell count before starting the treatment) (European Medicines Agency, 2013).

All patients provided written informed consent prior to entering the study.

2.3. Data collection

Fatigue, severity of depression and health-related QoL were assessed using validated French versions of self-questionnaires at inclusion, 6 months, 1 year and 2 years after treatment initiation. Other collected data included physical activity and treatment compliance as reported by the patient and occurrence of adverse events (AEs) throughout the study.

Fatigue experienced over the past 4 weeks was measured using EMIF-SEP, a validated French version of the MFIS widely used to measure fatigue in MS patients (Debouverie et al., 2008,2007; Téllez et al., 2005). MFIS is an abridged scale derived from the original 40-item Fatigue Impact Scale and is composed of 21 items each with a score of 0 to 4. It is easy to use in clinical practice and offers multidimensional score assessments of fatigue including physical (range 0–36), cognitive (range 0–40) and psychosocial dimensions (range 0–8). The total EMIF-SEP score ranges from 0 to 84 with higher scores indicating a greater impact of fatigue on daily life. The patient generally experiences fatigue when the total score is 38 or above (Téllez et al., 2005).

Depression was measured using a shortened 13-item version of the Beck Depression Inventory (BDI) with a total score ranging from 0 to 39: no depression (0–3), slight depression (4–7), moderate depression (8–15), severe depression (≥16) (Collet and Cottraux, 1986).

Health-related QoL was measured using the 10-item Two-Life Scale (TLS-QoL 10) an easy to use tool adapted to MS patients with a total score range ranging from 0 (good QoL) to 10 (highly impacted QoL) (Devy et al., 2013).

2.4. Statistical methods

Three study populations were assessed: the eligible population (patients who met the inclusion criteria and had previous treatment data available), the evaluable population (eligible patients who completed at least 1 post-inclusion follow-up visit), and the safety population (patients who took at least 1 teriflunomide tablet).

The primary endpoint (change from baseline in EMIF-SEP score after 2 years) was calculated in the evaluable population as the adjusted mean difference and 95% confidence interval (CI) using a mixed model adjusted for baseline score. Missing data were imputed with the last observation carried forward (LOCF) method. Change in EMIF-SEP score was also analysed descriptively according to previous MS treatment (interferon-β, glatiramer acetate or treatment-naïve).

In addition, the mean change in EMIF-SEP score after 2 years of teriflunomide treatment was compared to a theoretical change of +9 points without treatment using Student's t-test, with a hypothesis of a mean difference of at least -5 points between the two virtual treatment groups. This assumption was based on the findings of the TENERE study where mean change in Fatigue Impact Score at 48 weeks was +4.10 in patients treated with teriflunomide 14 mg compared with +9.10 in those treated with interferon-β (mean difference of -5 points) (Vermersch et al., 2014). However, it should be noted that the impact of interferon-β on fatigue varies across studies and its detrimental effect on fatigue remains controversial (Braley and Chervin, 2010; Patti et al., 2011). To detect the hypothesised difference of -5 points in fatigue score, 300 evaluable patients were required to ensure 80% power based on an estimated standard deviation (SD) of about 30 points and a bilateral α at 0.05 (unilateral at 0.025), assuming normal distribution. While this target sample size was not reached, variability of EMIF-SEP score was lower than estimated (observed SD: 18 points) and the actual sample size of 163 evaluable patients was sufficient to reach a statistical power >90% as calculated a posteriori.

Secondary endpoints (depression, QoL, physical activity, compliance with teriflunomide treatment, and occurrence of AEs) were analysed descriptively in the evaluable population.

3. Results

3.1. Study population and baseline characteristics

Of 217 patients recruited to the study, a total of 211 patients took at least one tablet of teriflunomide (safety population), 210 patients were included in the eligible population, and 163 in the evaluable population (Fig. 1). In all, 75/217 (34.6%) patients discontinued the study; the most common reasons for discontinuation were occurrence of an AE (22 patients), lack of efficacy of treatment (14 patients), or patients lost to follow-up (11 patients).

Baseline demographics and disease characteristics of the eligible population are presented in Table 1. Patients had a mean ± SD age of 45.4 ± 10.3 years, were in majority women (74.3%), and had a low mean ± SD EDSS score of 1.76 ± 1.43. The mean ± SD time from diagnosis of MS was 8.9 ± 8.2 years, and about half of the patients had no previous MS treatment (treatment-naïve). The mean ± SD number of relapses in the 2 years before inclusion was 0.8 ± 1.1. In average, patients experienced their last relapse 9.7 ± 11.0 months before entering

Table 1
Baseline demographics and disease characteristics in the eligible population.

	Total (N=210)
Age, mean (SD), years	45.4 (10.3)
Females, n (%)	156 (74.3)
Time from diagnosis of MS, mean (SD), years	8.9 (8.2)[a]
Number of relapses in the past 2 years, mean (SD)	0.8 (1.1)[b]
Time from last relapse, mean (SD), months	9.7 (11.0)[c]
EDSS score, mean (SD)	1.76 (1.43)[d]
Prior treatment*, n (%)	
Treatment-naïve	110 (52.4)
Interferon-β	64 (30.5)
Glatiramer acetate	36 (17.1)

[a] n = 208;
[b] n = 205;
[c] n = 118;
[d] n = 209.
* Within 3 months before inclusion. EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; SD, standard deviation.
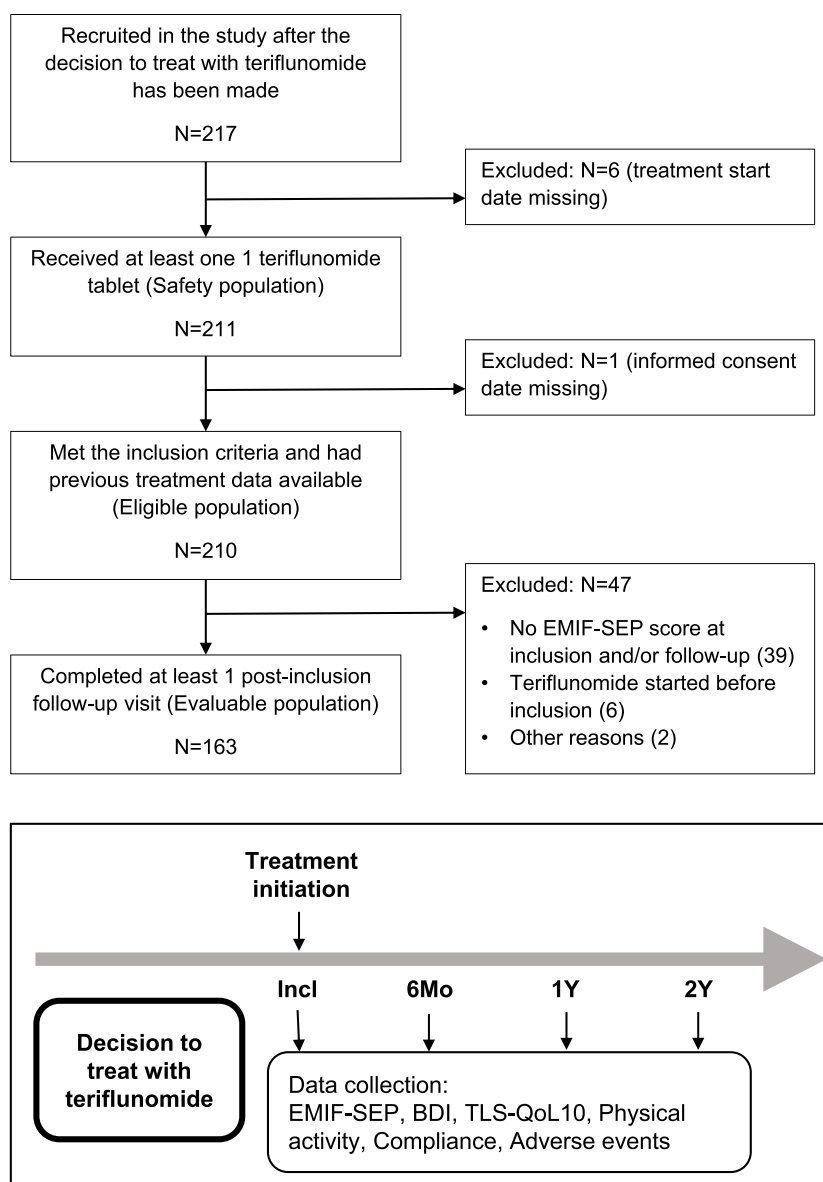

Fig. 1. Flow diagram of participants and study design.
BDI, Beck Depression Inventory; EMIF-SEP, French version of the Modified Fatigue Impact Scale in Multiple Sclerosis; Incl, Inclusion; Mo, Month; TLS-QoL10, Two-Life Scale - Quality of Life 10; Y, Year.

the study.

The mean (± SD) duration of treatment with teriflunomide was 2.0 ± 0.2 years.

3.2. Fatigue after 2-year treatment with teriflunomide

Mean ± SD total EMIF-SEP score was 32.8 ± 18.0 at baseline and 31.3 ± 19.1 at Year 2, resulting in a non-clinically significant mean change from baseline of –1.54 (95% CI: –4.02, 0.94) (Table 2). Similarly, no clinically significant change was noted after 2 years of treatment in the physical, cognitive, and psychosocial fatigue subscales as shown in Fig. 2.

The mean change in total EMIF-SEP score (–1.54) was significantly lower compared with a theoretical change of +9 points for untreated patients ($P<0.0001$).

The mean change (95% CI) in EMIF-SEP score from Baseline to Year 2 in patients who were previously treated with interferon-β or glatiramer acetate was –0.6 (–5.4, 4.2) and –1.4 (–7.4, 4.6), respectively. In treatment-naïve patients, the mean change (95% CI) from baseline to Year 2 was –2.2 (–6.3, 1.9). However, owing to the small number of patients in each subgroup, the actual impact of prior MS treatment on fatigue is difficult to ascertain.

3.3. Depression, health-related quality of life and physical activity

Mean ± SD BDI score was 5.9 ± 5.6 at baseline, indicating slight depression. Depression did not worsen after 2 years' treatment with teriflunomide, with a mean ± SD score of 5.0 ± 5.0 (mean change (95% CI) from baseline: –0.6 (–1.5, 0.3)) (Table 2).

Similarly, health-related QoL remained stable during the study: the mean ± SD TLS-QoL score was 2.6 ± 2.7 at Baseline and 2.2 ± 2.6 at Year 2 (mean change (95% CI) from baseline: –0.3 (–0.8, 0.1)) (Fig. 3).

The proportion of patients who reported physical activity at Year 1 and Year 2 (about 58%) was greater as compared to Baseline and 6 months (about 47%) (Table 2). The most frequently reported physical activity was walking.

3.4. Evolution of multiple sclerosis

The vast majority (>90%) of patients in the evaluable population did not have MS relapse over the 2 years of treatment. Less than 10% of patients experienced one relapse, and only one patient had two relapses during the study.

Table 2
Fatigue, depression and physical activity after teriflunomide treatment in the evaluable population.

	n	Total (N=163)
Fatigue (EMIF-SEP score)		
Mean (SD)		
Baseline	163	32.8 (18.0)
Year 2	163	31.3 (19.1)
Mean change from baseline (95% CI)	163	–1.54 (–4.02, 0.94)
Depression (BDI score)		
Mean (SD)		
Baseline	162	5.9 (5.6)
Year 2	121	5.0 (5.0)
Mean change from baseline (95% CI)	121	–0.6 (–1.5, 0.3)
Physical activity, n (%)		
Baseline*	208	96 (46.2)
Month 6	160	77 (48.1)
Year 1	147	86 (58.5)
Year 2	133	76 (57.1)

* Data at baseline are from the eligible population. BDI, Beck Depression Inventory; CI, Confidence interval; EMIF-SEP, French version of the Modified Fatigue Impact Scale in Multiple Sclerosis; SD, standard deviation.
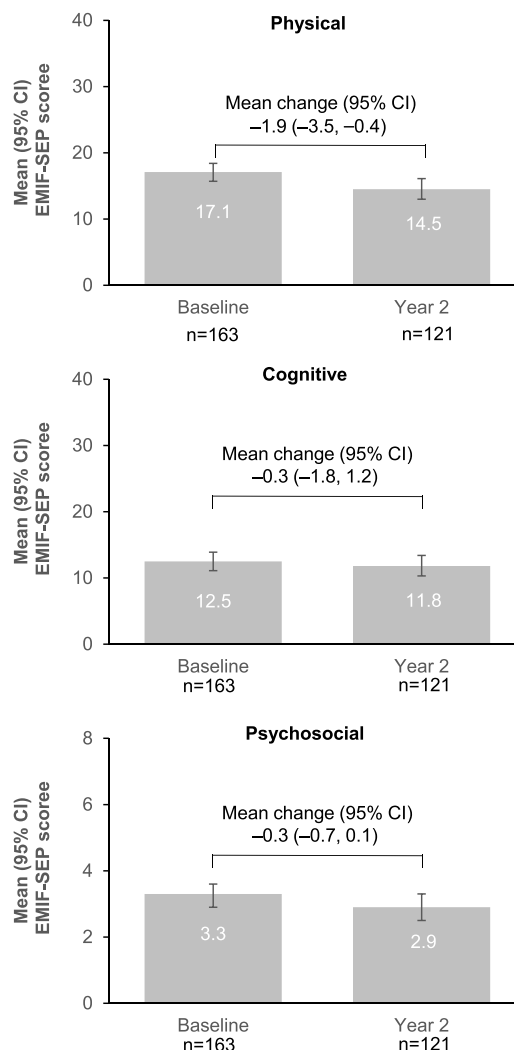

Fig. 2. Mean EMIF-SEP physical, cognitive, and psychosocial fatigue sub-scales score after teriflunomide treatment in the evaluable population.
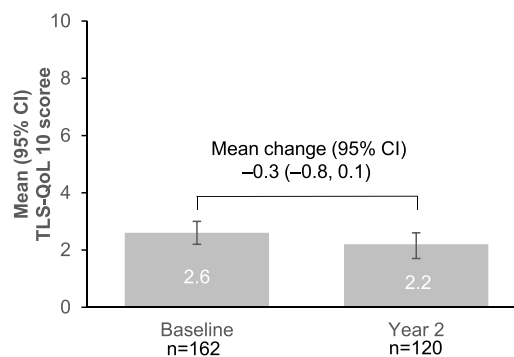

Fig. 3. Mean TLS-QoL 10 score after teriflunomide treatment in the evaluable population.
TLS-QoL 10, Two-Life Scale - Quality of Life 10.

3.5. Compliance with treatment

The compliance with treatment as self-reported by the patients was relatively high throughout the study and ranged between 90-93% at each visit. A total of 123 (92.5%) patients (of the 133 patients for which this information was available after 2 years) reported that they had never missed a dose.

3.6. Safety

The occurrence of AEs during the study is shown in Table 3. In all, 27.5% of patients who took at least 1 tablet of teriflunomide reported an AE. The most common AEs were hair thinning (MedDRA preferred term, alopecia; 6.2%) and diarrhoea (5.2%); all other AEs occurred in less than 1.5% of patients. A total of 14 serious AEs were reported of which 7 were considered by the investigator as related to teriflunomide treatment. Serious AEs included lymphopenia, increase in transaminases and alopecia (1 patient each). Overall, 22/211 patients (10.4%) permanently discontinued treatment because of the development of AEs. The most frequently reported AEs leading to treatment discontinuation were alopecia (5 patients; 2.4%), diarrhoea (4 patients; 1.9%) and acute pancreatitis (2 patients [1 serious]; 0.9%). There were no new or unexpected safety findings as compared to the known safety profile of teriflunomide.

4. Discussion

In this observational study conducted in real-life setting in France, the degree of fatigue as measured by EMIF-SEP remained constant in RRMS patients treated with teriflunomide over the first 2 years. Similarly, no clinically significant changes were observed on depression and QoL as self-reported by patients.

The safety and tolerability profile of teriflunomide in the study was consistent with that seen during clinical development. In two pooled safety analysis representing a cumulated exposure to teriflunomide of more than 6800 patient-years treated for up to 12 years, the most frequent AEs were globally similar to those observed in our study and included alanine aminotransferase increase, diarrhoea and hair thinning (Comi et al., 2016). The high treatment compliance (when information was available) observed throughout the 2-year treatment (>90%) may be in part explained by the good and manageable safety profile of teriflunomide.

The results on fatigue, QoL and depression are particularly meaningful as they show an absence of deterioration of all three parameters over a 2-year period. More than 90% of patients in this study were relapse-free during teriflunomide treatment although this was a cohort with a low rate of relapse at baseline. In placebo-controlled trials, teriflunomide demonstrated efficacy in preventing relapse and disability progression (Confavreux et al., 2014; O'Connor et al., 2011). The low relapse rate seen in our study, together with the stabilisation of the physical and general well-being of patients, may have contributed to the lack of negative impact on fatigue. In addition, several studies also indicate an independent relation between inflammation status and fatigue in MS (Heesen et al., 2006; Malekzadeh et al., 2015). This points to a possible role of the anti-inflammatory action of teriflunomide in stabilisation of fatigue.

The results of this observational study are in line with those observed in the two randomized, double-blind phase 3 trials that compared teriflunomide with placebo (TEMSO (O'Connor et al., 2011) and TOWER (Confavreux et al., 2014)). In these two studies, patients reported only small changes from baseline in Fatigue Impact Scale scores, with no significant differences between teriflunomide and placebo groups for mean changes at week 108 in TEMSO and at week 48 in TOWER (Confavreux et al., 2014; O'Connor et al., 2011). Here, we confirm and extend these results to the population of RRMS patients treated with teriflunomide in real clinical practice.

Moreover, in a study investigating the relationship between fatigue in MS and regional cortical and subcortical gray matter atrophy, MFIS score was significantly correlated with cortical thickness of the parietal lobe ($r = -0.50$, $P = 0.01$) (Pellicano et al., 2010). In a post-hoc analysis of the MRI data in TEMSO study by Structural Image Evaluation using Normalization of Atrophy (SIENA), teriflunomide significantly slowed whole brain volume loss over 2 years compared with placebo (Radue et al., 2017). Interestingly, recent evidence suggest that teriflunomide-induced reduction on whole brain atrophy may be driven by its effect on cortical regions (Zivadinov et al., 2019a,2019b). Therefore, the effect of teriflunomide on slowing cortical gray matter atrophy could also participate in the stabilisation of fatigue seen in our study.

In the randomised, single-blinded TENERE study, evolution of fatigue was less impacted by teriflunomide treatment as compared to patients treated with interferon-β (Vermersch et al., 2014). It is speculated that oral treatment with teriflunomide may not negatively impact fatigue as opposed to injectable interferon-β. However, the impact of interferon-β on fatigue varies across studies and its detrimental effect on fatigue remains controversial (Braley and Chervin, 2010; Patti et al., 2011). In our study, the mean change in fatigue during teriflunomide treatment was significantly reduced compared with a theoretical change of +9 points for untreated patients based on the results of TENERE study (see Statistical Methods) ($P < 0.0001$).

Notably, more patients reported physical activity after 1-year treatment with teriflunomide, and this improvement was maintained at 2 years. While the effect is modest, it is nonetheless clinically significant and may contribute to the non-progression of the disease and the general well-being of patients.

QoL was generally good at inclusion (score around 2) and was not impacted by teriflunomide treatment. This is consistent with the findings observed in the TERI-PRO study, an observational study that assessed QoL after 48 weeks (Coyle et al., 2018). Fatigue has been shown to be a major determinant of MS patients' perception of health and well-being, and the lack of worsening in fatigue may have played a role in the stabilisation of QoL (Green et al., 2017; Janardhan and Bakshi, 2002).

The main limitation of this study is the absence of a comparator group to determine the extent of a placebo effect or the effect of another disease-modifying drug on fatigue. Therefore, we compared the evolution of fatigue with that of a theoretical group without treatment, based on the results of a previous randomized controlled study (Vermersch et al., 2014). However, this virtual comparison should be interpreted with caution because of bias such as the use of a different fatigue scale or a different timepoint of evaluation.

Another limitation pertains to the definition of fatigue itself. Despite the use of a clinically validated fatigue scale in our study, fatigue remains a subjective symptom that lacks an unified definition and may have different interpretations based on cultural or educational backgrounds of patients (Braley and Chervin, 2010). Moreover, as the patients included in this cohort had mild active MS, the effects on relapse observed in this study should be interpreted with caution and not generalized to patients with other characteristics.

Table 3
Adverse events after teriflunomide treatment in the safety population.

	Total (N = 211)	
	No. of events	N (%) of patients
Any AE	87	58 (27.5)
AE in >1.5% of patients		
Alopecia	15	13 (6.2)
Diarrhoea	11	11 (5.2)
AE of special interest*	5	5 (2.4)
Serious AE**	14	10 (4.7)
AE leading to treatment discontinuation	34	22 (10.4)

* Lymphopenia, neutropenia, hepatobiliary disorder, hypertension and psoriasis (1 patient each).Patients could have more than 1 AE and could experience more than 1 occurrence of the same event. AE, adverse event.

** One case each of alopecia, angioedema, psoriasis, acute pancreatitis, ulcerative colitis, diverticular perforation, hernial eventration, varicose veins, intervertebral disc disorder, increased transaminase levels, depression with suicidal ideation, menorrhagia, lymphopenia, and cholangitis.

Conclusion

Fatigue scores remained low and stable in a large cohort of RRMS patients treated with teriflunomide 14 mg over 2 years in real-life setting. Teriflunomide did not negatively impact depression level or QoL. Because fatigue heavily impacts daily life of patients with MS, it is an important symptom to evaluate during clinical studies. Moreover, it is also a fundamental symptom to assess and manage in clinical practice as part of multidisciplinary care of MS patients.

Author statement

JDS: Concept/design of the study; Data acquisition and interpretation; Critical review and approval of manuscript; Accountable for accuracy and integrity. RD: Concept/design of the study; Data acquisition and analysis/interpretation; Critical review and approval of manuscript; Accountable for accuracy and integrity. EP: Concept/design of the study; Data acquisition and interpretation; Critical review and approval of manuscript; Accountable for accuracy and integrity. JPDM: Concept/design of the study; Data acquisition and interpretation; Critical review and approval of manuscript; Accountable for accuracy and integrity. OV: Concept/design of the study; Data acquisition and interpretation; Critical review and approval of manuscript; Accountable for accuracy and integrity. MK: Concept/design of the study; Data analysis and interpretation; Critical review and approval of manuscript; Accountable for accuracy and integrity. AG: Data analysis & interpretation; Critical review and approval of manuscript; Accountable for accuracy and integrity.

Funding

Declaration of Competing Interest

JDS: Provided consulting services and taken part in advisory boards for Sanofi. RD: Taken part in advisory boards for Merck, Sanofi Genzyme, and Novartis. EP: Invited to congresses and participated in symposium supported by Sanofi. JPD-M: Provided consulting services and taken part in advisory boards for Sanofi, Eisai, Novartis, and Pfizer. OV: Taken part in advisory boards, clinical trials, and oral communications for Biogen, Sanofi, Novartis, Roche, Merck Serono, Esai, and UCB Pharma in local, national, and international neurologic meetings. MK, AG: Employees of Sanofi, with ownership interest.

Acknowledgements

References

Ayache, S.S., Chalah, M.A., 2017. Fatigue in multiple sclerosis - Insights into evaluation and management. Neurophysiol. Clin. 47, 139–171. https://doi.org/10.1016/j.neucli.2017.02.004.

Bass, A.D., Van Wijmeersch, B., Mayer, L., Mäurer, M., Boster, A., Mandel, M., Mitchell, C., Sharrock, K., Singer, B., 2019. Multiple sclerosis impact on daily activities, emotional well-being, and relationships: the global vsMS™ survey. Int. J. MS Care 1537-2073, 2018–2087. https://doi.org/10.7224/1537-2073.2018-087.

Braley, T.J., Chervin, R.D., 2010. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. Sleep 33, 1061–1067. https://doi.org/10.1093/sleep/33.8.1061.

Chalah, M.A., Riachi, N., Ahdab, R., Créange, A., Lefaucheur, J.-P., Ayache, S.S., 2015. Fatigue in multiple sclerosis: neural correlates and the role of non-invasive brain stimulation. Front. Cell. Neurosci. 9, 460. https://doi.org/10.3389/fncel.2015.00460.

Collet, L., Cottraux, J., 1986. [The shortened Beck depression inventory (13 items). Study of the concurrent validity with the Hamilton scale and Widlöcher's retardation scale]. Encephale 12, 77–79.

Comi, G., Freedman, M.S., Kappos, L., Olsson, T.P., Miller, A.E., Wolinsky, J.S., O'Connor, P.W., Benamor, M., Dukovic, D., Truffinet, P., Leist, T.P., 2016. Pooled safety and tolerability data from four placebo-controlled teriflunomide studies and extensions. Mult. Scler. Relat. Disord. 5, 97–104. https://doi.org/10.1016/j.msard.2015.11.006.

Confavreux, C., O'Connor, P., Comi, G., Freedman, M.S., Miller, A.E., Olsson, T.P., Wolinsky, J.S., Bagulho, T., Delhay, J.-L., Dukovic, D., Truffinet, P., Kappos, L., TOWER Trial Group, 2014. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. Neurol. 13, 247–256. https://doi.org/10.1016/S1474-4422(13)70308-9.

Coyle, P.K., Khatri, B., Edwards, K.R., Meca-Lallana, J.E., Cavalier, S., Rufi, P., Benamor, M., Thangavelu, K., Robinson, M., Gold, R., Teri-PRO Trial Group, 2018. Patient-reported outcomes in patients with relapsing forms of MS switching to teriflunomide from other disease-modifying therapies: Results from the global Phase 4 Teri-PRO study in routine clinical practice. Mult. Scler. Relat. Disord. 26, 211–218. https://doi.org/10.1016/j.msard.2018.09.017.

Debouverie, M., Pittion-Vouyovitch, S., Brissart, H., Guillemin, F., 2008. Physical dimension of fatigue correlated with disability change over time in patients with multiple sclerosis. J. Neurol. 255, 633–636. https://doi.org/10.1007/s00415-008-0761-6.

Debouverie, M., Pittion-Vouyovitch, S., Louis, S., Guillemin, F., 2007. Validity of a French version of the fatigue impact scale in multiple sclerosis. Mult. Scler. 13, 1026–1032. https://doi.org/10.1177/1352458507077942.

Devy, R., Lehert, P., Varlan, E., Genty, M., Edan, G., 2013. A short and validated multiple sclerosis-specific health-related quality of life measurement for routine medical practice. Eur. J. Neurol. 20, 935–941. https://doi.org/10.1111/ene.12107.

European Medicines Agency, 2013. AUBAGIO (teriflunomide) 14 mg film-coated tablets: summary of product characteristics [WWW Document]. URL https://www.ema.europa.eu/en/documents/product-information/aubagio-epar-product-information_en.pdf (accessed 5.5.20).

Fisk, J.D., Pontefract, A., Ritvo, P.G., Archibald, C.J., Murray, T.J., 1994. The impact of fatigue on patients with multiple sclerosis. Can. J. Neurol. Sci. 21, 9–14.

Green, R., Cutter, G., Friendly, M., Kister, I., 2017. Which symptoms contribute the most to patients' perception of health in multiple sclerosis? Mult. Scler. J. - Exp. Transl. Clin 3, 2055217317728301. https://doi.org/10.1177/2055217317728301.

Gullo, H.L., Fleming, J., Bennett, S., Shum, D.H.K., 2019. Cognitive and physical fatigue are associated with distinct problems in daily functioning, role fulfilment, and quality of life in multiple sclerosis. Mult. Scler. Relat. Disord. 31, 118–123. https://doi.org/10.1016/j.msard.2019.03.024.

Heesen, C., Nawrath, L., Reich, C., Bauer, N., Schulz, K.-H., Gold, S.M., 2006. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? J. Neurol. Neurosurg. Psychiatry 77, 34–39. https://doi.org/10.1136/jnnp.2005.065805.

Janardhan, V., Bakshi, R., 2002. Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. J. Neurol. Sci. 205, 51–58. https://doi.org/10.1016/s0022-510x(02)00312-x.

Malekzadeh, A., Van de Geer-Peeters, W., De Groot, V., Teunissen, C.E., Beckerman, H., TREFAMS-ACE Study Group, 2015. Fatigue in patients with multiple sclerosis: is it related to pro- and anti-inflammatory cytokines? Dis. Markers 2015, 758314. https://doi.org/10.1155/2015/758314.

Multiple Sclerosis Clinical Practice Guidelines, 1998. Fatigue and Multiple Sclerosis: Evidence-Based Management Strategies For Fatigue In Multiple Sclerosis. Paralyzed Veterans of America, Washington. D.C.

Nourbakhsh, B., Julian, L., Waubant, E., 2016. Fatigue and depression predict quality of life in patients with early multiple sclerosis: a longitudinal study. Eur. J. Neurol. 23, 1482–1486. https://doi.org/10.1111/ene.13102.

O'Connor, P., Comi, G., Freedman, M.S., Miller, A.E., Kappos, L., Bouchard, J.-P., Lebrun-Frenay, C., Mares, J., Benamor, M., Thangavelu, K., Liang, J., Truffinet, P., Lawson, V.J., Wolinsky, J.S., 2016. Long-term safety and efficacy of teriflunomide. Neurology 86, 920–930. https://doi.org/10.1212/WNL.0000000000002441.

O'Connor, P., Wolinsky, J.S., Confavreux, C., Comi, G., Kappos, L., Olsson, T.P., Benzerdjeb, H., Truffinet, P., Wang, L., Miller, A., Freedman, M.S., TEMSO Trial Group, 2011. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N. Engl. J. Med. 365, 1293–1303. https://doi.org/10.1056/NEJMoa1014656.

Patti, F., Amato, M.P., Trojano, M., Bastianello, S., Tola, M.R., Picconi, O., Cilia, S., Cottone, S., Centonze, D., Gasperini, C., COGIMUS Study Group, 2011. Quality of life, depression and fatigue in mildly disabled patients with relapsing-remitting multiple sclerosis receiving subcutaneous interferon beta-1a: 3-year results from the COGIMUS (COGnitive Impairment in MUltiple Sclerosis) study. Mult. Scler. 17, 991–1001. https://doi.org/10.1177/1352458511401943.

Pellicano, C., Gallo, A., Li, X., Ikonomidou, V.N., Evangelou, I.E., Ohayon, J.M., Stern, S.K., Ehrmantraut, M., Cantor, F., McFarland, H.F., Bagnato, F., 2010. Relationship of cortical atrophy to fatigue in patients with multiple sclerosis. Arch. Neurol. 67, 447–453. https://doi.org/10.1001/archneurol.2010.48.

Penner, I.-K., Paul, F., 2017. Fatigue as a symptom or comorbidity of neurological diseases. Nat. Rev. Neurol. 13, 662–675. https://doi.org/10.1038/nrneurol.2017.117.

Radue, E.-W., Sprenger, T., Gaetano, L., Mueller-Lenke, N., Cavalier, S., Thangavelu, K., Panzara, M.A., Donaldson, J.E., Woodward, F.M., Wuerfel, J., Wolinsky, J.S., Kappos, L., 2017. Teriflunomide slows BVL in relapsing MS: A reanalysis of the TEMSO MRI data set using SIENA. Neurol. Neuroimmunol. Neuroinflammation 4, e390. https://doi.org/10.1212/NXI.0000000000000390.

Téllez, N., Río, J., Tintoré, M., Nos, C., Galán, I., Montalban, X., 2005. Does the modified fatigue impact scale offer a more comprehensive assessment of fatigue in MS? Mult. Scler 11, 198–202. https://doi.org/10.1191/1352458505ms1148oa.

Vermersch, P., Czlonkowska, A., Grimaldi, L.M.E., Confavreux, C., Comi, G., Kappos, L., Olsson, T.P., Benamor, M., Bauer, D., Truffinet, P., Church, M., Miller, A.E., Wolinsky, J.S., Freedman, M.S., O'Connor, P., TENERE Trial Group, 2014. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult. Scler. 20, 705–716. https://doi.org/10.1177/1352458513507821.

Yusuf, F.LA, Wijnands, J.M.A., Kingwell, E., Zhu, F., Evans, C., Fisk, J.D., Zhao, Y., Sutherland, J.M., Patrick, D.M., Marrie, R.A., Tremlett, H., 2020. Fatigue, sleep disorders, anaemia and pain in the multiple sclerosis prodrome. Mult. Scler. 1352458520908163 https://doi.org/10.1177/1352458520908163.

Zivadinov, R., Bergsland, N., Carl, E., Ramasamy, D.P., Hagemeier, J., Dwyer, M.G., Lizarraga, A.A., Kolb, C., Hojnacki, D., Weinstock-Guttman, B., 2019a. Effect of teriflunomide and dimethyl fumarate on cortical atrophy and leptomeningeal inflammation in multiple sclerosis: a retrospective, observational, case-control pilot study. J. Clin. Med. 8, 344. https://doi.org/10.3390/jcm8030344.

Zivadinov, R., Ramanathan, M., Hagemeier, J., Bergsland, N., Ramasamy, D.P., Durfee, J., Kolb, C., Weinstock-Guttman, B., 2019b. Teriflunomide's effect on humoral response to Epstein-Barr virus and development of cortical gray matter pathology in multiple sclerosis. Mult. Scler. Relat. Disord. 36, 101388. https://doi.org/10.1016/j.msard.2019.101388.