

Favorable benefit–risk ratio with teriflunomide treatment in relapsing–remitting multiple sclerosis: Results of the 2-year, multicenter, prospective, noninterventional TAURUS MS study in Austria

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ABSTRACT

Objectives: A prospective, multicenter, open-label, noninterventional study assessed the efficacy, safety, tolerability, and patient satisfaction with teriflunomide therapy over a 24-month follow-up period under real-world conditions in Austria.

Methods: An all-comer population aged ≥ 18 years was followed in clinic and office-based settings. The primary objective of the study was the annualized relapse rate after 12 and 24 months of teriflunomide treatment. Patient-reported outcomes included treatment satisfaction, health-related quality of life, and fatigue, and were assessed based on the Short Form Health-36, Fatigue Severity Scale, and Treatment Satisfaction Questionnaire for Medication (TSQM)-9 questionnaires.

Results: Thirty-one patients were included in the analysis, 23 of whom were still on treatment after 24 months. At 12 months ($n = 24$), the annualized relapse rate was 0.3 (SD, 0.8), which indicated a significant decrease compared to the annualized relapse rate of 1.0 (SD, 0.9) observed during the 12-month reference period prior to treatment initiation ($p = 0.009$). Similarly, after 24 months of follow-up ($n = 23$), the annualized relapse rate of 0.2 (SD, 0.8) was significantly lower than that during the last 24 months reference period prior to treatment initiation of 0.7 (SD, 0.8) ($p = 0.0003$). The Expanded Disability Status Scale score remained stable over 12 and 24 months. This also applied to patient-reported fatigue of the Fatigue Severity Scale, with a mean change of 0.1 (SD, 1.0). Patient treatment satisfaction as assessed by the TSQM-9 increased for all three domains (i.e., effectiveness, convenience, global satisfaction). This was confirmed by the physician and multiple sclerosis nurse ratings of patient treatment satisfaction and ease of use. Adverse events occurred in 38.7%, with hair thinning and diarrhea as the most common.

Conclusions: This noninterventional study showed a sustained favorable benefit–risk ratio for this disease-modifying treatment with teriflunomide over 24 months in patients with relapsing–remitting multiple sclerosis. Patient-reported outcomes and ratings performed by physicians and nurses showed overall trends to improvement for patient treatment satisfaction with teriflunomide treatment and its ease of administration.

1. Introduction

The hallmarks of multiple sclerosis (MS) include multifocal

inflammation and demyelination, which are accompanied by significant neuronal degeneration and axonal loss [1]. Relapsing–remitting MS (RRMS) is diagnosed for approximately 85% of MS cases [2]. RRMS is

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characterized by exacerbations at irregular intervals that are followed by partial or full recovery and periods of clinical stability. Without treatment, at least 50% of patients experience conversion of RRMS to secondary progressive MS within 15 years [3].

Although no cure for MS has been established to date, disease-modifying drugs have been developed with the aim of reducing relapse rates and decelerating disease progression. Based on the hypothesis that MS is primarily a T helper cell-mediated autoimmune disease, the immunomodulatory drug teriflunomide was evaluated in patients with RRMS [4]. Teriflunomide selectively and reversibly inhibits dihydro-orotate dehydrogenase, a key mitochondrial enzyme in the *de-novo* pyrimidine synthesis pathway, thereby leading to reduced proliferation of activated T and B lymphocytes, without causing cell death. Thus, the participation of these cells in potentially damaging immune attacks on the central nervous system is diminished.

The placebo-controlled ‘Teriflunomide Multiple Sclerosis Oral’ (TEMSO) and ‘Efficacy Study of Teriflunomide in Participants with Relapsing Multiple Sclerosis’ (TOWER) trials demonstrated clinical efficacy of teriflunomide 7 mg and 14 mg per day for approximately 2 years in a total of 1064 patients with relapsing MS [5,6]. Compared to the patients in the placebo arms, those in the experimental arms showed reduced exacerbation frequency and slower progression of disability, and also reduced numbers of cerebral lesions on magnetic resonance imaging (MRI). The most frequently reported adverse events (AEs) included influenza, infections of the upper respiratory and urinary tracts, paresthesia, diarrhea, alanine aminotransferase (ALT) elevation, nausea, and hair thinning. With respect to brain atrophy, a *post-hoc* analysis of TEMSO MRI data using the Structural Image Evaluation using Normalization of Atrophy (SIENA) method in a blinded manner demonstrated that compared to placebo, teriflunomide 14 mg significantly slowed the rate of brain volume loss over 2 years [7,8]. In 2013, teriflunomide 14 mg was approved by the European Medicines Agency as a once daily oral treatment for adult patients with RRMS [9].

However, outside clinical trials, the available data on the effectiveness of teriflunomide are limited, especially in real-life settings within larger and more diverse populations [10–22]. Therefore, we conducted a prospective, multicenter, open-label, noninterventional study of patients with RRMS who were assigned to treatment with teriflunomide: the TAURUS MS study.

2. Materials and methods

2.1. Study procedures and population

Office-based neurologists and neurologists in hospital-based Outpatient Departments in Austria participated in the TAURUS MS study. Each participating center received a file with three case report forms (CRFs). Data collection was performed in accordance with the protocol, applicable local regulations, and international guidelines. The physicians had to comply with specific local regulations and recommendations regarding handling of patient records, and they were responsible for the retention of documentation until the end of the registry.

The recommended dose of teriflunomide was 14 mg once daily, according to the summary of product characteristics [7]. Apart from this, no specifications were defined regarding diagnostics, therapy, or follow-up examinations. The physicians especially collected parameters that were part of their daily routine documentation, or that were derived from other sources, such as hospital discharge reports compiled during the observation period.

The completed CRFs were checked for completeness and hidden AEs by the noninterventional study management of Sanofi-Aventis Deutschland GmbH. The CRFs were then forwarded to the contract research organization factum GmbH for data entry, which was performed using the data management program DMSys®, version 5.1. The captured data were validated according to the check-up rules defined by the data validation plan.

Eligible patients were aged ≥ 18 years and had RRMS and no contraindications against teriflunomide treatment. The patients were required to sign an informed consent form and to be capable of completing the questionnaires in terms of motor and cognitive function. Cognitive impairment was no exclusion criterion. No exclusion criteria were defined, as this noninterventional study was intended to include an all-comer population.

2.2. Study endpoints

The primary objective of the study was the annualized relapse rate (ARR) after 12 and 24 months of teriflunomide treatment. Secondary efficacy objectives included the use of teriflunomide in daily practice, which was assessed based on the proportions of *de-novo* and switch patients, and the proportion of patients experiencing treatment interruptions, as well as compliance with the risk management plan for teriflunomide (i.e., performed ALT measurements in relation to recommended ALT measurements), patient treatment satisfaction, health-related quality of life, fatigue, physician assessment of patient treatment satisfaction, treatment adherence, number of MS relapses, Expanded Disability Status Scale (EDSS) scores during observation, and economic parameters. The safety endpoint related to the incidence of AEs.

For assessment of health-related quality of life, the Short Form Health-36 (SF-36) was used, and for assessment of fatigue, the Fatigue Severity Scale (FSS) was used. The SF-36 included evaluations of the physical and mental summary scores. Patient treatment satisfaction was measured using the Treatment Satisfaction Questionnaire for Medication (TSQM)-9. Here, the sum scores for the three domains of effectiveness, convenience, and satisfaction were analyzed. All of the questionnaires were completed at baseline and at 6, 12, 18, and 24 months, with the SF-36 and TSQM-9 also completed at 3 months.

For the physician assessment of patient satisfaction with the treatment, three questions were defined that were answered by the physicians at baseline and at 3, 6, 12, 18, and 24 months. These three questions had response options from 1 to 5, and were:

“How easy or difficult is it for the patient from your point of view to take the medication in its current form?” (1, “very difficult”; to 5, “very easy”);

“How easy or comfortable is it for the patient from your point of view to take the medication as prescribed?” (1, “very difficult and uncomfortable”; to 5, “very easy and comfortable”);

“How satisfied or dissatisfied is the patient from your point of view all in all with the medication?” (1, “very dissatisfied”; to 5, “very satisfied”).

For the use of teriflunomide and for treatment adherence, the following questions were answered by the physicians or the MS nurses, at baseline and at 3, 6, 12, 18 and 24 months:

“How well can the patient integrate the intake of teriflunomide in his daily routine?” (response options: very well, well, to a moderate degree, poorly, very poorly);

“How well can the patient integrate the intake of teriflunomide in his daily routine compared to the previous MS therapy?” (response options: much better, better, equally well, worse, much worse);

“At what time does the patient mostly take teriflunomide?” (response options: in the morning, at noon, in the evening).

The number of MS relapses included the total number, and also the number of events associated with hospitalizations, first/ s cortisone pulse therapy, plasmapheresis, and residual effects. Residual effects were defined as relapses treated with at least two cortisone pulse therapies, and relapses from which patients emerged with higher EDSS scores compared to their previous scores.

2.3. Monitoring of teriflunomide toxicity

The patients were monitored for common AEs of teriflunomide

treatment at regular intervals. This included measurements of blood pressure, ALT levels, infections, complete blood counts (including platelets), and other laboratory parameters. All of the patients were informed about potential treatment-related risks, including liver damage, hypertension, infections, and hematological disorders. Pregnancy counselling was provided for women of childbearing potential.

2.4. Statistical analysis

The statistical analysis was performed by factum GmbH (Offenbach, Germany). The analysis was carried out with the statistical tool SPSS for Windows (version 15.0.0). The confidence intervals of categorical variables were an exception here, as these were calculated using the statistical software BIAS, version 10.12. The numbers of steroid-dependent relapses before and after treatment with teriflunomide were analyzed according to the Poisson model.

A two-sided *p*-value <0.05 was taken as uncorrected statistical significance level. Non-parametric tests, such as Wilcoxon Matched-Pairs Signed-Ranks Test, were used for comparisons.

The per-protocol set was composed of all of the treated patients who complied with the protocol. The safety analysis set contained all of the patients for whom CRFs were available, and in addition, the patients with recorded AEs or serious AEs but without the CRFs available.

2.5. Ethical considerations

The study was compliant with Austrian laws on bioethics and was also approved by the Ethical Committee of upper Austria (EC number O-34-15). The patient and physician personal data that were included in the company databases were treated in compliance with all locally applicable laws and regulations. When archiving or processing personal data pertaining to physicians and/or patients, the company took all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

3. Results

Seven Austrian neurologists participated in this study, three of whom were hospital based and four of whom were office based. The data were collected from October 12, 2015, until March 12, 2019. None of the patients violated the inclusion criteria, and no retrospective documentation from before August 1, 2015, was used.

3.1. Patient characteristics at baseline

Case report forms were available for 31 patients, all of whom were included in the per-protocol dataset. The patient characteristics are described in Table 1. Two thirds were females, and most of them were employed. In the majority of cases, MS had been present for several years. The median EDSS score was 1.5 (interquartile range, 2.5), with the scores ranging from 0.0 to 5.0. Most patients (90.3%) had EDSS score \leq 3.5. The most common MS-associated or MS-induced symptoms/ diseases included fatigue (35.5% of patients), depression (29.0%), and bladder dysfunction (25.8%).

Only 9.7% of patients had not experienced any relapses within the previous 24 months prior to the baseline visit. The mean overall number of MS relapses over the previous 24 months was 1.5 ± 0.8 . All of the patients underwent cranial MRI. Data on the number of T2-weighted lesions and gadolinium-enhanced lesions were available for 6 and 28 patients, respectively. In the group evaluable for T2 lesions, 50.0% had 6–10 lesions, while gadolinium-enhanced lesions were considerably less frequent in the respective group, with 75% of patients showing none.

3.2. Multiple-sclerosis-specific pretreatment

Almost 60% of patients ($n = 18$) had been treated with previous

Table 1
Patient demographic data at baseline.

Characteristic	Detail	n	Value
Mean age (years)	Women	19	41.2 \pm 11.1
	Men	12	41.9 \pm 10
Sex (n, %)	Female	19	61.3
	Male	12	38.7
Employment status (n, %)	Regular full-time employment (\geq 30 h/week)	16	51.6
	Regular part-time employment (\geq 15–29 h/week)	3	9.7
	Underemployed or not regularly employed (<15 h/week)	0	0
	Not employed	12	38.7
Multiple sclerosis history (n, years)	Time since first symptoms	31	11.9 \pm 11.1
	Time since diagnosis	31	9.5 \pm 10.3
	Time between the first clinical signs and diagnosis	31	2.4 \pm 5.6
Expanded Disability Status	Median at baseline	31	1.5 IQR, 2.5
Scale score (n, %)	\leq 3.5	28	90.3
	>3.5	3	9.7
Relapses (past 24 months) (n, %)	Mean	31	1.5 \pm 0.8
	0	3	9.7
	1	13	41.9
	2	13	41.9
	3	2	6.5
Brain MRI findings, mean (SD)	Time of last brain MRI before baseline visit, quarters	30	4.7 \pm 5.0
	Number of T2 lesions	6	6.7 \pm 3.8
	Number of gadolinium-enhanced lesions	28	0.4 \pm 0.9
Multiple-sclerosis-associated/ induced symptoms (n, %)	Fatigue	11	35.5
	Depression (major depressive disorder)	9	29
	Cognitive deficits	4	12.9
	Spasticity	4	12.9
	Bladder dysfunction	8	25.8
	Other	11	35.5

MRI = Magnetic Resonance Imaging; SD = standard deviation; IQR = interquartile range.

disease modifying therapies, while 41.9% were treatment naïve. The most commonly prescribed MS medications included interferon (IFN)- β 1a, IFN- β 1b, glatiramer acetate, and immunoglobulins (Table 2). The main reasons for termination of the previous treatments were adverse reactions (66.7%) and lack of efficacy (61.1%). In 61.1%, both the physicians and patients had made the decision to discontinue the previous medication. A total of 12 patients (38.7%) had discontinued their previous therapy within 6 months prior to initiation of teriflunomide,

Table 2
Multiple-sclerosis-specific drugs used prior to study inclusion (multiple entries possible).

Treatment	Route	(n)	(%)
Total patients	–	31	100
Any	–	18	58.1
IFN- β 1a	IM	8	25.8
IFN- β 1a	SC	6	19.4
IFN- β 1b	SC	5	16.1
Glatiramer acetate	SC	5	16.1
Azathioprine	PO	1	3.2
Immunoglobulin	IV	4	12.9
Other	–	2	6.5
None	–	13	41.9

SC = subcutaneous; IFN- β = Interferon-Beta; IM = intramuscular; IV = intravenous; PO = per os.

while 19 (61.3%) were receiving no treatment at that time. The most common reasons for this were “no need of treatment” (36.8%), “lack of trust in efficacy” (21.1%) and “initial diagnosis/ initial treatment” (21.1%).

For the 12 previously treated patients, the physicians or MS nurses rated the patient satisfaction with their last MS medication. The extent of discomfort due to AEs experienced with the most recently used MS drug was very pronounced in 50% of these cases, while the ease of administration was primarily given an intermediate rating. In terms of overall patient satisfaction with their previous medication, 50% of these patients were rated here as “rather dissatisfied”. With regard to adherence to previous treatment, the physicians and nurses estimated that two thirds of patients (66.7%) had taken 90% or more of the prescribed daily doses.

3.3. Administration of teriflunomide

At the time of the analysis, the mean observation period was 631.7 days (standard deviation [SD], 289.7 days). After 24 months, 23 patients (74.2%) were still on treatment, whereas 7 (22.6%) had been lost to follow-up. Teriflunomide therapy was discontinued in 1 patient (3.2%), due to an AE. No patient stopped the medication due to lack of efficacy, pregnancy or the wish to become pregnant, the wish for a treatment break, or assumed lack of compliance.

3.4. Relapses

Follow-up data on the numbers of relapses after 12 and 24 months were available for 24 and 23 patients, respectively. During the last 12 months preceding the start of teriflunomide therapy, the ARR was 1.0 (SD, 0.9; median: 1.0, IQR: 1.50, min: 0, max: 3.0). After 12 months of teriflunomide treatment, there was a significant 0.7 decrease in ARR, to 0.3 (SD, 0.8; median: 0, IQR: 0, min: 0, max: 3.0; $p = 0.009$). Similarly, compared to the ARR of 0.71 (SD, 0.84; median: 1.0, IQR: 1.0, min: 0, max: 3.0) during the last 24 months prior to the prescription of teriflunomide, the ARR after 24 months of follow-up was significantly decreased by 0.5, to 0.2 (SD, 0.8; median: 0, IQR: 1.0, min: 0, max: 3.0; $p = 0.0003$) (Fig. 1).

3.5. Expanded disability status scale

In the group of 25 patients where EDSS was assessed both at baseline and at 12 months, the median EDSS score showed no change (median EDSS: 1.5, IQR: 1.5). In the 19 patients evaluable for EDSS at both baseline and 24 months, the median EDSS score also remained stable (median EDSS: 1.5, IQR: 2.5).

3.6. Compliance with the risk management plan: Alanine aminotransferase measurements

Assessments of the ALT levels before the start of treatment with teriflunomide were reported for all of the patients. The majority had regular follow-up measurements until month 24, although only a minority underwent the two-weekly ALT assessments in the first 6 months of treatment and every 8 weeks thereafter that was recommended by the summary of product characteristics [7]. However, it is possible that not all liver enzyme measurements were recorded, or that monitoring was conducted by a general practitioner without reporting of the results to the neurologist.

3.7. Patient-reported outcomes

None of the patient-reported outcomes significantly favored the treatment from a statistical point of view, although in their entirety, they underscored the clinical benefit derived from the treatment. The physical and mental SF-36 summary scores showed only small differences during the observation period. In 24 patients, the mean physical summary score indicated an increase of 0.8 (SD, 7.2; median: -1.1, IQR: 8.4 min: -11.9, max: 15.2) between baseline and their last visit. The mean mental summary score indicated a reduction of 3.6 (SD, 8.3; median: -1.4, IQR: 7.7, min: -26.3, max: 12.5). Similarly, only small differences were seen for the FSS score ($n = 25$), with a mean, nonsignificant, difference between baseline and the last visit of 0.1 (SD: 1.0; median: 0.3, IQR: 1.0, min: -2.1, max: 2.0 1.0; $p > 0.05$).

The summary scores for all of the three domains of TSQM-9 also showed improved trends on treatment with teriflunomide (Fig. 2). Between baseline and the last visit, the mean effectiveness score indicated an increase of 15.1 (SD, 32.4; $n = 7$; median: 0, IQR: 61.1, min: -16.7, max: 66.7). In the patients whose previous MS-specific therapy had been discontinued within 6 months of the start of teriflunomide ($n = 3$), the

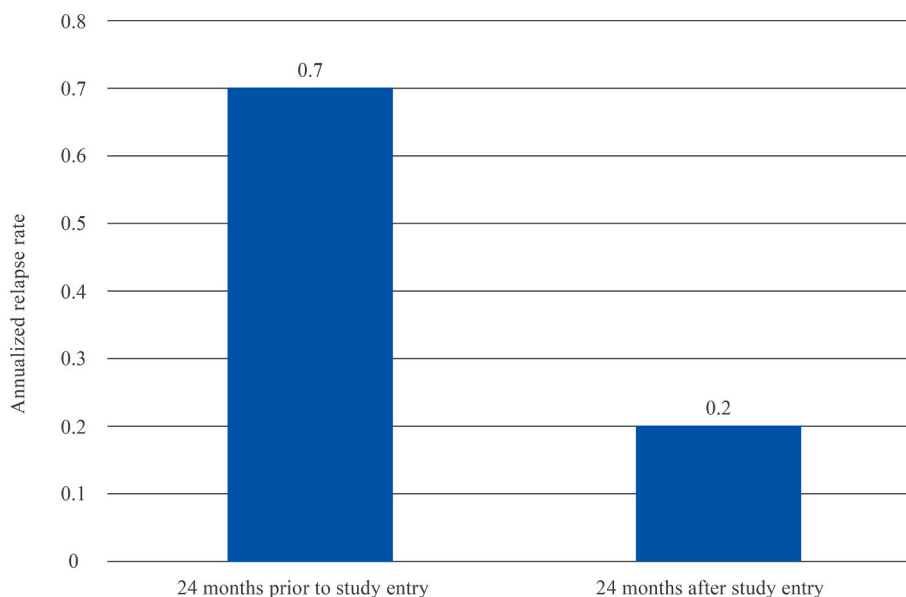


Fig. 1. Mean annualized relapsed rates for the last 24 months prior to study entry and the first 24 months of the study.

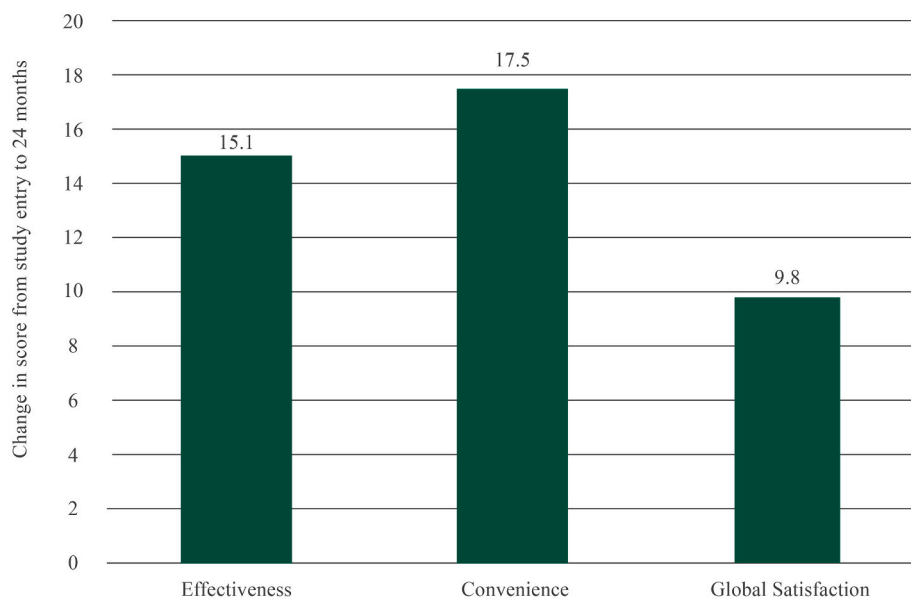


Fig. 2. Treatment Satisfaction Questionnaire for Medication (TSQM-9): changes in effectiveness, convenience, and global satisfaction scores from study entry to 24 months.

mean TSQM-9 score indicated nonsignificant increases of 35.2 (SD, 27.4; median: 22.2, IQR: 50, min: 16.7, max: 66.7; $p > 0.05$) between baseline and 12 months, and of 16.7 (SD, 43.4; median: -5.6, IQR: 77.8, min: -11.1, max: 66.7; $p > 0.05$) between baseline and 24 months. For the convenience score, there was again an indication of an increase, of 17.5 (SD, 19.9; $n = 7$; median: 16.7, IQR: 33.3, min: -5.6, max: 44.4) between baseline and the last visit. The patients whose pretreatment had been recently discontinued ($n = 3$) showed nonsignificant mean differences of -3.7 (SD, 11.6; median: 0, IQR: 22.2, min: -16.7, max: 5.6; $p > 0.05$) at 12 months, and 3.7 (SD, 11.6; median: 0, IQR: 22.2, min: -5.56, max: 16.67; $p > 0.05$) at 24 months.

Also, the mean global satisfaction score showed an increasing trend of 9.4 (SD, 26.5; $n = 8$; median: 0, IQR: 37.5, min: 21.4, max: 57.1) between baseline and the last visit. In the recently treated group ($n = 4$), the mean differences compared to baseline were not significant, at 18.8 (SD, 30.5; median: 28.6, IQR: 41.1, min: -25, max: 42.9; $p > 0.05$) at 12 months and 6.3 (SD, 20.3; median: 0, IQR: 23.2, min: -10.7, max: 35.7; $p > 0.05$) at 24 months.

3.8. Patient treatment satisfaction: The physicians' view

The physician ratings of the treatment satisfaction of the patient also failed to reach significance, but they do at least indicate sustained improvements on treatment with teriflunomide. For all three questions, the mean scores showed increasing trends during the observation period ($n = 8$). The score for the question “How easy or difficult is it for the patient from your point of view to take the medication in its current form?”, tended to increase, from 3.5 at baseline to 4.4 at 12 months (mean difference: 0.9 [SD, 1.1]; median: 0.5, IQR: 1.50, min: 0, max: 3.0) and to 4.6 at 24 months (mean difference: 1.1 [SD, 1.1]; median: 1.0, IQR: 2, min: 0, max: 3.0).

For the question “How easy or comfortable is it for the patient from your point of view to take the medication as prescribed?”, the score was 3.6 at baseline, with indications of increases to 4.4 at both 12 months (mean difference: 0.8 [SD, 1.0]; median: 0.5, IQR: 1.0, min: 0, max: 3.0) and 24 months (mean difference: 0.8 [SD, 1.3]; median: 0.5, IQR: 1.50, min: -1.0, max: 3.0).

The greatest difference was seen with respect to the question “How satisfied or dissatisfied is the patient from your point of view all in all with the medication?”, where the baseline score was 2.1 compared to

3.9 at 12 months (mean difference: 1.8 [SD, 1.0]; median: 2.0, IQR: 1.50, min: 0, max: 3.0) and 4.0 at 24 months (mean difference: 1.9 [SD, 1.0]; median: 1.5, IQR: 2.0, min: 1.0, max: 3.0). The ratings at each time point for all three of these questions thus demonstrated indications of overall improvement after the initiation of teriflunomide treatment compared to baseline (Fig. 3 A-C).

3.9. Use of teriflunomide and treatment adherence: physicians' and nurses' views

The physicians and nurses also rated the question “How well can the patient integrate the intake of teriflunomide in his daily routine?” as “very well” or “well” for >90% of the patients. Approximately 90% could integrate the administration of teriflunomide into their daily routine “much better” or “better” than their previous MS therapy. Almost all of the patients were taking teriflunomide in the morning (range, 30.4%–48.0% across all evaluation time points) or in the evening (range, 52.0%–69.6% across all evaluation time points).

3.10. Adverse events

The safety analysis set included all 31 patients. Overall, 23 AEs occurred in 12 patients (38.7%). The most frequently reported AEs were hair thinning and diarrhea (6.5%, $n = 2$ each) (Table 3). In two patients (6.5%), two serious AEs occurred: major depression, and respiratory tract infection, with the latter not deemed treatment-associated by the treating physician. No pregnancies occurred, and none of the patients died during this noninterventional study.

The mean ALT levels increased during the first 3 months of teriflunomide treatment but returned to baseline levels on continued treatment ($n = 25$). Only minor changes in hemoglobin concentrations were observed in the course of the 24-month treatment period. Leukocyte counts decreased a little, as did the thrombocyte counts. Six infections occurred in four patients during the treatments (i.e., nasopharyngitis, abscess, influenza, onychomycosis, otitis media, respiratory tract infection; $n = 1$ for each).

4. Discussion

The TAURUS MS study was a prospective noninterventional study

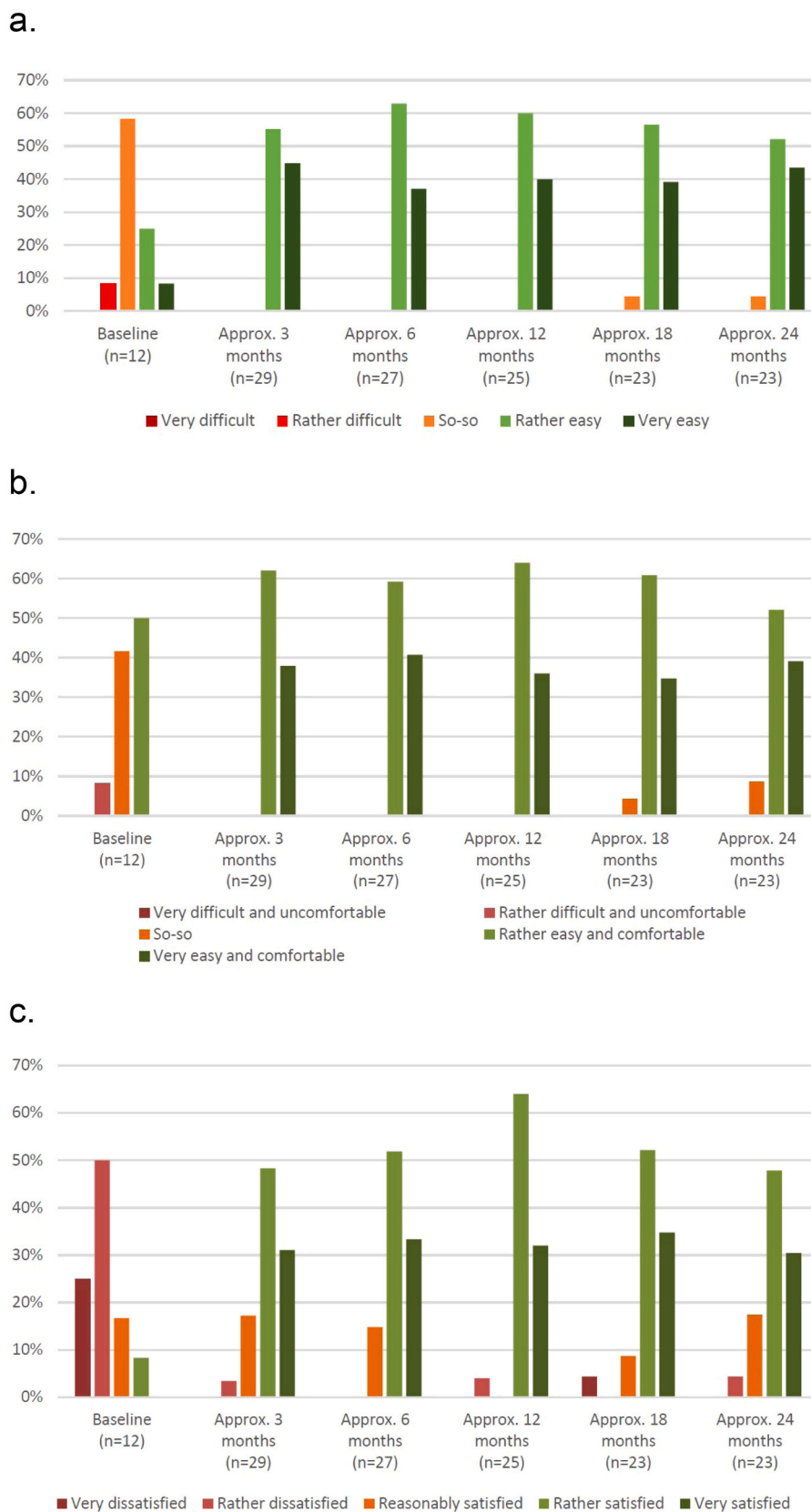


Fig. 3. A-C. Physician ratings at baseline and through the study period. (A) “How easy or difficult is it for the patient from your point of view to take the medication in its current form?” (B) “How easy or comfortable is it for the patient from your point of view to take the medication as prescribed?” (C) “How satisfied or dissatisfied is the patient from your point of view all in all with the medication?”

Table 3

Adverse events seen for $\geq 1.0\%$ of the patients, according the Medical Dictionary for Regulatory Activities preferred terms (multiple entries possible).

Adverse event	(n)	(%)
Total patients	31	100
Hair thinning*	2	6.5
Diarrhea	2	6.5
Abscess of the jaw	1	3.2
Bladder disorder	1	3.2
Cognitive disorder	1	3.2
Dizziness	1	3.2
Fatigue	1	3.2
Headache	1	3.2
Influenza	1	3.2
Lymphopenia	1	3.2
Major depression	1	3.2
Nasopharyngitis	1	3.2
Nausea	1	3.2
Onychomycosis	1	3.2
Otitis media	1	3.2
Pain	1	3.2
Pyrexia	1	3.2
Respiratory tract infection	1	3.2
Weight loss	1	3.2

* Medical Dictionary for Regulatory Activities (MedDRA) preferred term is alopecia.

designed to assess real-world treatment with the immunomodulatory agent teriflunomide in patients with RRMS over a 24-month observation period. In addition to decreases in the ARR compared to the respective reference periods prior to the baseline visits, the study revealed overall trends to improvement for patient treatment satisfaction. These results were supported by the physician assessments of patient satisfaction, which showed indications of improvements of all of the scores included. More than 90% of the patients perceived the use of teriflunomide as easy and could easily integrate it into their daily routines, especially when compared to previous agents. Disability according to EDSS and fatigue as measured by FSS remained stable. For health-related quality of life according to the SF-36 score, the mean physical summary score increased a little, while the mean mental summary score decreased. In summary the patient-related outcomes did not meet a significant level favoring teriflunomide treatment. But the summary scores for all of the three domains of TSQM-9 showed improved trends on treatment with teriflunomide. Between baseline and the last visit, the mean effectiveness score indicated an increase of 15.1 (SD, 32.4). This is in line with prior publications showing a significant improvement with teriflunomide treatment [12,21]. Therefore, the small sample size is rather responsible for not reaching significance than the mentioned magnitude of improvements in the patient-related outcomes.

Patient-reported outcomes play an increasingly important role in daily clinical practice as they are derived directly from patients and include symptoms, function, health status, and health-related quality of life [23]. Cognitive dysfunction, also in the early phases of the disease, might influence patient-reported outcomes in terms of completeness and understanding because patients with multiple sclerosis tend to show impaired short-term memory and information processing speed as well as difficulty sustaining attention [24].

Also, teriflunomide was generally well tolerated, with an AE rate of 38.7% and two serious events (6.5%), one of which did not appear to be treatment related. Transient ALT elevations were observed, which have been reported for teriflunomide before. None of the patients developed any liver disorder, and none died during the observation period.

Although patient treatment satisfaction is an important determinant of adherence, data on patient satisfaction in the setting of disease-modifying agents have been scarce to date. Studies have generally been restricted to small patient populations who received specific drugs. Nevertheless, convenience is undoubtedly a crucial factor in the context of these agents, as they need to be administered daily or weekly for

years. A retrospective study demonstrated increased exacerbation risk with lessening treatment adherence to IFN- β [25].

The necessity for intramuscular or subcutaneous application, as is the case for IFN- β and glatiramer acetate, can represent a serious obstacle to persistent use, and thus to the prevention of relapses. Oral administration certainly confers advantages here. Drugs that are taken orally, such as fingolimod and teriflunomide, have already been shown to improve treatment adherence and treatment satisfaction [26–28], while according to another study, these outcomes were only moderate with IFN- β compounds and glatiramer acetate [29]. Nevertheless, the recent systematic review and meta-analysis performed by Nicholas et al. (2020) showed that there remains room for improvement for patients with MS, as within 1 year, approximately one in five included in studies did not adhere to, and one in four discontinued, their daily oral disease-modifying medications [30].

Of course, perceived efficacy and tolerability are equally important for patient compliance. A study that investigated treatment adherence identified lack of activity and emergence of AEs as reasons for treatment discontinuation in 30% to 50% and up to 50% of cases, respectively [31]. A meta-analysis of 50 randomized trials and 93 observational studies by Giovannoni et al. (2012) indicated that lack of efficacy and side effects were the main reasons for discontinuation of IFN- β and glatiramer acetate, with discontinuation rates of 17% to 36% [32]. Influenza-like symptoms (with IFN- β) and injection site reactions (with IFN- β and glatiramer acetate) constituted the most common side effects; here, the AE rates remained high in clinical trials that encompassed observation periods of more than 2 years, and treatment discontinuation rates increased over time. Patti et al. (2012) revealed that IFN- β treatment can worsen headache in patients with pre-existing headache or cause new-onset headache [33]. In a systematic review, Costello et al. (2008) identified a number of factors that can reduce treatment adherence, such as fear of injections, lack of perceived efficacy, AEs, and issues with complex treatment regimens [34].

Teriflunomide demonstrated clinical activity and low AE rates for patients with relapsing MS in the pivotal TEMSO and TOWER trials [5,6]. These observations are supported here by the TAURUS MS study. No patient stopped the medication due to lack of efficacy or assumed lack of compliance.

Previous prospectively collected data on real-life use of disease-modifying treatments in Austria based on the Austrian MS Treatment Registry have shown similar activities of the oral agents fingolimod, dimethyl fumarate, and teriflunomide with respect to relapse rates [10,11]. At the international level, different studies showed similar no evidence of disease activity (NEDA) rates across teriflunomide and dimethyl fumarate treatment within the first year; also, they revealed no differences between these two groups regarding time to first relapse in the first 38 months of treatment [16,17]. Discontinuations rates were similar across the two oral drugs [18]. On the other hand, real-world data from the Italian MS Register suggested that first-line oral treatment, compared to injectables, was associated with lower risk of new relapses and discontinuation of treatment [19].

The German noninterventional, prospective, longitudinal, observational TAURUS-MS I study was conducted between 2014 and 2017 by a total of 307 office-based and hospital-based neurologists [12]. TAURUS-MS I and the Austrian TAURUS MS trial were performed independently, although they were based on the same study design. In TAURUS-MS I, 1128 patients were eligible for the efficacy analysis. The majority of these switched to teriflunomide from other MS treatments. According to the analysis, the mean ARR was halved, from 0.9 in the 24 months preceding study entry, to 0.4 in the 24 months after start of therapy ($p \leq 0.001$), while EDSS and FSS scores remained stable. In patients who had received previous MS treatments, TSQM-9 values after 24 months had improved by 8.1 for effectiveness, 17.0 for convenience, and 15.3 for global satisfaction ($p \leq 0.001$ each, compared with study entry).

Similarly, a *post-hoc* analysis of the phase IV Teri-PRO study that assessed teriflunomide use and patient-reported outcomes in the USA (n

= 545) and other countries ($n = 455$) revealed significant improvements in TSQM global satisfaction scores and the effectiveness, side effects, and convenience subscale scores from baseline to week 48 (all $p < 0.0001$) [13]. Disability measures remained stable from baseline to week 48 in all of the patients despite differences in baseline scores between the two geographic groups. Overall, these data suggest efficacy of teriflunomide despite differences in baseline demographics and possible cultural and management differences between the USA and other countries.

Insights gained from this noninterventional study are based on a clinically relevant observation period of 2 years. On the other hand, the number of patients evaluated was lower than expected. The small number of cases in this observational study was due to the limited number of centers and study participants willing to participate. However, we think that our results can add relevant knowledge to the current understanding of teriflunomide effectiveness and safety in a real-world setting for several reasons: In contrast to an Italian survey, the TAURUS MS study was designed in a prospective way [20]. Furthermore, different recent studies did not include patient-related outcomes as an outcome parameter [20,22]. Nevertheless, despite the small sample size, the results support those of the German TAURUS MS I study, which showed a significant decrease in the mean ARR within 24 months of initiation of teriflunomide treatment, plus significantly improved patient satisfaction [12]. Also, the TERI-PRO study revealed significant improvements in treatment satisfaction scores following the switch to teriflunomide regardless of the reason for treating with teriflunomide [21]. Furthermore, real-world outcomes from the Danish Multiple Sclerosis Registry showed a favorable relapse-free and progression-free rate [22]. Finally, patient-related outcomes in our study showed a similar improvement concerning treatment satisfaction compared with previous surveys [12,21]. Overall, these findings convey a strong signal with respect to high usability of teriflunomide treatment in daily practice.

Potential limitations of real-world setting studies include low internal validity, lack of quality control surrounding data collection, and susceptibility to multiple sources of bias (e.g., different follow-up intervals, underreporting of mild relapses, EDSS assessment) affecting the comparison of patient outcomes. In everyday clinical practice, patients' and physicians' attitudes towards the choice of treatment may be influenced by non-recordable clinical or subclinical conditions that may in turn influence future disease activity.

Finally, the main limitation of our study is the small sample size, which partly explains failure to reach significance in patient-reported outcomes. In addition, the number of included patients decreased during the follow-up and therefore results of various patient-reported outcomes were only available in a subset of patients.

5. Conclusions

This noninterventional study shows sustained efficacy of disease-modifying therapy with teriflunomide in patients with RRMS over a 24-month treatment period. The benefit–risk ratio for teriflunomide treatment remained favorable and was consistent with the benefit–risk ratio in previous trials. Patient-reported outcomes and ratings performed by physicians and nurses showed overall trends to improvement for patient treatment satisfaction with teriflunomide treatment and its ease of administration. These are important aspects, particularly with respect to adherence to long-term therapy.

Author contributions statements

MG contributed patients, supervised the data collection, contributed to the statistics, and assisted with writing the manuscript.

MMA contributed patients and reviewed the manuscript.

MH contributed patients and reviewed the manuscript.

CH-R was the medical representative of Sanofi-Aventis GmbH, Austria.

HKS contributed patients and reviewed the manuscript.

AT contributed patients and reviewed the manuscript.

KU contributed patients and reviewed the manuscript.

FL contributed patients and reviewed the manuscript.

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Data availability statement

Qualified researchers may request access to study documents including the clinical study report, study protocol, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of our trial participants. Further details on the Sanofi data-sharing criteria, eligible studies, and process for requesting access can be found at: <https://www.clinicalstudydatarequest.com/>.

Declaration of Competing Interest

MG has received support and honoraria for research, consultation, lectures, and education from Almirall, Bayer, Biogen, Celgene, Genzyme, MedDay, Merck, Novartis, Octapharma, Roche, Sanofi Aventis, Shire and TEVA ratiopharm.

MMA has received support and honoraria for research, consultation, lectures, and education from Celgene, Eli-Lilly, Genzyme, Merck, Novartis, Roche and Sanofi Aventis.

MH declares no conflicts of interest.

CH-R is full-time employee of Sanofi-Aventis Austria GmbH.

HKS declares no conflicts of interest.

AT declares no conflicts of interest.

KU declares no conflicts of interest.

FL has received support and honoraria for research, consultation, lectures, and education from Actelion, Almirall, Bayer, Biogen, Celgene, Genzyme, MedDay, Merck, Novartis, Octapharma, Roche, Sanofi Aventis, and Teva Ratiopharm.

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