




Treatment Satisfaction with Teriflunomide in Patients with Multiple Sclerosis: A Systematic Review of Observational Studies

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Abstract

Background: Research on treatment satisfaction with treatments of multiple sclerosis (MS) is essential for delivering patient-centered care and improving treatment adherence. We aimed to review studies that have used the Treatment Satisfaction Questionnaire for Medication (TSQM) to assess treatment satisfaction with teriflunomide in patients with MS.

Methods: PubMed, Scopus, Web of Science, PsycINFO, the Cochrane Library, and Google Scholar were searched by 2 independent reviewers to identify all relevant studies. Studies were selected based on the inclusion and exclusion criteria. The quality of observational studies was appraised using the 14-item National Institute of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Results: The search strategy was employed and 97 possible publications were found. After carefully reviewing the titles, abstracts, and full texts, a total of 9 articles have been selected for inclusion in the review. In all studies, teriflunomide had been prescribed in the treatment group, and in all studies, some patients had received previous disease-modifying therapies (DMTs). Study periods of all studies were between 3 months to 24 months. The results showed that all studies were of relatively high quality. In all studies, 4 domains of TSQM, especially the convenience domain, were improved after treatment with teriflunomide. Mean scores of the convenience domain in patients treated with teriflunomide were higher than other DMTs but some studies showed that some other DMTs may provide higher scores in other domains of TSQM.

Conclusion: Treatment with teriflunomide improves satisfaction in patients with MS.

Keywords: Teriflunomide, TSQM, Disease-Modifying Therapies, Systematic Review, Questionnaire

Conflicts of Interest: None declared

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Introduction

Multiple sclerosis (MS) is a chronic, unpredictable, and often debilitating neurological disorder that affects the central nervous system (1, 2). MS is an autoimmune inflammatory disorder of the CNS resulting in demyelination and ax-

onal damage, thus interfering with the transmission of signals between the brain and other parts of the body (3). This usually manifests as a wide range of symptoms that may include numbness or weakness in limbs, slurred speech,

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↑What is “already known” in this topic:

Teriflunomide offers the convenience of being taken orally just once a day, which has shown its efficacy in reducing relapses in patients with relapsing-remitting multiple sclerosis. It is important to determine treatment satisfaction with teriflunomide alone in different periods or in comparison with other disease-modifying therapies from patients’ perspectives to improve patient-centered care.

→What this article adds:

Treatment with teriflunomide improves satisfaction in patients with MS. If the route of drug administration is the priority, teriflunomide 14 mg appears to be the best treatment in the aspect of convenience. However, if the efficacy of treatment is the priority, natalizumab seems to be the best treatment.

blurred or double vision, muscle stiffness or spasms, fatigue, and cognitive impairment (4-7).

Research on treatment satisfaction with drugs related to the treatment of MS is essential for delivering patient-centered care, improving treatment adherence, enhancing quality of life, guiding clinical decision-making, optimizing healthcare resource utilization, and promoting patient education (8-13).

Teriflunomide is considered one of the first-line treatment options for relapsing forms of MS (14). Teriflunomide has demonstrated effectiveness in decreasing the occurrence of relapses in individuals with relapsing forms of MS. Additionally, it has been found to contribute to the deceleration of physical disability progression and decrease the number of new or enlarging lesions seen on MRI scans (15). Teriflunomide may commonly cause side effects such as diarrhea, nausea, hair loss, and increased levels of liver enzymes (16). The clinical development of new disease-modifying therapies (DMTs) for relapsing-remitting multiple sclerosis, in recent years, has given rise to an increasing number of treatment alternatives (17). Disease-modifying therapies (DMTs) for MS have received approval due to their effectiveness in decreasing disease activity, particularly in terms of clinical relapses (18). These medications work by suppressing the immune system to prevent further damage to the myelin sheath (19).

Fingolimod, teriflunomide, dimethyl fumarate, and cladribine are examples of oral DMTs for MS (20). Interferon beta (IFN β)-1a, IFN β -1b, and glatiramer acetate are examples of injectable DMTs for MS (21). Oral DMTs are frequently linked to enhanced treatment adherence and patient satisfaction when contrasted with injectable therapies, primarily because they offer a less cumbersome method of administration and improved tolerability (21). Teriflunomide is an oral disease-modifying therapy that is administered once daily and serves as an important treatment alternative for individuals diagnosed with relapsing-remitting MS and also patients with active progressive MS and clinically isolated syndrome (22).

Patient satisfaction with treatment is regarded as influential in health-related decision-making, especially concerning chronic illnesses (23-25).

Additionally, research indicates that patient satisfaction is a significant predictor of sustained continuity of care, appropriate medication usage, and compliance with the treatment plan (25-28).

The current study aimed to review studies that have used the TSQM to assess treatment satisfaction with teriflunomide in patients with MS. The study question was what the impact of treatment with teriflunomide alone or in comparison with other DMTs is on treatment satisfaction in patients with MS.

Methods

The Treatment Satisfaction Questionnaire for Medication (TSQM) is an instrument designed to assess patient satisfaction regarding their medication, and it has been demonstrated to be both a valid and reliable tool (25).

The TSQM consists of 4 subscales: effectiveness, side effects, convenience, and global satisfaction. Scores for each

subscale are computed on a scale from 0 to 100, where higher scores reflect greater patient satisfaction with the medication (25).

The investigation adhered to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) during its course (29).

The research question was formulated according to the PICO format:

P: Patients with MS, I: treatment with teriflunomide, C: DMTs, O: Treatment satisfaction.

Search Strategy

PubMed, Scopus, Web of Science, PsycINFO, the Cochrane Library, and Google Scholar were searched for eligible articles until 25 August 2023 by 2 independent reviewers to identify all relevant studies assessing treatment satisfaction with teriflunomide in patients with MS. A broad search strategy was performed with the keywords ("multiple sclerosis" OR ("multiple" AND "sclerosis") OR ("Sclerosis" AND "Disseminated") OR "Disseminated Sclerosis" OR "MS" OR ("Multiple Sclerosis" AND "Acute Fulminating")) AND ("teriflunomide" OR "RS 61980" OR "Aubagio" OR "HMR1726" OR "HMR-1726" OR "A 771726" OR "A 1726" OR "A771726" OR "A-771726" OR "A77 1726") AND (satisfaction)).

Study Eligibility

Studies were included if they (1) focused on relapsing forms of multiple sclerosis; (2) investigated the use of teriflunomide; (3) utilized TSQM to assess treatment satisfaction; (4) were published in English; (5) were observational; (6) focused on adults (≥ 18 years old). Studies were excluded if they (1) were designed as case reports or case series; (2) were not full-text peer-reviewed articles; (3) lacked sufficient details or did not report TSQM domains; (4) were review articles; (5) book chapters; (6) letters/editorials/notes/presentations; (7) focused on progressive forms of MS or other neurological conditions; (8) focused on patients < 18 years; (9) and were clinical trials. No time bound was used to search for studies. The titles and abstracts were evaluated for eligibility by 2 independent authors. Full-text versions of all articles deemed potentially relevant were acquired and assessed to ascertain their compliance with the predetermined inclusion criteria. Any disagreements were settled through consensus reached via discussion.

Data Extraction

After selecting the studies, 2 authors independently gathered pertinent information, which included the names of the authors, the year of publication, study name, study type, country of study, number of centers in the study, publications, pretreatment, treatment group, study period, results of 4 domains of TSQM, and demographic characteristics—including age range, sex, and mean age—were analyzed in each included study.

Quality Assessment

The quality of observational studies, including cohort

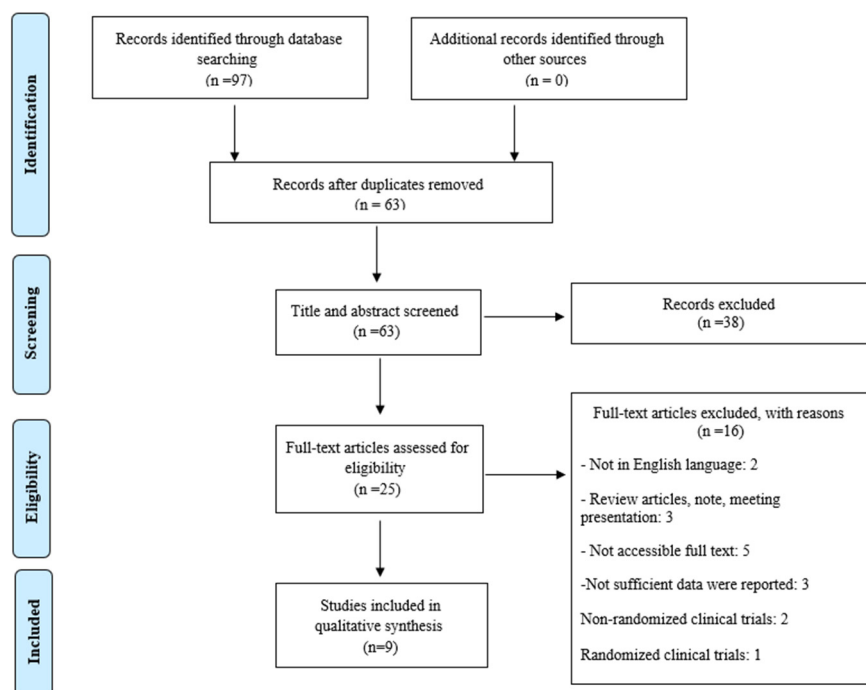


Figure 1. PRISMA flow diagram of literature search

studies and cross-sectional studies, was appraised using the 14-item National Institute of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. In 14 items of the NIH's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, quality was rated as poor (0–4 out of 14 questions), fair (5–10 out of 14 questions), or good (11–14 out of 14 questions) (30). Quality assessment was conducted by 2 authors, while any disagreements among the remaining authors were addressed through discussion and consensus.

Data Analysis

In the current study, we synthesized the results of all studies, including 7 cohorts and 2 cross-sectional studies qualitatively. Then, in cohort studies, we calculated the mean TSQM domain scores at baseline, 6 months, 12 months, and 24 months after treatment with teriflunomide in patients with MS including DMT-naïve patients and patients who switched from previous DMT. Subsequently, we presented these results on graphs separately.

Results

Search Results

A total of 97 possible publications were discovered through the employed search strategy. A total of 34 studies were identified as duplicates, while 38 studies were excluded after the screening and analysis of titles and abstracts due to their failure to meet the eligibility criteria. Finally, the full texts of 25 studies were examined. At this stage, 2 non-English studies, 3 review articles, note and meeting presentations, 2 non-randomized clinical trials, and 1 randomized clinical trial (RCT) were removed. Also, 5 studies whose full-texts were not accessible and 3 studies

with insufficient data were removed. Finally, 9 remaining articles were included in the qualitative synthesis. The PRISMA flowchart is presented in Figure 1.

Data Extraction

Nine studies were observational, including 7 cohorts and 2 cross-sectional studies. In all studies, teriflunomide had been prescribed in the treatment group, and some patients had received previous DMTs. Study periods of all studies were between 3 months and 24 months. Characteristics of these studies are provided in Table 1.

Quality Assessment

The quality of observational studies was assessed using the 14-item NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (30). The results showed that all studies were of relatively high quality. Eight studies of observational studies had fair quality and one of them had good quality. The results of the quality assessment are presented in Table 2 by each item in the 14-item NIH's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Data Analysis

Effectiveness

In all studies, the scores of effectiveness domain in patients treated with teriflunomide were high. In 3 studies, the mean effectiveness score significantly increased by 5.8 ± 29.9 , $P \leq 0.001$ (31), 15.1 ± 32.4 , $P \leq 0.05$ (37), and 6.6 , $P \leq 0.001$ (34) in all patients between baseline and the last follow-up visit. In 1 study, the mean effectiveness score at week 48: 63.85 ± 19.50 increased in comparison with week 24: 63.19 ± 18.09 in all patients (35).

Treatment Satisfaction with Teriflunomide in Patients with MS

Table 1. General characteristics of selected studies

Author (year)	Study name	Study type	countries	No. of centers	Publications	Pre-treatment (No. of participants)	Treatment group (No. of participants)	Age range	Male (%)	Mean age \pm SD (year)	Study period	Version of TSQM
Kallmann et al. (2019) (31)	TAURUS-MS	Observational (cohort)	Germany	307	Therapeutic Advances in Neurological Disorders	Previous DMT discontinued \leq 6 months prior to study entry: <ul style="list-style-type: none"> • IFNβ-1a intramuscular (74) • IFNβ-1a subcutaneous (105) • IFNβ-1b subcutaneous (74) • Glatiramer acetate subcutaneous (119) • Azathioprine oral (4) • Other (82) • Last MS medication not known (135) • No treatment \leq 6 months prior to start of teriflunomide (504) • No data regarding previous treatment (31) 	14 mg teriflunomide daily (1128)	20 y-73 y	32.5	44.9 \pm 9.7	24 months	TSQM 9
Kallmann et al. (2021) (32)	TAURUS-MS	Observational (cohort)	Germany	307	Therapeutic Advances in Neurological Disorders	- No pre-treatment (228) - Pre-treatment stopped \leq 6 months (593): Of the recently pre-treated patients, 253 had received interferon- β (IFN- β), and 119 glatiramer acetate (i. e. injection therapies)	- 14 mg teriflunomide daily (1128)	\geq 18 y	32.5	44.9 \pm 10.2	24 months	TSQM 9
Nunes et al. (2023) (33)	TeriLIVE-QoL	Observational (Cohort)	Portugal	16	Brain and Neuroscience Advances	Injectable <ul style="list-style-type: none"> • Interferon β-1a (28) • Glatiramer acetate (24) • Peginterferon β-1a (7) • Interferon β-1b (5) Oral <ul style="list-style-type: none"> • Dimethyl fumarate (9) • Fingolimod (1) • Infusion (1) • Natalizumab (1) 	14 mg teriflunomide daily (99)	23y-76y	31.3	47.0 \pm 11	24 months	TSQM 1.4
Dardiotis et al. (2022) (34)	AURELIO	Observational (cohort)	Greece	26	Neurol Ther	Glatiramer acetate and all forms of interferon beta (123)	Teriflunomide 14 mg/day (282)	18y-72y	37.2	44.8 \pm 11	24 months	TSQM 1.4

Table 1. Continued

Author (year)	Study name	Study type	countries	No. of centers	Publications	Pre-treatment (No. of participants)	Treatment group (No. of participants)	Age range	Male (%)	Mean age \pm SD (year)	Study period	Version of TSQM
Hardy et al. (2022) (35)	AubPRO	Observational (cohort)	Australia	13	BMJ Neurology Open	Patients who had previously been treated: <ul style="list-style-type: none"> • glatiramer acetate (15) • beta-interferons (13) • fingolimod (11) • fumaric acid (8) • daclizumab (1) • natalizumab (1) Prior to their most recent therapy, 20 patients had received multiple other DMTs: <ul style="list-style-type: none"> • beta-interferons (18) • glatiramer acetate (9) • fingolimod (3) • natalizumab (3) • fumaric acid (2) 	teriflunomide 14 mg/day (103)	≥ 18 y	20.4	49.5 \pm 11	24 weeks and 48 weeks	TSQM 1.4
Hestvik et al. (2022) (36)	Teri-LIFE	Observational (cohort)	Denmark, Norway and Sweden	17	Multiple Sclerosis and Related Disorders	<ul style="list-style-type: none"> • Interferons (60) • Glatiramer acetate (14) • Dimethyl fumarate (9) • Other (3) 	Teriflunomide 14 mg once-daily (200)	≥ 18 y	29.5	44.1 \pm 10.4	6 months and 24 months	TSQM 1.4
Guger et al. (2022) (37)	TAURUS -MS	Observational (cohort)	Austria	7	eNeurologicalSci	<ul style="list-style-type: none"> • Any (18) • IFN-β 1a IM (8) • IFN-β 1a SC (6) • IFN-β 1b SC (5) • Glatiramer acetate SC (5) • Azathioprine PO (1) • Immunoglobulin IV (4) • Other (2) • None (13) 	Teriflunomide 14 mg once daily (31)	≥ 18 y	38.7	Men: 41.9 \pm 10 Women: 41.2 \pm 11.1	24 months	TSQM 9

Table 1. Continued

Author (year)	Study name	Study type	countries	No. of centers	Publications	Pre-treatment (No. of participants)	Treatment group (No. of participants)	Age range	Male (%)	Mean age \pm SD (year)	Study period	Version of TSQM
Turčáni et al. (2020) (38)	SKARLET	Observational (cross-sectional)	Slovakia	10	Patient Preference and Adherence	<ul style="list-style-type: none"> • 232 patients (55.6%) had received a previous DMT • Drugs were not reported 	<ul style="list-style-type: none"> • Teriflunomide oral (81) • Interferon beta-1a (subcutaneous -SC) injections (71) • Fingolimod oral (58) • Dimethyl fumarate oral (51) • Glatiramer acetate 40 mg injections (44) • Natalizumab infusion (41) • Interferon beta-1a (intramuscular -IM) injections (22) • Interferon beta-1b (Novartis) injections (17) • Alemtuzumab infusion (10) • Glatiramer acetate 20 mg injections (8) • Peginterferon beta-1a injections (8) • Interferon beta-1b (Bayer) injections (4) • Unknown treatment (2) • Total (417) 	19y-69y	32.6	38.85 \pm 11.07	≥ 3 months and ≤ 2 years	TSQM 9
Lanzillo et al. (2020) (39)	Not reported	Observational (cross-sectional)	Italy	5	Neurological Sciences	<ul style="list-style-type: none"> • Glatiramer acetate: 1 (1-2) • Interferons: 1 (1-2) • Dimethyl fumarate: 2 (1-3) • Teriflunomide: 2 (2-3) • All patients: 1 (0-6) 	<ul style="list-style-type: none"> • Glatiramer acetate parenteral (37) • Interferons parenteral (156) • Dimethyl fumarate oral (62) • Teriflunomide oral (25) • Total (280) 	> 18y- \square 65 y	36.8	36.9 \pm 11.2	At least 1 year	TSQM 1.4

Table 2. Results of quality assessment of observational studies using 14-items NIH's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Kallmann et al. (2019) (31)	Kallmann et al. (2021) (32)	Nunes et al. (2023) (33)	Dardiotis et al. (2022) (34)	Hardy et al. (2022) (35)	Hestvik et al. (2022) (36)	Guger et al. (2022) (37)	Turčáni et al. (2020) (38)	Lanzillo et al. (2020) (39)
1. Was the research question or objective in this paper clearly stated?	✓	✓	✓	✓	✓	✗	✓	✓	✓
2. Was the study population clearly specified and defined?	✓	✓	✓	✓	✓	✓	✓	✓	✓
3. Was the participation rate of eligible persons at least 50%?	✓	✓	✓	✓	✓	✓	✓	✓	✓
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	✓	✓	✓	✓	✓	✓	✓	✓	✓
5. Was a sample size justification, power description, or variance and effect estimates provided?	✗	NA	✓	✓	✓	✓	NA	✓	✗
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓	✓	✓	✓	✓	✓	✓	✓	✓
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓	✓	✓	✓	✓	✓	✓	✓	✓
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	✓	✓	✓	✓	✓	✓	✓	✓	✓
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓	✓	✓	✓	✓	✓	✓	✓	✓
10. Was the exposure(s) assessed more than once over time?	NA	NA	NA	NA	NA	NA	NA	NA	NA
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓	✓	✓	✓	✓	✓	✓	✓	✓

Poor (0–4 out of 14 questions), fair (5–10 out of 14 questions), or good (11–14 out of 14 questions); NA: not applicable, NR: not reported

Table 3. Results of TSQM domains of selected studies

	Effectiveness	Convenience	Global satisfaction	Side effects
Kallmann et al. (2019) (31)	<p>For the effectiveness scale, the mean values at study entry (n = 829), 3 months (n = 879), 6 months (n = 777), 12 months (n = 664), 18 months (n = 542), 24 months (n = 444), and at the last follow-up visit (irrespective of treatment duration, n = 942) were 60.8, 67.7, 67.9, 69.9, 70.4, 71.0 and 67.5, respectively.</p> <p>The mean effectiveness score increased by 5.8 ± 29.9, $p < 0.001$ points: mean score at study entry (60.8), last follow-up visit (67.5).</p> <p>The mean effectiveness score in patients who discontinued a previous DMT within 6 months of study entry: increased by 9.2 ± 28.0 between study entry and 12 months and 8.1 ± 27.7 between study entry and 24 months.</p>	<p>For the convenience scale, the mean values at study entry (n = 854), 3 months (n = 896), 6 months (n = 793), 12 months (n = 667), 18 months (n = 546), 24 months (n = 446), and at the last follow-up visit (n = 950) were 74.8, 89.8, 90.5, 90.8, 91.2, 90.9, and 90.2, respectively.</p> <p>The mean convenience score increased by 15.60 ± 27.41, $p < 0.001$ points: mean score at study entry (74.8), last follow-up visit (67.5).</p> <p>The mean change from study entry to 12 and 24 months for the convenience scale in patients who discontinued a previous DMT within 6 months of study entry were 16.8 ± 26.4 and 17.0 ± 26.6 respectively.</p>	<p>For the global satisfaction scale, the mean values at study entry (n = 854), 3 months (n = 894), 6 months (n = 791), 12 months (n = 663), 18 months (n = 544), 24 months (n = 444), and at the last follow-up visit (n = 947) were 62.5, 72.4, 73.3, 74.8, 76.9, 77.5, and 72.3, respectively.</p> <p>The mean global satisfaction score increased by 9.82 ± 29.1, $p < 0.001$ points: mean score at study entry (62.5), last follow-up visit (72.3).</p> <p>The mean change from study entry to 12 and 24 months for the global satisfaction scale in patients who discontinued a previous DMT within 6 months of study entry were 12.6 ± 28.0 and 15.3 ± 27.4 respectively.</p>	Not reported
Kallmann et al. (2021) (32)	<p>In patients pre-treated with injectable therapies, mean effectiveness score improved substantially after 24 months compared with baseline effectiveness $+7.1 \pm 28.6$ points, $p < 0.01$.</p>	<p>In patients pre-treated with injectable therapies, mean convenience score improved substantially after 24 months compared with baseline convenience $+17.3 \pm 27.2$ points, $p < 0.001$.</p> <ul style="list-style-type: none"> Effects on the convenience TSQM scale was numerically smaller in patients aged 46 years and above compared with the younger age groups. 	<p>In patients pre-treated with injectable therapies, mean global satisfaction score improved substantially after 24 months compared with baseline global satisfaction $+15.9 \pm 25.4$ points, $p < 0.001$.</p> <ul style="list-style-type: none"> Effects on the global satisfaction TSQM scale was numerically smaller in patients aged 46 years and above compared with the younger age groups. 	Not reported
Nunes et al. (2023) (33)	<p>Mean effectiveness score in DMT-naïve patients had no significant alterations being registered at any timepoint, when compared to the 6-month period. It was 71.7 ± 3.6, 80.7 ± 4.5, 75.9 ± 5.1 at months 6, 12 and 24 respectively.</p> <p>Mean effectiveness score in patients who switched from previous DMT was 62.9 ± 2.5, 71.8 ± 2.5, 71.4 ± 2.3 at baseline, months 12 and 24 respectively.</p>	<p>Mean convenience score in DMT-naïve patients had no significant alterations being registered at any timepoint, when compared to the 6-month period. It was 92.7 ± 5.3, 93.3 ± 0.0, 95.6 ± 11.9 at months 6, 12 and 24 respectively.</p> <p>Mean convenience score in patients who switched from previous DMT was 73.4 ± 4.7, 87.9 ± 7.0, 86.6 ± 7.1 at baseline, months 12 and 24 respectively.</p>	<p>Mean global satisfaction score in DMT-naïve patients had no significant alterations being registered at any timepoint, when compared to the 6-month period. It was 77.3 ± 2.2, 80.1 ± 2.5, 86.7 ± 2.1 at months 6, 12 and 24 respectively.</p> <p>Mean global satisfaction score in patients who switched from previous DMT was 66.3 ± 2.9, 77.1 ± 2.0, 78.7 ± 2.2 at baseline, months 12 and 24 respectively.</p>	<p>Few patients reported side effects at months 12 and 24. Mean side effects score was 73.2 ± 3.1 and 77.1 ± 7.3 at months 12 and 24 respectively.</p> <p>Mean side effects score in patients who switched from previous DMT was 54.1 ± 2.9, 67.9 ± 3.3, 81.3 ± 3.3 at baseline, months 12 and 24 respectively. Mean side effects scores showed no significant alterations at any timepoint (12 months: $p = 0.269$; 24 months: $p = 0.198$).</p>

Table 3. Continued

	Effectiveness	Convenience	Global satisfaction	Side effects
Dardiotis et al. (2022) (34)	Results for the TSQM at 24 months showed significant improvements in mean effectiveness score (+6.6, $p < 0.0001$). <ul style="list-style-type: none"> similar improvements and statistically significant outcomes also identified at the interim 12-month timepoint 	Results for the TSQM at 24 months showed significant improvements in mean convenience score (+ 1.9, $p < 0.0001$). <ul style="list-style-type: none"> similar improvements and statistically significant outcomes also identified at the interim 12-month timepoint 	Results for the TSQM at 24 months showed significant improvements in mean global satisfaction score (+ 8.1, $p < 0.0001$). <ul style="list-style-type: none"> similar improvements and statistically significant outcomes also identified at the interim 12-month timepoint 	Results for the TSQM at 24 months showed a non-significant improvement in mean side effects score (+1.1, $p < 0.0001$). <ul style="list-style-type: none"> similar improvements and statistically significant outcomes also identified at the interim 12-month timepoint
Hardy et al. (2022) (35)	Mean (SD) effectiveness score was high at both weeks 24 and 48: (week 24: 63.19 ± 18.09); (week 48: 63.85 ± 19.50). Compared with week 24, at week 48, mean TSQM score was improved in the effectiveness domain in patients who were treatment naïve.	Mean (SD) convenience score was high at both weeks 24 and 48: (week 24: 87.48 ± 14.90); (week 48: 88.97 ± 12.25). Compared with week 24, at week 48, mean TSQM score was improved in the convenience domain in patients who were treatment naïve.	Mean (SD) global satisfaction score was high at both weeks 24 and 48: (week 24: 59.55 ± 25.00); (week 48: 64.51 ± 23.86). Compared with week 24, at week 48, mean TSQM score was improved in the global satisfaction domain in patients who were treatment naïve. Compared with week 24, at week 48, mean TSQM score was improved in the global satisfaction domain in patients who were previously on either another oral medication or an injectable DMT.	Mean (SD) side effects score was high at both weeks 24 and 48: (week 24: 79.52 ± 25.96); (week 48: 83.61 ± 22.44). Compared with week 24, at week 48, mean TSQM score was improved in side effects domain in patients who were previously on either another oral medication or an injectable DMT.
Hestvik et al. (2022) (36)	Previously treated: Baseline (63.3), month 6 (63), month 24 (66.3) Treatment naïve: Month 6 (59.3), month 24 (64.5)	Previously treated: Baseline (72.9), month 6(93.2), month 24(93.4) Treatment naïve: Month 6 (91.6), month 24 (93.3)	Previously treated: Baseline (60.4), month 6(72.1), month 24(73.5) Treatment naïve: Month 6 (63.2), month 24 (68.6)	Previously treated: Baseline (73), month 6(84.9), month 24(88.6) Treatment naïve: Month 6 (78.2), month 24 (86.2)
Guger et al. (2022) (37)	Between baseline and the last visit, the mean effectiveness score indicated an increase of 15.1 ± 32.4 ; 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 mean TSQM-9 score indicated nonsignificant increases of 35.2 ± 27.4 ; min: 16.7, max: 66.7, $p > 0.05$ between baseline and 12 months, and of 16.7 ± 43.4 ; min: - 11.1, max: 66.7, $p > 0.05$ between baseline and 24 months	There was an indication of an increase, of 17.5 ± 19.9 ; 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 \pm 11.6; min: - 16.7, max: 5.6, $p > 0.05$ at 12 months, and 3.7 \pm 11.6; min: - 5.56, max: 16.67, $p > 0.05$ at 24 months.	The mean global satisfaction score showed an increasing trend of 9.4 ± 26.5 ; 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 ± 30.5 ; min: - 25, max: 42.9, $p > 0.05$ at 12 months and 6.3 ± 20.3 ; min: - 10.7, max: 35.7, $p > 0.05$ at 24 months.	Not reported

Table 3. Continued

	Effectiveness	Convenience	Global satisfaction	Side effects
Turčáni et al. (2020) (38)	Score: (68.15; 66.56–69.75) Effectiveness ranged from 71.95 (natalizumab) to 65.41 (interferon beta-1a subcutaneous). Teriflunomide(n=81): 67.15 (62.80; 71.50) Interferon beta-1a SC (n=71): 65.41 (61.28; 69.55) Fingolimod (n=58): 69.64 (65.68; 73.59) Dimethyl fumarate (n=51): 69.39 (65.04; 73.74) Glatiramer acetate 40 mg (n=44): 68.56 (65.60;71.52) Natalizumab (n=41): 71.95 (67.33; 76.57) Interferon beta-1a IM (n=22): 68.18 (59.05; 77.31) Interferon beta-1b (n=17): 67.65 (60.56; 74.73)	Score: (75.05; 73.49–76.61) The greatest difference among DMTs was for convenience, with a range from 85.12 (teriflunomide) to 65.36 (interferon beta-1b) Teriflunomide(n=81): 85.12 (82.07; 88.16) Interferon beta-1a SC (n=71): 69.58 (65.56;73.59) Fingolimod (n=58): 81.70 (77.68; 85.73) Dimethyl fumarate (n=51): 79.85 (75.88; 83.81) Glatiramer acetate 40 mg (n=44): 66.92 (63.70; 70.14) Natalizumab (n=41): 74.80 (70.46; 79.13) Interferon beta-1a IM (n=22): 66.41 (59.14; 73.68) Interferon beta-1b (n=17): 65.36 (59.09; 71.63)	Score: (66.94; 65.26–68.62) Global satisfaction ranged from 71.25 (natalizumab) to 62.18 (interferon beta-1b) Teriflunomide(n=81): 69.58 (65.56;73.59) Interferon beta-1a SC (n=71): 63.58 (59.26; 67.91) Fingolimod (n=58): 68.47 (64.27; 72.68) Dimethyl fumarate (n=51): 67.79 (63.13; 72.44) Glatiramer acetate 40 mg (n=44): 65.58 (62.10; 69.07) Natalizumab (n=41): 71.25 (65.74; 76.77) Interferon beta-1a IM (n=22): 64.29 (56.47; 72.10) Interferon beta-1b (n=17): 62.18 (54.42; 69.95)	Not reported
Lanzillo et al. (2020) (39)	Glatiramer acetate: 64.2 ± 23.9 Interferon: 64.2 ± 23.0 Dimethyl fumarate: 63.5 ± 22.9 Teriflunomide: 55.6 ± 20.7	Glatiramer acetate: 66.9 ± 15.3 Interferon: 70.9 ± 20.1 Dimethyl fumarate: 84.0 ± 20.9 (Significantly higher than interferon, p=0.001) Teriflunomide: 86.1 ± 15.7 (Significantly higher than interferon, p=0.001)	Glatiramer acetate: 61.5 ± 20.2 Interferon: 58.4 ± 22.2 Dimethyl fumarate: 57.4 ± 24.7 Teriflunomide: 57.2 ± 19.9	Glatiramer acetate: 30.4 (0) (0–68.8) Interferon: 39.6 (43.8) (0–68.8) Dimethyl fumarate: 54.1 (71.9) (0–81.3) (Significantly higher than interferon) Teriflunomide: 17.6 (0) (0–28.1) (Significantly lower than interferon)

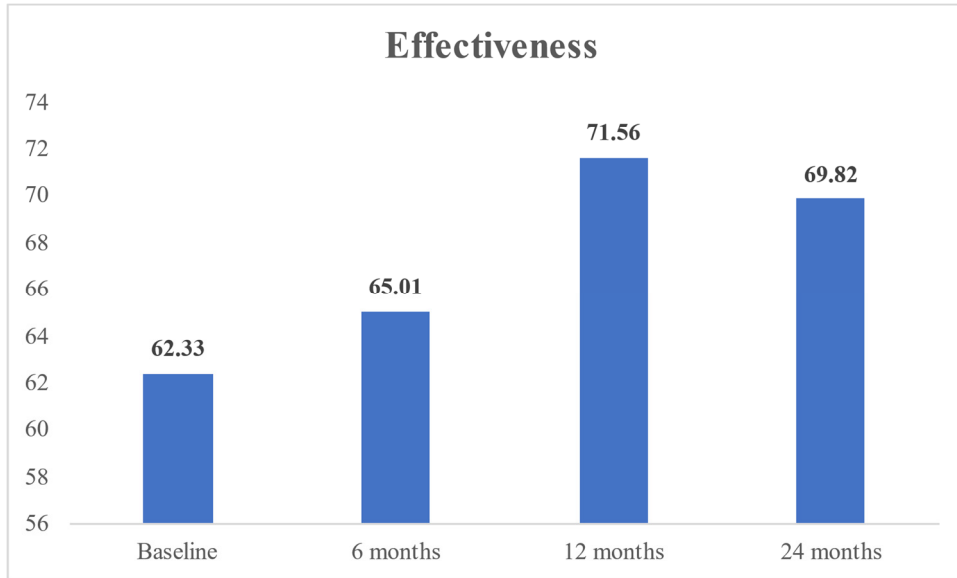


Figure 2. Calculated mean scores of effectiveness domain at baseline, 6 months, 12 months and 24 months after treatment with teriflunomide in cohort studies

In 3 studies, mean effectiveness scores increased at the last follow-up visits compared with the first follow-up visits in DMT-naïve patients (33, 35, 36), while in one of them, changes were not significant (33). In 5 studies, mean effectiveness scores increased at the last follow-up visits compared with baseline in patients who switched from previous DMT (31, 32, 33, 36, 37), while in one of them, changes were not significant (37). The calculated mean scores of effectiveness domain at baseline, 6 months, 12 months, and 24 months after treatment with teriflunomide in mentioned studies are presented in Figure 2.

In 2 studies, the effectiveness scores of teriflunomide were compared to other DMTs (38, 39). In one of them, the effectiveness score of teriflunomide was higher than Interferon beta-1a SC but lower than fingolimod, dimethyl fumarate, glatiramer acetate 40 mg, natalizumab, interferon beta-1a IM, and Interferon beta-1b (38). In another study, the effectiveness score of teriflunomide was nonsignificantly lower than glatiramer acetate, interferon, and dimethyl fumarate (39).

Convenience

In all studies, the scores of convenience domain in patients treated with teriflunomide were high. In 3 studies, the mean convenience scores significantly increased by 15.60 ± 27.41 ($P \leq 0.001$) (31), 17.5 ± 19.9 ($P \leq 0.05$) (37), and 1.9 ($P \leq 0.001$) (34) in all patient groups between baseline and the last follow-up visit. In one study, the mean convenience score at week 48: 88.97 ± 12.25 increased compared with week 24: 87.48 ± 14.90 in all patient groups (35). In 3 studies, mean convenience scores increased at the last follow-up visits compared with the first follow-up visits in DMT-naïve patients (33, 35, 36), while in one of them, changes were not significant (33). In 5 studies, mean convenience scores increased at the last follow-up visits compared with baseline in patients who switched from previous

DMT (31- 33, 36, 37), while in one of them, changes were not significant (37). The calculated mean scores of the convenience domain at baseline, 6 months, 12 months, and 24 months after treatment with teriflunomide in mentioned studies are presented in Figure 3.

In 2 studies, convenience scores of teriflunomide were compared to other DMTs (38, 39). In one of them, the convenience score of teriflunomide was higher than all other DMTs, including Interferon beta-1a SC, fingolimod, dimethyl fumarate, glatiramer acetate 40 mg, natalizumab, interferon beta-1a IM, and Interferon beta-1b (38). In another study, convenience scores of teriflunomide and dimethyl fumarate were significantly ($P \leq 0.001$) higher than interferons, while the score of teriflunomide was higher than dimethyl fumarate (86.1 versus 84) (39).

Global Satisfaction

In all studies, the scores of the global satisfaction domain in patients treated with teriflunomide were high. In 3 studies, the mean global satisfaction score significantly increased by 9.82 ± 29.1 ($P \leq 0.001$) (31), 9.4 ± 26.5 ($P \leq 0.05$) (37), and 8.1 ($P \leq 0.001$) (34) in all patient groups between baseline and the last follow-up visit. In one study, the mean global satisfaction score at week 48: 64.51 ± 23.86 increased compared with week 24: 59.55 ± 25 in all patients (35). In 3 studies, mean global satisfaction scores increased at the last follow-up visits compared with the first follow-up visits in DMT-naïve patients (33, 35, 36), while in one of them, changes were not significant (33). In 5 studies, mean global satisfaction scores increased at the last follow-up visits compared with baseline in patients who switched from previous DMT (31- 33, 36, 37), while in one of them, changes were not significant (37). In one study, compared with week 24, at week 48, the mean TSQM score was improved in the global satisfaction domain in patients who



Figure 3. Calculated mean scores of convenience domain at baseline, 6 months, 12 months and 24 months after treatment with teriflunomide in cohort studies

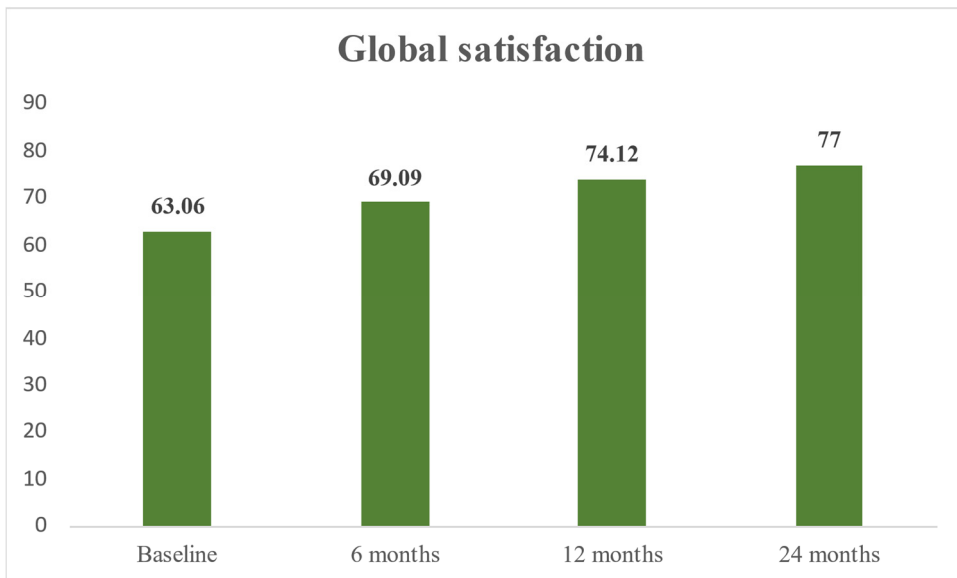


Figure 4. Calculated mean scores of global satisfaction domain at baseline, 6 months, 12 months and 24 months after treatment with teriflunomide in cohort studies

were previously on either another oral medication or an injectable DMT (35). The calculated mean scores of the global satisfaction domain at baseline, 6 months, 12 months, and 24 months after treatment with teriflunomide in mentioned studies are presented in Figure 4.

In 2 studies, global satisfaction scores of teriflunomide were compared to other DMTs (38, 39). In one of them, the global satisfaction score of teriflunomide was higher than all other DMTs, including Interferon beta-1a SC, fingolimod, dimethyl fumarate, glatiramer acetate 40 mg, interferon beta-1a IM, and Interferon beta-1b, except natalizumab (38). In another study, global satisfaction score of teriflunomide was nonsignificantly lower than glatiramer acetate, interferon, and dimethyl fumarate (39).

Side Effects

In one study, the mean side effects score increased by 1.1 ($P < 0.001$) in all patients between baseline and last follow-up visit (34) (higher values indicating less side effects). In another study, the mean side effect score was 73.2 ± 3.1 and 77.1 ± 7.3 at months 12 and 24, respectively (33). In one study, the mean side effects score at week 48 (83.61 ± 22.44) increased compared with week 24 (79.52 ± 25.96) in all patients (35). In another study, the mean side effects score increased at month 24 compared with month 6 in DMT-naïve patients, which was 86.2 and 78.2, respectively (36). In 2 studies, the mean side effects score increased at the last follow-up visits compared with baseline in patients who switched from previous DMT (33, 36) but in one of them mean side effects scores showed no significant alterations at any timepoint (12 months: $P = 0.269$; 24 months:

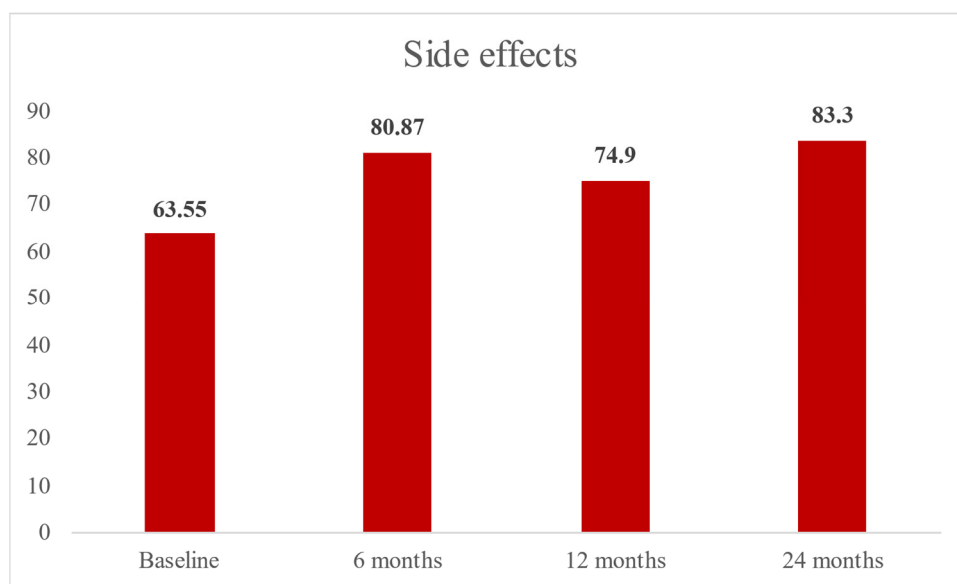


Figure 5. Calculated mean scores of side effects domain at baseline, 6 months, 12 months and 24 months after treatment with teriflunomide in cohort studies

$P = 0.198$) (33). In one study, compared with week 24, at week 48, the mean TSQM score was improved in the side effects domain in patients who were previously on either another oral medication or an injectable DMT (35). The calculated mean scores of side effects domain at baseline, 6 months, 12 months and 24 months after treatment with teriflunomide in mentioned studies are presented in Figure 5.

In one study, the side effects score of teriflunomide was compared to other DMTs (39). In this study, the side effects score of teriflunomide was significantly ($P < 0.001$) lower than interferon (39).

The results of TSQM domains of studies reviewed in this systematic review are presented in Table 3.

Discussion

Teriflunomide is a pharmaceutical agent indicated for the treatment of relapsing forms of MS (40). It works by reducing inflammation in the central nervous system, which can help slow the disease's progression (41). Treatment satisfaction with teriflunomide can vary depending on individual experiences and expectations (42).

The present study aimed to systematically review studies that have used the TSQM to assess treatment satisfaction with teriflunomide in patients with MS. A total of 9 studies were incorporated into this systematic review. In all studies, 4 domains of TSQM, especially the convenience domain, were improved after treatment with teriflunomide. Mean scores of the convenience domain in patients treated with teriflunomide were higher than other DMTs but some studies showed that other DMTs may provide higher scores in different domains of TSQM. In all studies, 4 domains of TSQM were improved in patients who had previously been treated and also in treatment naïve patients. The 14-item TSQM Version 1.4 offers evaluations in 4 areas: effectiveness, convenience, global satisfaction, and side effects. TSQM Version 9 does not include the side effects domain.

In this systematic review, TSQM Version 9 was used in 4 studies (31, 32, 37, 38). Therefore, side effects domain was not measured in these studies. In the rest of studies, TSQM Version 1.4 was used.

Teriflunomide works by the inhibition of de novo pyrimidine synthesis and thus the inhibition of lymphocytes proliferation. It has been approved to be used in clinically isolated syndrome, clinically definite multiple sclerosis, and in active progressive MS. It is a once daily tablet available in 2 doses of 7mg and 14 mg; however, the 7 mg daily tablet has shown to be inferior to Interferon beta1a in controlling relapses, and therefore the 14 mg dose is preferred. Compared to placebo, teriflunomide 14 mg daily results in 31% to 36% reduction in annualized relapse rate, and 80% reduction in gadolinium-enhancing lesions. The most frequently observed side effects of teriflunomide are nausea, headache, and reversible hair thinning. Other side effects include elevated blood pressure, hepatotoxicity, and neuropathy (43). In 1 RCT, treatment satisfaction with 2 doses of teriflunomide, including 7 mg and 14 mg, and also IFN β -1a SC 44 μ g were compared. The mean scores at week 48 in 3 domains of TSQM—including convenience, global satisfaction, and side effects, were significantly improved with both doses of teriflunomide compared with IFN β -1a. However, scores in the effectiveness domain did not significantly differ between teriflunomide 14 mg and IFN β -1a SC 44 μ g but were lower with teriflunomide 7 mg (44).

In the Coyle et al study (45), scores of all domains of TSQM decreased at week 48 in comparison with week 4 after treatment with teriflunomide in all patients with MS. Scores of all domains of TSQM in patients who switched from previous DMT increased at week 48 compared with baseline after treatment with teriflunomide but scores of all domains of TSQM at week 48 were lower than week 4 ones.

In Coyle et al study (46), in the United States, patients with MS were prescribed teriflunomide 7 mg or 14 mg once

daily but patients in the rest of the world (ROW) were prescribed teriflunomide 14 mg once daily. The mean scores of all domains of TSQM improved at week 48 compared with the baseline in both ROW and the United States.

Based on the results of the present study, if the route of drug administration is the priority, teriflunomide 14 mg appears to be the best treatment in the aspect of convenience. However, if efficacy of treatment is the priority, natalizumab seems to be the best treatment. The results of some studies were in line with those of the current study. In Spelman et al's study, natalizumab demonstrates greater efficacy than fingolimod in managing relapses within this population characterized by elevated rates of new inflammatory activity and, furthermore, both fingolimod and natalizumab surpass the effectiveness of first-line injectable therapies (47). In Hersh et al's study, patients transitioning from natalizumab to moderate disease-modifying therapy (DMT), as opposed to high-efficacy therapy, experienced a relatively heightened risk of disease activity during the initial 6 months after the cessation of natalizumab, and this increased risk persisted over a 24-month period, resulting in greater progression of disability (48). Lower-efficacy DMTs are like glatiramer acetate, interferon beta, and teriflunomide, moderate-efficacy DMTs are like dimethyl fumarate, fingolimod and high-efficacy DMTs includes natalizumab, ocrelizumab, rituximab, and alemtuzumab (48). In another study, it was shown the initiation of teriflunomide therapy without a washout period for natalizumab was associated with a minimal resurgence of disease activity. This finding indicates that clinicians might view this approach as a valuable strategy for transitioning clinically stable patients from natalizumab to an alternative treatment (49).

However, it is important to note that not all patients may experience the same level of satisfaction with teriflunomide. Some patients may experience side effects such as diarrhea, nausea, and hair loss, which can impact their overall satisfaction with the treatment (50). Additionally, some patients may not experience significant improvements in their MS symptoms, which can also impact their satisfaction with the treatment.

The literature indicates a correlation between elevated treatment satisfaction, enhanced compliance, and better clinical outcomes (51). Overall, treatment satisfaction with teriflunomide appears to be generally high among patients with relapsing forms of MS. However, individual experiences may vary, and patients need to discuss their expectations and concerns with their healthcare provider to determine whether teriflunomide is the right treatment option for them.

This review had some limitations. First, some studies had not reported results of side effects domain of the TSQM because of the use of TSQM Version 9. Second, most studies had been performed in Europe. More research is needed in other parts of the world with different socioeconomic situations and contexts, which may impact study results, especially in patients with MS. Third, in none of the studies, the study period was >24 months. It may be needed to do more research with study periods >24 months to determine

the long-term impact of teriflunomide on treatment satisfaction in patients with multiple sclerosis. Fourth, in rare studies, subgroup analysis by age, sex, and pretreatment had been performed. Subgroup analysis by age, sex, and pretreatment, results in a wider understanding of the difference in satisfaction with treatment between different groups of patients.

Conclusion

Treatment with teriflunomide improves satisfaction in patients with MS but it is helpful to do more studies on comparing TSQM domains of treatment with teriflunomide with other DMTs ones. If route of drug administration is the priority, teriflunomide 14 mg appears to be the best treatment in the aspect of convenience. However, if efficacy of treatment is the priority, natalizumab seems to be the best treatment.

Authors' Contributions

Design and study team: Hamid Pourasghari, Mohammad Ali Rezaei, Samad Azari, Fahimeh Haji Akhondi. Conceptualization: Hamid Pourasghari, Mohammad Ali Rezaei, Fahimeh Haji Akhondi. Formal analysis: Mohammad Ali Rezaei, Samad Azari. Writing, reviewing, and editing: Hamid Pourasghari, Mohammad Ali Rezaei, Samad Azari, Fahimeh Haji Akhondi.

Ethical Considerations

This study was approved by the Research Ethics Committee of Iran University of Medical Sciences (IR.IUMS.REC.1402.397).

Acknowledgment

None.

Conflict of Interests

The authors declare that they have no competing interests.

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