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The patient-reported outcomes for the new brand-generic teriflunomide in relapsing-remitting multiple sclerosis

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ABSTRACT

Background: Patient-reported outcomes (PROs) provide valuable insights into the impact of disease-modifying therapies (DMTs) on patients' daily lives and disease progression. This study evaluates treatment satisfaction and tolerability among patients using a brand-generic Teriflunomide (Tebazio®, 14 mg tablet) manufactured by Zistdaru Danesh Biopharmaceuticals.

Materials and Methods: A Phase IV observational study was conducted on patients with Relapsing-Remitting Multiple Sclerosis (RRMS) who were either initiated on or switched to Teriflunomide 14 mg. The primary focus was on the medication's safety. Patient satisfaction was measured using the Treatment Satisfaction Questionnaire for Medication [Version 1.4] (TSQM-14). Additionally, medication adherence and discontinuation rates were monitored.

Results: Of the 235 RRMS patients enrolled, participated in this study, all received the Teriflunomide treatment orally on a daily basis. Over the 18-month follow-up period, 25.96 % of patients discontinued the treatment. Discontinuation was mainly due to adverse events (11 %), lack of patient willingness to continue (12.7 %), and disease progression (4.2 %). The most commonly reported adverse events included dermatologic disorders, elevated liver enzymes, and gastrointestinal issues. TSQM-14 scores demonstrated significant improvements over the 18-month period. A high medication adherence rate of 98.1 % was also recorded.

Conclusion: Patients reported notable satisfaction with Teriflunomide, as reflected in their TSQM scores, which suggests a likelihood of improved patient adherence. The 14 mg brand-generic Teriflunomide was well-accepted by Iranian RRMS patients, with no significant concerns arising during the study. These findings also highlight the significance of patient-reported outcomes in DMTs, with potential benefits for adherence and clinical practice.

1. Introduction

Multiple Sclerosis (MS) is a chronic autoimmune, neurodegenerative disorder characterized by inflammation, demyelination, and axonal damage within the central nervous system (CNS) [1]. Globally, the disease burden is evident, with an estimated 2.8 million individuals

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diagnosed with MS as of 2020 [2].

Treatment strategies for MS are multifaceted, ranging from oral to injectable modalities, tailored to the disease's severity and progression [3]. Of these, oral disease-modifying therapies (DMTs) have gained momentum due to their comparative ease of administration and favorable patient compliance [4]. Teriflunomide, an oral DMT, emerges as a key player in the relapsing-remitting multiple sclerosis (RRMS) management. [5].

Patient-reported outcomes (PROs) stand at the forefront of this shift, offering invaluable insights into the treatment's effectiveness from the patient's perspective [6]. The increasing international emphasis on patient-reported outcome measures (PROMs), as highlighted by the OECD's health ministers, supports this. These measures are designed to actively engage patients, capturing their health-related quality of life, healthcare experiences, and satisfaction with the treatments received. The international collection of this data plays a pivotal role in refining health services to better address patient-specific needs [7,8]. It's also been substantiated that elevated PRO scores align with improved clinical outcomes such as lower Expanded Disability Status Scale (EDSS) scores and reduced relapse rates [9,10].

Recent trials elucidate the notable efficacy and safety profile of the branded Teriflunomide variant, Aubagio, in managing RRMS. These studies underscore its potential in decreasing relapse rates and mitigating disease progression [11–14]. However, global disparities in drug accessibility and cost constraints have necessitated the production of generic alternatives.

While the branded Teriflunomide has been extensively studied, empirical data on Tebazio (generic counterpart to Aubagio produced by Zistdaru Danesh co.) remains scant. This study, therefore, sets out to rigorously evaluate Tebazio in terms of patient satisfaction and safety profile assessment.

2. Materials and methods

2.1. Study design, ethical considerations, and objectives

This study was designed as a Phase IV, longitudinal, multicenter, open-label, single-cohort observational study, conducted at four medical sites on patients with confirmed MS. The protocol was adhered to the ethical guidelines outlined in the Declaration of Helsinki and secured approval from the Institutional Review Board and the Ethics Committee of Tehran University of Medical Sciences (reference: IR.TUMS.NI.REC.1398.033). All participants provided informed consent before their inclusion in the study.

2.2. Study population

Patients with a confirmed diagnosis of RRMS, as determined by the revised McDonald criteria from 2017 [15], were enrolled in the study. They were administered Teriflunomide 14 mg on a daily regimen. To qualify for inclusion, participants needed to be at least 18 years of age. Rigorous exclusion criteria were established to ensure participant safety. Specifically, individuals with renal dysfunction, indicated by a Glomerular Filtration Rate (GFR) below 30 ml/min, or those with hepatic impairment classified under Child-Pugh Class C, were not considered for the study. Additionally, those showing hypersensitivity to Teriflunomide, those who had been administered corticosteroids or other immunosuppressants within the 30 days preceding the study, and lactating or pregnant individuals were also excluded.

2.3. Treatment protocol

Teriflunomide (Tebazio®) was administered as an oral disease-modifying agent for managing relapsing forms of multiple sclerosis. Prior to initiation, liver function, and potential pregnancy were assessed. Participants received a daily dose of 14 mg, with ongoing liver function monitoring. Women of childbearing age were advised to use effective contraception during the treatment.

2.4. Study endpoints and data collection

The primary objective of this investigation was to comprehensively assess the safety profile of Teriflunomide. This involved a detailed evaluation and documentation of any adverse events or side effects patients experienced. These events were systematically captured during regular clinical visits and monthly tele-visits throughout the 18-month research duration.

For secondary endpoints, we measured changes in patient satisfaction levels over 18 months. This assessment utilized the validated 14-item Treatment Satisfaction Questionnaire for Medication [Version 1.4] (TSQM-14), designed to ascertain patient contentment with their current medication regimen.

Moreover, patient adherence to the medication protocol was evaluated using the Medication Possession Ratio (MPR). An MPR threshold of $\geq$ 80 % was set as the standard, indicating patients who consistently followed their prescribed DMT.

$$\text{Medication Possession Ratio} = \frac{\textit{Number of days supply held during evaluation period}}{\textit{Numbers of days in evaluation period}}$$

Lastly, data regarding the rate of treatment discontinuation, reasons for such decisions, and any recorded relapses were diligently extracted from patient medical records.

2.5. Statistical analysis

Prior to implementing parametric tests, the assumption of data normality was verified using the Kolmogorov-Smirnov test. Quantitative variables, depending on their distribution, were summarized either as mean (with standard deviation) or as median (accompanied by the interquartile range). Qualitative or categorical variables were described in terms of frequencies and their corresponding percentages.

For the comparison of quantitative datasets, the independent samples t-test or the Mann-Whitney U Test was employed based on the data distribution. Categorical variables were assessed using Pearson's chi-square test or, when appropriate, Fisher's exact test. All statistical analyses were performed using RStudio version 4.3.1 (RStudio, Inc., Boston, MA, USA).

2.5.1. Sample size calculation

To determine the sample size, we referred to research conducted by Connor et al. [16]. The observed prevalence of headache was 18.7 %. Based on this frequency and aiming for a precision of 6 % with a 95 % confidence interval ($\alpha = 0.05$), a minimum sample size of 163 patients was deduced to be adequate.

3. Results

3.1. Demographics and baseline characteristics

Between September 2019 and October 2022, 235 patients were recruited, with each participant receiving a single dose of Teriflunomide, thereby constituting the safety population. All participants were switchers from interferon beta or glatiramer acetate. Out of the initial cohort, 174 patients (74 %) successfully completed the treatment regimen (Fig. 1). The demographic details and baseline attributes of the participants are elucidated in Table 1. Analyzing the baseline Expanded Disability Status Scale (EDSS) scores, the results suggest that the cohort predominantly exhibited mild disease manifestations, reflected by a mean score of 1.6 ($\pm$ 1).

3.2. Primary endpoint - safety evaluation

Throughout the study, various adverse events (AEs) were

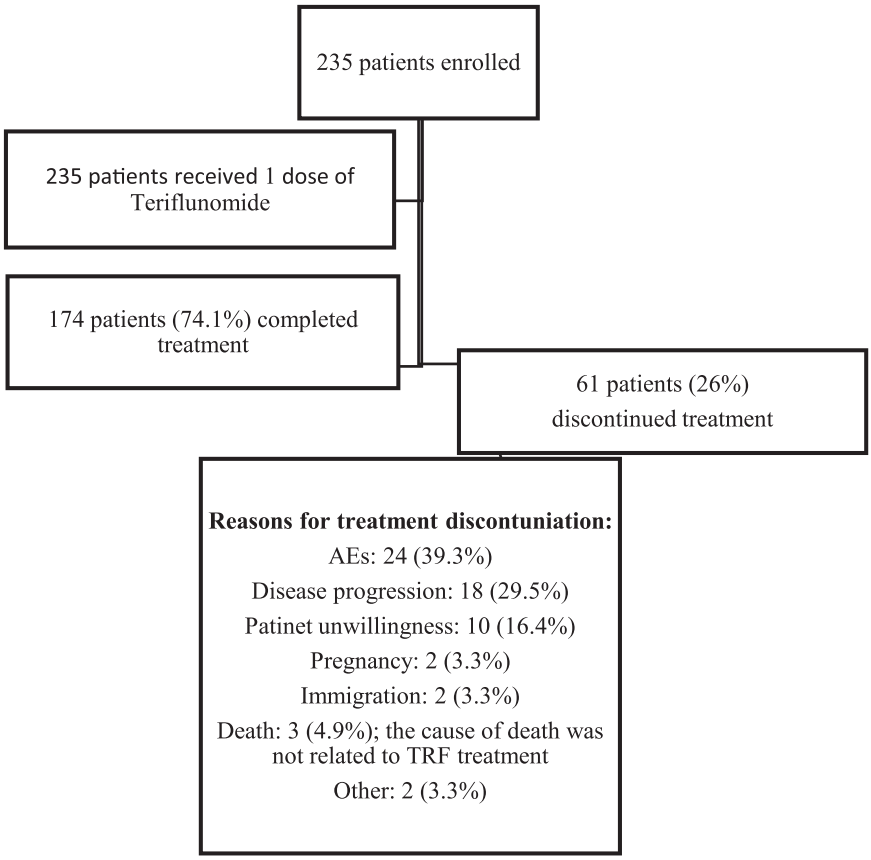

Fig. 1. Consort Flow diagram depicting the trajectory of patients through the Teriflunomide observational study. The chart outlines the number of patients who completed the regimen, and reasons for discontinuation.

Table 1
Demographics and baseline disease characteristics.

Characteristic		value
Gender (female), n (%)		151 (64 %)
Age (years), mean (±SD)		41.6 (± 5)
Disease duration (years), mean (± SD)		6.6 (± 6.8)
Baseline EDSS		1.6 (± 1)
Previous DMTs, n (%)	Treatment - naive	74 (31.8 %)
	Interferons	99 (41.9 %)
	Glatiramer acetate	32 (13.6 %)
	Dimethyl fumarate	12 (5.1 %)
	Fingolimod	4 (1.7 %)
	Teriflunomide (another brand)	5 (2.1 %)
	Natalizumab	3 (1.3 %)
	Rituximab	6 (2.5 %)
Reason for discontinuing prior treatment	inconvenience	45 %
	Intolerance to prior administration mode	25 %
	Side effects/risk of side effects	15 %
	Other	15 %

documented among the participants. As detailed in Table 2, the most prevalent AEs included hair thinning, defined as a noticeable reduction in hair density, assessed by patients, which affected 34 % of the subjects. Elevated levels of ALT and AST were observed in 15.7 % of patients. Diarrhea and abdominal pain were other notable AEs, affecting 8.9 % and 6.8 % of the cohort, respectively. Less common but still significant AEs ranged from pruritus to hypertension, each affecting less than 6 % of the population. On the less frequent spectrum, AEs such as urticaria, blurred vision, and weight gain each presented in less than 2 % of the subjects.

3.3. Secondary endpoints

3.3.1. Patient satisfaction

Treatment satisfaction was assessed using the TSQM-14 questionnaire at the onset of the study and subsequently at intervals of 6, 12, and 18 months following the initiation of the treatment.

Notably, there was a marked enhancement in the effectiveness scores at each time interval when compared to the baseline. The effectiveness scores rose significantly by 4.1 %, 4.4 %, and 8.8 % at the 6, 12, and 18-month, respectively (P: <0.05, <0.001).

Similarly, the scores reflecting patient satisfaction with respect to side effects displayed significant elevations from the baseline at all recorded intervals. Specifically, satisfaction concerning side effects rose by 5.6 %, 7.5 %, and 9.8 % during the study, in that order (P: <0.05, P:<0.001).

In case of Convenience area, significant improvement at each time point in comparison to the baseline was observed with increments of 8.4 %, 10.1 %, and 10.9 % at study intervals, respectively.

In terms of overall satisfaction, there was a pronounced uptrend over the span of 18 months relative to the baseline, registering an average escalation of 6.8 % (P: <0.001). Although there were ascensions noted at the 6 and 12-month post-treatment periods, these were not deemed to be of statistical significance.

A detailed breakdown of the TSQM scores is shown in Table 3.

3.3.2. Medication adherence

Medication adherence was diligently assessed on a monthly basis throughout the study. The Medication Possession Ratio (MPR), a metric

Table 2
Adverse Events.

Adverse Events	Number	Percentage	Adverse Events	Number	Percentage
Hair thinning	80	34.1 %	Urticaria	3	1.3 %
Elevated ALT & AST	37	15.7 %	Constipation	2	0.9 %
Diarrhea	21	8.9 %	Blurred vision	2	0.9 %
Abdominal pain	16	6.8 %	Weight gain	2	0.9 %
Headache	13	5.5 %	Flushing	2	0.9 %
Pruritus	12	5.1 %	Fecal incontinence	2	0.9 %
Dry skin	10	4.3 %	Decrease libido	2	0.9 %
Weight loss	10	4.3 %	Pain	2	0.9 %
Hypertension	9	3.8 %	Thrombocytopenia	1	0.4 %
Leukopenia	8	3.4 %	Tooth pain	1	0.4 %
Paresthesia	8	3.4 %	Skin Hypersensitivity reaction	1	0.4 %
Bloating	7	3 %	Reflux	1	0.4 %
Nausea	7	3 %	Influenza	1	0.4 %
Acne	6	2.6 %	Increased appetite	1	0.4 %
Vertigo	6	2.6 %	Aphthous ulcer	1	0.4 %
Tachycardia	4	1.7 %	Anxiety	1	0.4 %
loss of appetite	4	1.7 %	Fever	1	0.4 %
Myalgia	4	1.7 %	Carpal tunnel syndrome	1	0.4 %
Hyperbilirubinemia	4	1.7 %	Urinary frequency	1	0.4 %
Skin hyperpigmentation	3	1.3 %	Rhinitis	1	0.4 %
Hypersensitivity reaction	3	1.3 %	Upper respiratory infection	1	0.4 %
Mouth dryness	3	1.3 %	Fatigue	1	0.4 %
Irregular menstruation	3	1.3 %	Dermatologic allergic reaction	1	0.4 %
Arthralgia	3	1.3 %			

Table 3
Comparative Evaluation of TSQM-14 scores Over an 18-Month Period Following Teriflunomide Initiation.

Time		Effectiveness	Side effect	Convenience	Overall satisfaction
Baseline	Mean	62.6	71.5	70.3	62.2
	Std. Deviation	21.1	26.3	19.8	21.4
	N	190	187	188	188
6 months	Mean	66.7 *	77.1 *	78.6 **	64.5
	Std. Deviation	19.8	25.3	17.7	21.5
	N	181	183	183	184
12 months	Mean	67 *	79.1 **	80. 3 **	65.3
	Std. Deviation	19.5	26.1	18.5	23
	N	150	153	152	152
18 months	Mean	71.4 **	81.3 **	81.1 **	69.1 **
	Std. Deviation	20	23.3	18.7	21.8
	N	128	128	129	128

Statistics: The TSQM-14 scores at each time point (6, 12, and 18 months) were compared to the baseline using paired t-tests or Wilcoxon signed-rank tests, depending on the normality of the data distribution, which was verified with the Kolmogorov-Smirnov test. Mean scores and standard deviations are presented for each time point, with significant changes from the baseline indicated by asterisks (*P < 0.05, **P < 0.001).

that reflects the patient's adherence to the prescribed therapy, was determined to be 98.1 % over the course of the 18-month treatment duration. This high MPR suggests consistent compliance with the Teriflunomide regimen among the study participants, emphasizing the drug's acceptability and possibly its perceived benefits by the patients.

3.3.3. Discontinuation rates

Of the 235 recruited patients, 174 patients (74.1 %) persisted with Teriflunomide therapy until the study's conclusion. However, 61 (26 %) opted to discontinue their treatment for diverse reasons, as detailed in Table 4.

Specifically, disease progression was the main reason for 12 patients to cease their Teriflunomide regimen. A closer look at therapeutic adjustments reveals that 8 of these patients transitioned to ocrelizumab, 3 to rituximab, and one made a switch to natalizumab.

3.3.4. Proportion of patients with relapses

During the 18-month observational period, 6 % of the enrolled patients, exhibited an episode of MS relapse.

Table 4
Discontinuation Reasons.

Discontinuation Reasons	**Number of Patients**	**Percentage of total enrolled patients**
Progression	12	5.1 %
Physician Decision (based on underlying diseases)	15	6.4 %
Adverse Events (AEs)	23	9.8 %
Hair Thinning	5 (22 % of AEs)	-
Elevated liver enzymes	7 (30 % of AEs)	-
Diarrhea	3 (13 % of AEs)	-
Anaphylactic Reaction	1 (4.3 % of AEs)	-
Dermatologic Allergic Reaction	3 (13 % of AEs)	-
Abdominal pain	2 (8.7 % of AEs)	-
Hypertension	2 (8.7 % of AEs)	-
Intent to become pregnant	1	0.4 %
immigration	2	0.8 %
Patient Unwillingness	8	3.4 %
Death (unrelated to the medication or disease)	3	

4. Discussion

In our study, we observed that patients with MS who underwent treatment with Teriflunomide demonstrated a notable enhancement in overall satisfaction over an 18-month follow-up period. Throughout the duration of the study, all domains of the TSQM showed statistically significant elevations when compared to baseline measurements. Further analysis revealed a medication adherence rate of 98.1 %, suggesting a commendable adherence to the prescribed medication regimen. It's noteworthy to mention that throughout the study duration, we did not identify any new or concerning safety signals.

PROs provide unique insights into treatment outcomes from the patient's perspective. They stand as pivotal metrics for gauging treatment efficacy as perceived by the patient. The literature offers ample support for the importance of PROs as significant indicators of therapeutic success [17].

Employing tools like the TSQM-14 questionnaire in conjunction with PROs offers an in-depth understanding of the impact of treatment from a patient-centric viewpoint. The consistent enhancements in TSQM-14 scores across domains - including effectiveness, side effects, convenience, and overall satisfaction - validate the positive influence of Teriflunomide on patients' quality of life. Our findings align with the AURELIO study [18], which analyzed outcomes for patients treated with Teriflunomide over a median follow-up of 24 months. The study highlighted beneficial impacts on quality of life (QoL), efficacy, safety outcomes, and a commendable level of treatment satisfaction in both treatment-naïve and previously treated patients within a Greece cohort suffering from RRMS. Additionally, our findings are in harmony with other research efforts, such as the study orchestrated by Hardy et al., focusing on an Australian patient cohort [19].

The data from this study underscores a favorable benefit-risk ratio, further solidifying Teriflunomide's position as a well-tolerated and efficacious DMT for RRMS. It accentuates the importance of meticulously managing any adverse events to bolster patient tolerance and thereby, extend the duration of treatment. Additionally, our investigation offers insights into the underlying considerations that influence physicians' prescribing decisions for Teriflunomide. Such findings resonate with the results observed in both the 2018 trial by Thach et al. and the study by Vermersch et al. [19,20]. These investigations draw attention to a growing preference for oral therapies, especially when considering a shift from injectable formats, highlighting an essential element in the process of therapeutic decision-making.

Certain adverse events were prominently observed, specifically hair thinning, an elevation of liver enzymes, and fever, which served as principal reasons for discontinuing the treatment. This aligns coherently with the enduring safety and efficacy previously delineated in the TEMSO trial [20], A subsequent real-world study reiterated these findings, marking discontinuation rates oscillating between 12 % and 15 % [21]. In our assessment, Teriflunomide exhibited favorable tolerability among the majority of participants. The documented discontinuation rate of 25.9 % in our study seems to be in harmony with prior investigations. Distinctively, AEs led to a 10.3 % premature discontinuation rate of Teriflunomide, paralleling a German study's findings where 8.6 % of enrollees ceased Teriflunomide use due to AEs [22] Similar patterns emerge in various other studies [20,21,23].

The challenge of adherence often stems from the side effects that can adversely impact a patient's quality of life. Hence, it becomes crucial to furnish comprehensive information about the proposed treatment, encompassing potential risks and side effects. Our data elucidates an impressive adherence rate of 98.1 % throughout the treatment phase, drawing parallels with a Finnish cohort that reported a 91.7 % adherence rate [24]. This commendable adherence rate can, to some extent, be ascribed to Teriflunomide's once-daily dosing schedule, recognizing that adherence generally dwindles with escalating daily doses [25].

It is imperative to recognize the limitations inherent to our study. The study's observational design may introduce potential biases. Furthermore, as our dataset originates exclusively from four academic centers, caution is advised when generalizing our findings to broader contexts.

4.1. Conclusion

In conclusion, our observational study on MS patients underscored a marked enhancement in overall patient satisfaction, as reflected in the TSQM outcomes. This is further corroborated by the consistent improvements observed across various domains such as effectiveness, side effects, convenience, and overall satisfaction. Teriflunomide's notable influence on patients' quality of life, mirrored by the high medication adherence rate, combined with its reassuring safety profile and the favorable benefit-risk ratio, solidifies its stature in therapeutic decisions. Given the growing demand for more tolerable and effective treatment options, particularly when transitioning from injectable therapies, Teriflunomide stands out as a compelling option for patients considering a switch from other DMTs.

These findings highlight also the critical role of patient-reported outcomes in the comprehensive evaluation of DMTs. By incorporating the patient's perspective on treatment efficacy, side effects, and overall satisfaction, these outcomes offer essential insights that extend beyond traditional clinical measures. This patient-centered approach not only enhances our understanding of how therapies affect daily life but also plays a crucial role in optimizing treatment adherence, which can lead to improved clinical outcomes. Moreover, integrating patient-reported outcomes into clinical practice enables healthcare providers to make more informed and personalized treatment decisions, aligning therapies with patient needs and preferences.

However, while these findings are promising, it is essential to acknowledge the limitations of observational studies and the potential biases that may influence the interpretation of these results. Therefore, future research across diverse settings and populations will be invaluable in further validating these insights.

Institutional Review Board Statement

The protocol was adhered to the ethical guidelines outlined in the Declaration of Helsinki and secured approval from the Institutional Review Board and the Ethics Committee of Tehran University of Medical Sciences (reference: IR.TUMS.NI.REC.1398.033).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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CRediT authorship contribution statement

Roya Abolfazli: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Funding acquisition, Conceptualization. **Seyed Massood Nabavi:** Validation, Resources. **Amirreza Azimi:** Resources. **Mohammadali Nahayati:** Resources. **Kurosh Gharagozli:** Resources. **Hamidreza Torabi:** Resources. **Monireh Ghazaeian:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Zahra Rezagholi:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Sara Samadzadeh:** Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology,

Investigation, Formal analysis, Conceptualization.

Declaration of Competing Interest

All authors declare that they have no financial, personal, or other interests related to the subject matter of this paper that could create a potential conflict of interest.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

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