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Original article

Use of follow-on fingolimod for multiple sclerosis: Analysis of effectiveness and patient reported outcomes in a real-world clinical setting

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ABSTRACT

Background: Follow-on disease modifying therapies (FO-DMTs) do not always require Phase III studies. There are concerns that cheaper FO-DMTs are only used to reduce healthcare costs. However, the well-being of people with MS (pwMS) should be a priority. We aimed to evaluate the efficacy, safety and treatment satisfaction of one of the FO- Fingolimod (FTY) used in Turkey with the approval of Turkish Ministry of Health.
Methods: PwMS under FTY were recruited from 13 centers and real-world data and answers of satisfaction and adherence statements of pwMS on FTY treatment were analyzed.
Results: Data of 239 pwMS were obtained. The duration of FTY treatment was 2.5 ± 0.8 (1–4) years in pwMS who were included in the study and whose treatment continued for at least one year. Significant decreases in annual relapse rate ($p < 0.001$), Expanded Disability Status Scale ($p < 0.001$) and neuroimaging findings ($p < 0.001$) were observed. While 64% of the patients were satisfied and 71.5% were found to adherent with this FO-FTY.
Conclusion: This multicenter retrospective study found that the efficacy, safety and treatment adherence of a prescribed FO-FTY were consistent with the results of real-world studies. Studies including real-world data may provide guidance to address issues related to FO-FTY use.

1. Introduction

Effective disease-modifying therapy (DMT) is important in preventing disease-related disability in multiple sclerosis (MS) (Gajofatto et al., 2015; Dutta and Trapp, 2014). The prices of DMTs used in people with MS (pwMS) have steadily increased over the past few decades. A cross-sectional study investigated the direct and indirect burden of MS disease and reported that DMTs accounted for the largest proportion of costs in the early stages of the disease (Brownlee et al., 2022). The global MS drug market is expected to reach US$27.8 billion by 2025 (Rivera,

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2019). The societal and economic impact of these costs is of international concern for health systems, which devote an increasing proportion of financial resources to MS care (Rivera, 2019).

In the early 2000s, biosimilar molecule manufacturers initiated the concept of producing biosimilar treatment options for MS (Rivera, 2019). The term "follow-on (FO) drug " is used as a general term covering generics, complex generics and biosimilars (Bell et al., 2018). While there is some variation between international organizations in terms of terminology, specific regulations, and how these regulations are implemented in practice, there are standards for regulatory requirements for the evaluation and approval of FO drugs (Moss and Cohen, 2019). However, it should be noted that in some countries there may be deviations from the standards set by the FDA, the European Medicines Agency (EMA) and the World Health Organization that may harm the well-being of patients (Skromne-Eisenberg et al., 2017).

FO-DMTs have become available in 2016 in Turkey. While generic forms of glatiramer acetate were being used in some other countries (Brownlee et al., 2022), the first FO-DMT to be used in Turkey is FTY. Brand drug Gilenya was approved by the Turkish Ministry of Health in April 2011 and started to be prescribed with full reimbursement for RRMS patients between 0 and 5.5 EDSS scores, if disease activity persists after at least one year of Interferon and/or Glatiramer acetate treatment. Since 2016, FO-FTY drugs have entered the market and started to be prescribed by MS specialists.

The debate on FO-DMT legislation and how to address issues related to its use has increased in recent years. Brownlee et al. discussed overarching principles and made specific recommendations for implementation. In order to register the generic form of FO-DMT, quality assessment in the laboratory with data such as particle size distributions, inorganic matter, heavy metal content and bioequivalence testing is the most reliable method (Brownlee et al., 2022). The Panel supports the current case-by-case regulatory approach. Otherwise, they note, phase III clinical trials may not be necessary if sufficient similarity can be achieved. It is also recommended that drug manufacturers establish accessible databases for long-term outcomes and take responsibility for facilitating follow-up, including real-world data (Brownlee et al., 2022; Correale et al., 2014).

Therefore, we wanted to create a retrospective multicenter study with the largest possible number of patient participants and a long-term follow-up period. The aims of our study were to assess patients' adherence to treatment, to evaluate the long-term efficacy of FTY after at least 12 months of treatment, to characterize the demographic and clinical profile of treated patients, and to evaluate the safety profile of a FO-FTY, which is being used, in a real-world setting.

2. Materials and methods

This study is a retrospective, non-interventional, clinical-based, multicenter study for evaluating real-world data and a cross-sectional study to assess treatment satisfaction in pwMS treated with FO-FTY which was licensed by the Turkish Ministry of Health in 2017.

This study was conducted in accordance with the International Conference of Compliance Guidelines for Good Clinical Practice and the Declaration of Helsinki. Institutional review board/independent ethics committee approved the protocol and all changes (reference number 2020.163.06.25) prior to the study. Participants approved retrospective data collection from study centers and consented to medical record review with a written informed consent form.

2.1. Study population

PwMS between the ages of 18 and 65 who were diagnosed with relapsing MS, agreed to participate in the study, whose Expanded Disability Status Scale (EDSS) ranged from 0 to 5.5 and who were using FTY for at least one year were included. Patients with insufficient and inconsistent data and with a follow-up period of less than one year were excluded from the study. Patient-related data (demographic, clinical and laboratory) were collected retrospectively from 13 participating study centers by reviewing the medical records of past/current people with relapsing MS who were initiated on one of the FO- FTY used in Turkey with the approval of Turkish Ministry of Health.

2.2. Efficacy and safety data collection of study population

DMT used before and after FTY treatment, the last DMT used, duration of FTY use, and the reason for stopping the drug were determined. Disability grades at baseline, 6th, 12th and 24th months were evaluated with "EDSS" after treatment initiation. EDSS was calculated from the documented neurologic exams retrospectively and scored from 0 to 10 by assessment of functional systems (Kurtzke, 1983). Worsening of disability one year after initiation of treatment was defined as a 1.5-point increase if the initial EDSS score was 0, a 1.0-point increase if the initial EDSS score was <5.5, or a 0.5-point increase if the initial EDSS score was ≥ 5.5 (Cree et al., 2021). Clinical relapse was defined as new or recurrent neurological symptoms that persisted for 24 h or longer without fever or infection (McDonald et al., 2001). Annual relapse rate (ARR) and duration of high dose methylprednisolone (HDMP) were determined as the number of relapses in the year before and after pwMS started FTY treatment (Biernacki et al., 2022). The number of newly developed T2 hyperintense and gadolinium (Gd)-enhancing lesions of brain and cervical spinal cord before and at least 6 months after treatment were determined retrospectively (Hou et al., 2021). Treatment-related side effects and the reasons for discontinuing treatment were examined. Side effects were evaluated in two groups as those associated with the first dose administration and those observed under treatment. Discontinuation from FTY therapy was defined as the treating physician's decision to terminate FTY follow-up and switch the patient to another DMT (Russo et al., 2022).

2.3. MS oral treatment adherence and satisfaction survey of pwMS

After discussing with the authors participating in the study, it was decided that statements and questions should evaluate drug satisfaction, side effects, ease of access to drug and adherence. Since there is no Turkish validated scale measuring oral treatment satisfaction and adherence in pwMS, a total of 18 questions or statements (14 5-point Likert statements, 1 yes/no, 2 4-options multiple-choice and 1 5-coptions multiple choice questions) were created. Oral treatment satisfaction was evaluated with 12 and ease of access to drugs with 2 5-point Likert expressions. Side effect profile was evaluated with 1 yes/no and 2 4-option multiple-choice questions, and adherence was evaluated with 1 5-options multiple-choice question. This questionnaire was named as "Multiple Sclerosis Oral Treatment Satisfaction and Adherence Questionnaire" (MS-OTAS) and validation study of the questionnaire is in prewriting process.

2.4. Statistical analysis

The PASW Statistics 25 for Windows statistical package program was used for data transfer and analysis. Mean, standard deviation, percentage, and minimum–maximum expressions were used to express the variables. The normality distribution of the variables was evaluated with the Shapiro-Wilk test. The Wilcoxon signed-rank test was used to compare those not showing a normal distribution. The Mann-Whitney U test was used in the evaluation of two independent groups, and the Kruskal-Wallis test was used in the evaluation of more than two independent groups. A p value of less than 0.05 was considered significant.

Statistical analysis for the total satisfaction assessment of the whole group ($n = 214$), it was assumed that those pwMS who responded "strongly agree", "agree" and "no opinion" to all statements had no dissatisfaction with the medication. For each positive statement, those who responded "strongly agree" and "agree" were considered to have

high satisfaction and those who responded "no opinion", "disagree" and "strongly disagree" were considered to have low satisfaction. In the analysis of responses to statements on access to medication, the method used for satisfaction statements was applied, and responses to side effect and adherence questions were expressed as percentages.

3. Results

3.1. Demographic feature of pwMS

Real-world data from 239 pwMS who had been under FTY treatment for at least one year were assessed. The mean age of the pwMS was 38.7 ± 9.8 (18–65) years, 175 (73.2%) were female and 64 (26.8%) were male. The demographic characteristics of the individuals included are presented in Table 1 and the disease modifying therapies used before FTY treatment are presented in Table 2.

3.2. Efficacy of fingolimod

One hundred ninety (79.5%) of pwMS experienced at least one relapse in the year before treatment (mean ARR: 1.0 ± 0.8 (0–5)). One hundred eighty-three (76.6%) received high-dose methylprednisolone (HDMP) therapy (mean duration: 5.2 ± 3.9 (0–20) days) and 15 (6.3%) received HDMP with once-a-month regimen.

Relapse occurred in 32 patients (13.4%) on the 1st year after treatment (mean ARR:0.2 ± 0.4 (0–3)). The mean HDMP treatment day was 0.9 ± 2.5 (0–20). Significant decrease was observed in the mean ARR ($p < 0.001$) and HDMP usage ($p < 0.001$) (Table 3). Relapse-free rate according to months is presented in Fig. 1.

The mean baseline EDSS value was 2.3 ± 1.2 (0–5.5). On the sixth month of therapy there was a statistically significant reduction in the mean EDSS (2.2 ± 1.2 (0–5.5)) scores ($p < 0.001$). The mean EDSS value at the 24th month ((2.2 ± 1.3 (0–6)) was also lower than the mean baseline EDSS ($p = 0.005$). Analyzes obtained baseline and one year after FTY treatment are summarized in Table 3.

Analysis of EDSS values of 239 patients who continued fingolimod treatment showed that 196 (82.0%) had no change, 34 (14.2%) improved and 9 (3.8%) worsened. No significant difference was observed between these three groups in terms of ARR and HDMP usage. In comparison of before treatment disability scores it was seen that mean EDSS was higher in worsening group (3.2 ± 1.3 (1.5–5)) than improved (3.0 ± 1.3 (1–5.5)) and stable (2.2 ± 1.2 (0–5.5)) groups ($p = 0.002$).

MRI examinations showed a significant decrease in the number of newly developing T2 hyperintense lesions ($p < 0.001$) and Gd-enhancing lesions ($p < 0.001$) (Fig. 2).

Table 1
Characteristics of the pwMS on fingolimod treatment for at least one year.

Characteristics		All pwMS ($n = 239$)
Age (years)	Mean ± SD (range)	38.7 ± 9.8 (18–65)
Gender	Female	175 (73.2%)
	Male	64 (26.8%)
Education level	Secondary	96 (40.2%)
	High school	83 (34.7%)
	University	60 (25.1%)
MS[a] type	RMS	231 (96.7%)
	PRMS	8 (3.3%)
Duration of disease (years)	Mean ± SD (range)	8.6 ± 5.0 (1.0–30.6)
Age of disease onset (years)	Mean ± SD (range)	30.4 ± 9.0 (10–58)
EDSS[b]	Mean ± SD (range)	2.3 ± 1.2 (0–5.5)
Comorbidity	No	200 (83.7%)
	Endocrinological	17 (7.1%)
	Cardiac	7 (2.9%)
	Rheumatological	3 (1.3%)
	Respiratory	2 (0.8%)
	Hematological	2 (0.8%)
	Headache	2 (0.8%)
	Others	6 (2.5%)

[a] : Multiple sclerosis.
[b] : Expanded Disability Status Scale.

Table 2
Evaluation of DMTs used before fingolimod treatment.

Data before fingolimod treatment		Participants ($N = 239$)
Duration of using fingolimod (years)	Mean±SD (range)	2.5 ± 0.8 (1–4)
DMT[a] used just before starting fingolimod treatment	n (%)	
Interferon β 1b		46 (19.2%)
Interferon β 1a		88 (36.8%)
Glatiramer acetate		55 (23.0%)
Natalizumab		2 (0.8%)
Naive		18 (7.5%)
Others (AZA[b], teriflunamide, DMF[c])		30 (12.6%)
1 DMT	n (%)	179 (74.9%)
≥ 2 DMT	n (%)	42 (17.6%)
Reasons for switching to fingolimod treatment	n (%)	
Clinical activation (relapse)		180 (75.3%)
Enjection difficulties		
Difficulties due to application		18 (7.5%)
Skin related side effects		6 (2.5%)
Progression of the disease		11 (4.6%)
MRI[d] activation		6 (2.5%)

[a] : Disease-modifying therapies.
[b] : Azathioprine.
[c] : Dimethyl fumarate.
[d] : Magnetic resonance imaging.

3.3. Treatment satisfaction, QoL and adherence of pwMS

Two hundred fourteen (89.5%) pwMS responded to MS-OTAS questionnaire. There were 137 pwMS (64%) who did not report dissatisfaction by not responding negatively for all statements in the post-medication satisfaction questionnaire evaluated with 12 statements. According to the findings obtained from the 12 5-point Likert statements evaluating satisfaction, when the total number of individuals who responded "Strongly agree" and "Agree" was determined, it was observed that the highest rate was in the statements "I think that the drug I used is treating me" and the lowest rate was in the statements "The drug I used, caused my emotional state to improve and my depressive complaints to decrease". The rates of statements related to access to medication were also higher than satisfaction (Fig. 3).

The number of pwMS who consulted a physician due to side effects was 50 (23.4%). Only 46 (21.5%) of the pwMS stated that the medication negatively affected their physical or mental state. Sixteen (7.5%) reported increased amnesia, 26 (12.1%) reported feeling more tired, and 4 (1.9%) reported feeling moodier. Twenty-two (10.3%) of the patients stated that they had a few days, three (1.4%) 7–10 days, three (1.4%) more than 10 days, 28 of them reported they lost workdays due to drug use. The number of pwMS who consulted a physician due to side effects was 50 (23.4%) (Fig. 4). One hundred fifty-three (71.5%) of pwMS were adherent to the treatment (Fig. 5).

3.4. Safety and treatment discontinuation

In all centers participating in the study, the first dose was administered in the hospital under a 6 h observation period. Bradycardia, a first dose side effect, was observed in 11 (4.6%) of the pwMS during treatment administration. None of them required treatment discontinuation.

Long-term side effects were observed in seven (3.3%) patients. Elevated liver enzymes were recorded in two (0.8%), low lymphocytes levels (<200/mm^3) in two (0.8%), tuberculosis meningitis in one (0.4%), frequent flu infections in one (0.4%) and basal cell carcinoma in one (0.4%) patient.

Table 3
The analyzes obtained one year before and one year after FTY treatment in terms of ARR, HDMP and EDSS analyzes obtained just before and one year after FTY treatment.

	EDSS[a]			ARR[b]			Usage time of HDMP[c]		
	Before fingolimod treatment	12th month of fingolimod treatment	p	12 months before fingolimod treatment	12th month of fingolimod treatment	p	12 months before fingolimod treatment	12th month of fingolimod treatment	p
All participants ($n = 239$)	2.3 ± 1.2 (0–5.5)	2.1 ± 1.2 (0–6)	<0.001	1.0 ± 0.8 (0–5)	0.2 ± 0.4 (0–3)	<0.001	5.2 ± 4.0 (0–20)	0.9 ± 2.5 (0–20)	<0.001
PwMS[d] with injection therapy just before fingolimod ($n = 189$)	2.3 ± 1.3 (0–5.5)	2.1 ± 1.3 (0–6)	<0.001	1 ± 0.8 (0–5)	0.2 ± 0.4 (0–3)	<0.001	5.0 ± 4.0 (0–20)	0.8 ± 2.2 (0–10)	<0.001
PwMS with oral therapy just before FTY[e] ($n = 30$)	2.8 ± 1.0 (1.5–5)	2.4 ± 0.9 (0–5)	0.004	1.3 ± 0.8 (0–4)	0.1 ± 0.3 (0–1)	<0.001	6.0 ± 4.1 (0–17)	0.6 ± 2.0 (0–7)	<0.001
Naive ($n = 18$)	2.1 ± 1.1 (0–4)	1.8 ± 1 (0–3)	0.02	1.1 ± 0.5 (0–2)	0.06± 0.3 (0–1)	<0.001	6.7 ± 2.6 (0–12)	0.8 ± 2.3 (0–7)	0.001
1 DMT[f] ($n = 179$)	2.3 ± 1.2 (0–5.5)	2.1 ± 1.3 (0–6)	<0.001	1 ± 0.8 (0–5)	0.1 ± 0.4 (0–3)	<0.001	5.1 ± 3.9 (0–20)	0.7 ± 2.0 (0–10)	<0.001
≥ 2 DMT ($n = 42$)	2.5 ± 1.3 (0–5.5)	2.2 ± 1.2 (0–5.5)	0.001	1 ± 0.7 (0–2)	0.3 ± 0.6 (0–3)	<0.001	5.4 ± 4.4 (0–14)	1.5 ± 3.9 (0–20)	<0.001

[a] : Expanded Disability Status Scale.
[b] : Annual relapse rate.
[c] : High dose methylprednisolone.
[d] : People with multiple sclerosis.
[e] : Fingolimod.
[f] : Disease modifying therapy.

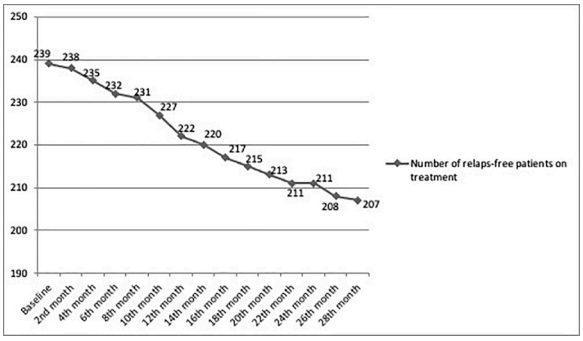

Fig. 1. Of the 239 pwMS who started treatment, 222 (92.9%) were free of relapse at the 12th month and 211 (88.3%) at the 24th month of the treatment.

Twenty-one (8.8%) patients discontinued FTY treatment. The mean duration of FTY usage in discontinued patients was 1.8 ± 0.6 (1.0–3.5) years. The reasons for discontinuation were as follows; relapse (clinical/radiologic activity) in fifteen, abnormal liver enzymes/lymphocyte levels in two, other side effects in two (tuberculosis meningitis, basal cell carcinoma), voluntary in one and pregnancy in one patient.

4. Discussion

This study presents real-world data retrospectively evaluating the efficacy and safety of one of the FO- FTYs prescribed in Turkey. As mentioned in the consensus recommendations reported by Brownlee et al. (2022), long-term post-marketing real-life data are necessary to maintain confidence in FO-DMTs. Since patient-reported outcomes (PROMs) will increase the reliability of the data, we also evaluated patient satisfaction and adherence to treatment cross-sectionally. Analysis of data from 239 pwMS with high disease activity and with a long follow-up receiving FO- FTY treatment revealed that the efficacy and safety results were in line with previous studies of the brand drug. Patient satisfaction and treatment adherence were also adequate (Barrero et al., 2020; Roux et al., 2017; Haas et al., 2019; Ziemssen et al., 2022).

Our results revealed that FO-FTY-treated pwMS showed a decrease in ARR from 1.0 to 0.2. No relapse was observed in 92% of patients at the end of the first year and 88% at the end of the second year. It is noteworthy to note that significant reductions in ARR were observed, including naive patients, regardless of the number of DMTs or DMTs used before FO-FTY treatment. The significant decrease in the frequency of relapses also led to a significant decrease in the use of intravenous HDMP. Mean EDSS values decreased from 2.3 ± 1.2 to 2.2 ± 1.2 at six months and 2.1 ± 1.2 at one year. Although this mean improvement did not appear to be clinically significant, statistical analysis revealed a

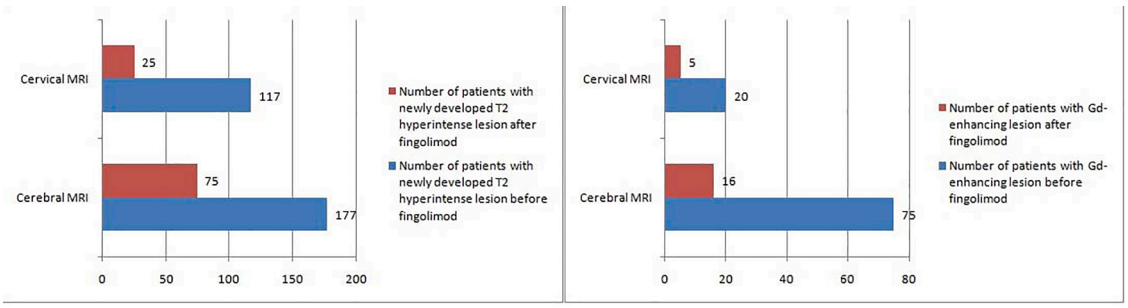

Fig. 2. At least 75% reduction in the number of T2 hyperintense lesions was detected in both brain and cervical spinal MRI. A 78.7% reduction in the number of Gd-enhancing lesions was observed in brain MRI and 75% in cervical spinal MRI.

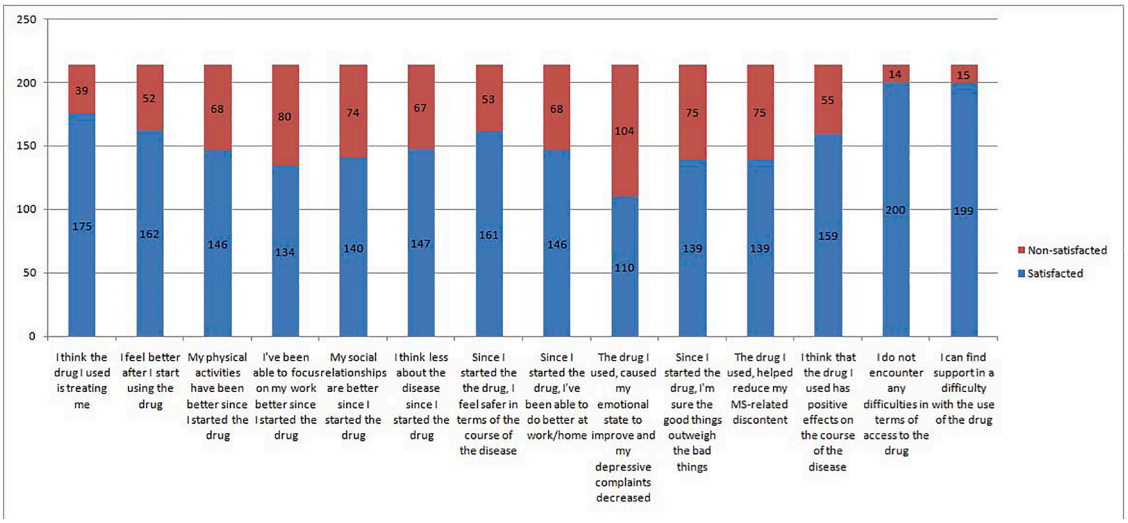

Fig. 3. Responses to the statements about satisfaction and ease of access to drugs given to pwMS under fingolimod treatment are summarized. The section shown in blue at the bottom of the column represents the number of individuals who answered, "strongly agree" and "agree" to the statements. The part shown in red at the top of the column represents the number of individuals who answered, "no opinion", "disagree" and “strongly disagree".

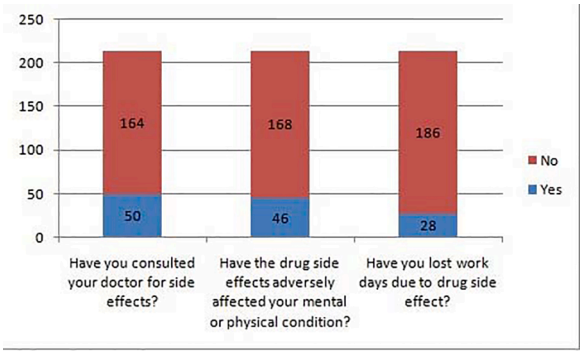

Fig. 4. The answers given to the questions about drug side effects are presented. The section shown in blue at the bottom of the column shows the number of individuals who answered "yes", and the section shown in red at the top of the column shows the number of individuals who answered "no" to the questions.

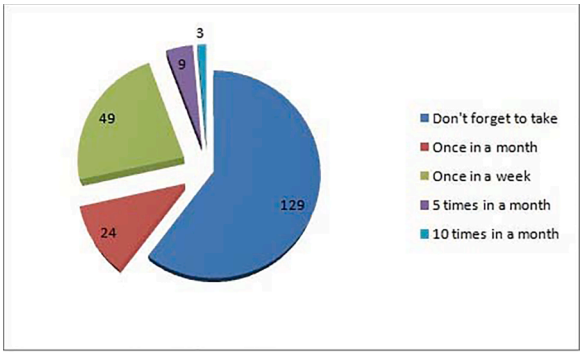

Fig. 5. Data on treatment adherence are presented. The proportion of pwMS who reported forgetting medication once a month or less was (71.5%).

significant result. When the EDSS values of the study group were analyzed according to the definitions of disability pattern according to EDSS change (Cree et al., 2021), 82.0% of the study group showed no change, 14.2% showed improvement and 3.8% showed worsening. The fact that pwMS with increasing disability were those with high disability at baseline supports studies reporting the importance of the window of opportunity for treatment (Lattanzi et al., 2020). When the studies evaluating the change in EDSS with 2 years of follow-up in real-world settings are examined, it is seen that decreases from 2.5 to 2.0 (Correia et al., 2016), from 2.87 to 2.06 (Uzunköprü et al., 2021), from 2.6 to 2.26 (AL-Hashel et al., 2014) were reported. Therefore, although the average improvement in EDSS values appears to be low, we believe that this statistical significance, even at low p-values, represents a positive impact of treatment on neurological findings. According to the analysis of neuroimaging parameters, we found a reduction of more than 75% in the number of both T2 hyperintense lesions and Gd-enhancing lesions. The efficacy of fingolimod treatment has been demonstrated in phase III trials and its efficacy on ARR, EDSS and MR activity has been supported by studies evaluating real-world data (Gajofatto et al., 2015; Ziemssen et al., 2022; Calabresi et al., 2014, 2015). This post-marketing study of FO-FTY was in line with these studies and revealed significant increase in the number of relapse-free patients and a statistically significant decrease in EDSS score and MRI activity.

FO-DMTs also need to be therapeutically equivalent to their reference product in terms of safety. It is unlikely that adverse events and treatment failure will be eliminated when switching between the reference product and FO-DMTs. Observations of increased frequency of known adverse events, emergence of new adverse events, differences in immunogenicity or efficacy profile with the reference product should be shared with the pharmacovigilance officers. Our results revealed that adverse reactions and inadequate treatment response to FO-FTY occurred with the same frequency (6.7%–10.4%) as the reference product (Ziemssen et al., 2022; Uzunköprü et al., 2021; Tichá et al., 2017; Bourdin et al., 2021). There were no cases of treatment discontinuation due to side effects in the first dose administration and in follow-up treatment was discontinued in only 4 (2%) cases due to side effects.

PROMs are another topic that has become more popular in recent years. Data reporting the satisfaction and adherence with the DMTs used by pwMS are rapidly taking place in the literature. Satisfaction has been reported to be higher in pwMS whom switched to FTY from injectable DMTs (Hunter et al., 2020; Fox et al., 2014) and pwMS using FTY therapy found to be more satisfied from the ones without treatment before (Mékiès et al., 2018; Hanson et al., 2013). We found that, at the end of a mean follow-up period of 2.5 years, 91% of pwMS continued treatment. In line with the literature (Hanson et al., 2013), 64% of patients reported high treatment satisfaction. According to the three expressions with the highest satisfaction, 82% of the patients stated that

the drug treated them, 76% felt better after starting the treatment, and 75% felt safe in terms of the course of the disease (Fig. 3). Treatment satisfaction and adherence to treatment are parameters that are closely related to each other. Patient compliance with prescribed medications is so important for treatment efficacy and favorable therapeutic outcome. Studies have reported that patients under FTY treatment have higher adherence compared to both injectable and oral DMTs (Earla et al., 2020; Johnson et al., 2017). In this study, 85 (%39.7) of pwMS missed at least 1 dose of FTY in the last month. It was determined that 129 (60.3%) of the patients had high adherence to treatment. Majority of patients reported that they had no problems accessing medication. This result may be related to the health insurance system in Turkey. Most DMTs are prescribed on a fully reimbursed basis and hospital procedures are also covered by insurance. Given the rising costs associated with DMTs, there has been a significant increase in the FO drug market in Turkey, in recent years.

4.1. Limitations

The limitations of our study are mostly owing to the retrospective nature of the data collection. The incidence of missing data in our analysis was very low and the patients' data were entered prospectively in the national MS registry. However, EDSS of non-scheduled visits were calculated from documented neurologic examinations and this increases variability in scoring compared to formal in-person examinations. Differences in neuroimaging protocols and scanners between centers could not be eliminated, and the investigators in the study were asked to retrospectively review the image findings from the images available in hospital databases. Therefore, only the number of T2-hyperintense lesions and the number of Gd-enhancing lesions could be used in the study. Data from patients with deteriorating disabilities and subgroup analysis of the small sample sizes require caution in interpreting. Satisfaction and engagement survey data were collected from patients on a self-reported web-based questionnaire. The authors acknowledge that this may limit the generalizability of the study, as the population without access to the Internet or with little interest in this technology may not be representative.

5. Conclusions

In summary the use of FO-DMTs that do not meet standards is a major public health concern with both clinical and economic consequences. Patients using FO-FTY that do not meet proprietary and internationally recognized specifications for quality parameters may be at risk (Correale et al., 2014). Although the gold standard is the evaluation of the solubility, bioavailability and pharmacokinetic/pharmacodynamic profile of FO-FTY, studies using real-world data are important in the evaluation of efficacy and safety in cases where these evaluations cannot be performed. In this study, real-world data analyses of one of the FO-FTYs prescribed by MS specialists in Turkey revealed results consistent with previous studies in terms of efficacy, safety, adherence and satisfaction. Human health is always the priority, so compliance to risk management plans for FO-DMTs is important for effective and safe treatment. Studies including real-world data may provide guidance to address issues related to FO-FTY use.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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