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Fingolimod real life experience in non-naive multiple sclerosis patients

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ABSTRACT

Objectives: Fingolimod is approved in Turkey or the treatment of cases of multiple sclerosis (MS) which cannot be controlled with first-line treatments. There is limited information about its efficacy and safety in clinical practice in Turkey. The aim of this study was to evaluate the efficacy and safety of fingolimod treatment in patients with relapsing-remitting multiple sclerosis who were prescribed fingolimod by the Multiple Sclerosis specialists of Bursa Uludağ University Department of Neurology.

Methods: This is a single-center observational study evaluating 142 patients using fingolimod who were followed up for at least 12 months in our center between April 2015 and October 2022. Efficacy results were evaluated in terms of mean number of attacks, annualized relapse rate, relapse-free patient rate, disease progression, clinical and radiological disease activity, and no evidence of disease activity (NEDA-3). The safety outcomes are the rates of treatment-related severe adverse events and patients' continuation rates.

Results: Over 12 months of treatment with fingolimod, the average number of attacks decreased by 94.6%, the annual relapse rate decreased by 87%, and most patients did not relapse (83.1%). Alongside this, in 76.4% of cases, there was no disability progression and in 83.3% of cases, magnetic resonance imaging (MRI) activation was not observed. Excluding replacement due to ineffectiveness, 89.4% of patients continued fingolimod therapy. Cardiac events, treatment-related infections and a decreased lymphocyte count were observed as side effects.

Conclusion: In our center, switching from first-line treatments to fingolimod was effective in reducing disease activity in patients with multiple sclerosis.

Keywords: Fingolimod, real world, observational study, relapsing-remitting multiple sclerosis

MS is a chronic autoimmune, neurodegenerative disease of the central nervous system characterized by inflammation, demyelination, and loss of axons [1]. Clinically, the disease often progresses with recurrence and improvement of neurological symptoms; this form is classified as "relapsing-remitting MS" (RRMS). The most common symptoms include visual defects, spasticity, weakness, ataxia, and sensory symptoms such as bowel and bladder incontinence, fatigue, depression, numbness, or pain. For the last two decades, treatment strategies for MS have been aimed at reducing the frequency of attacks and slowing the progression of the disease. Classical immunomodulatory treatments such as interferon

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beta (IFN β) and glatiramer acetate (GA) used in primary care (which have been found to positively change the course of the disease in the treatment of RRMS), reduce the annualized relapse rate (ARR) by approximately 30% [2]. Fingolimod is the first oral MS drug approved by multiple countries for second-line therapy and it was first used in Turkey after a license was obtained in April 2011. Fingolimod prevents lymphocytes from leaving the lymph node and thymus with lysophospholipid receptors known as sphingosine-1 phosphate. Randomized clinical controlled trials and real-world data have demonstrated the efficacy of fingolimod on attack frequency and magnetic resonance imaging. Improvement was shown for relapse, radiologic activity, disability progression and brain atrophy compared with IFN β-1a and placebo [3-5]. Clinical experience in day-to-day practice will be beneficial for physicians and other healthcare professionals caring for people with MS. In this study, we present the outcomes of patients with RRMS treated with fingolimod for at least 12 months as a single-center clinical trial.

METHODS

Study Design

This study is a single-center, observational, retrospective review of the medical records of 142 patients treated with fingolimod 0.5 mg as part of standard clinical practice in our center between April 2015 and October 2022. Patients who started fingolimod at least 12 months ago and had no missing data were included were included in the study. The local ethics committee (Uludag University Faculty of Medicine Clinical Tesearches Ethics Board) reviewed and approved the study protocol (2022-16/35).

Study Population

The study population consists of patients with RRMS over 18 years under the treatment of neurologists specializing in MS. Patients were included in the study if they were diagnosed with RRMS according to the revised 2017 McDonald or earlier criteria at least 12 months before initiation of fingolimod and if they had continued fingolimod treatment for at least 12 months without interruption (<4 weeks). Before starting fingolimod, patients had to have been under follow-up for at least six months.

Patients were divided into two subgroups based on disease-modified therapy (DMT) use before fingolimod initiation: those who had received one DMT before and those who had received two or more prior DMTs. Those who had switched from induction therapies to fingolimod were not grouped due to the low number of patients. The patients were evaluated in four similarly distributed groups (12-23, 24-35, and ≥48 months) according to the duration of use. The groups were similarly distributed when grouped according to the number of previous treatments (one or two and above), age at diagnosis, first EDSS, and previous ARR.

Outcome Criteria

As outcome measures under fingolimod, the following were evaluated: ARR, rate of patients without relapse, rate of patients without disability progression (one point increase above Expanded Disability Status Scale (EDSS) baseline level, 1.5 point increase if EDSS 0), proportion of patients without new t2 lesion or new enhancement lesion on MRI and proportion of patients without both relapse and disability progression, and MRI activation. Relapses were defined as the appearance of new neurological deficits occurring at least 30 days after the onset of a previous event and lasting more than 24 hours in the absence of fever or infection. The ARR was calculated as the number of relapses divided by the exact (decimal) number of years on fingolimod treatment.

Sex and age were evaluated as demographic data. Clinical features included reasons for starting fingolimod treatment, DMTs used before fingolimod, final EDSS scores at the start, end, or if ongoing, disease duration before fingolimod initiation, the total number of attacks before and after fingolimod, and MRI activation. In terms of safety data, serious adverse events that required discontinuation, change or interruption of treatment were evaluated.

Statistical Analysis

The Shapiro-Wilk test was used to examine the data to determine whether or not it was normally distributed. The results were presented as mean±standard deviation, median (minimum-maximum), or frequency and percentage. Normally distributed data were compared using independent samples t-test or

one-way ANOVA. Kruskal Wallis and Mann-Whitney U tests were used for non-normally distributed data. The Bonferroni test was used as a multiple comparison test. Paired data were analyzed using the Paired t-test or Wilcoxon signed rank test. Categorical variables were compared using Pearson's chi-square test and Fisher's exact test between groups. P<0.05 was considered as the significance level. Statistical analyses were performed with IBM SPSS ver.28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.).

RESULTS

Population and Pre-Fingolimod Data

A total of 142 patients, 106 women (74.6%) and 36 (25.4%) men, were included in the study. The mean age at which the patients were diagnosed was 31.26±8.83 (18-60) years and the mean time from diagnosis to start of fingolimod treatment was 76.55±51.58 (8-244) months.

Different DMTs were used in 142 patients before fingolimod use. 98 patients (69%) used one DMT and 41 patients (28.9%) used 2 or more. In three patients was switched to fingolimod for de-escalation. The most commonly used DMT is IFN β. Their average usage time was 48.97±32.1 (5-189) months. The mean total number of attacks was 2.64±1.32(1-12), and the number of attacks was 1.33±0.92(0-5) when using DMT at the last use (at least six months). The ARR was 0.61±0.50 (0.11-3), and the ARR in the latest DMT was 0.47±0.48 (0-2.4). Disease onset was mean EDSS 1.18±0.92 (0-6.5), and mean fingolimod onset was 2.02±1.38 (0-6). The most frequently cited reasons for switching to fingolimod are as follows: the ineffectiveness of previous therapy, followed by adverse events or patient request, and de-escalation therapy (Table 1).

Usage Process and Subgroups

The mean duration of fingolimod use was

Table 1. Baseline data before fingolimod

		n (%) / mean (SD)
All previous disease-modifying therapies*	Interferon beta	98 (50.7%)
	Glatiramer acetate	58 (30.1%)
	Teriflunomide	28 (14.5%)
	Dimethyl fumarate	6 (3.1%)
Most recent previous disease-modifying therapy*	Interferon beta	57 (41.3%)
	Glatiramer acetate	50 (36.2%)
	Teriflunomide	25 (18.1%)
	Dimethyl fumarate	6 (4.4%)
Total number of attacks (mean)	Total	2.64±1.32
	In the last previous DMT	1.33±0.92
Annualized relapse rate	Total	0.61±0.50
	In the last previous DMT	0.47±0.48
EDSS	Disease onset	1.18±0.92
	Fingolimod onset	2.02±1.38
Reason for switch	Ineffectiveness	115 (81%)
	Adverse events or patient request	26 (16.2%)
	After induction therapy	3 (2.1%)

*Except for induction treatments

Descriptive statistics were given as mean±standard deviation or frequency (n) with percentage.

34.15±16.17 (12-85) months. In contrast, the distribution according to age at diagnosis (P=0.851) and first EDSS (P=0.201) was similar in the subgroups according to the time from diagnosis to fingolimod use (<24 months, 24-48 months, 48-72 months, 72-96 months, and >96 months), as expected, the number of attacks per previous year (P<0.001) and the number of previous attacks (P<0.001) increased as the time between diagnosis and start of fingolimod treatment increased.

Efficacy Results

The mean number of attacks after starting fingolimod treatment in all patients was 0.15±0.40 (0-2) compared to previous DMT use (1.33±0.92(0-5)) with an 88.8% reduction (P<0.001), total mean before fingolimod (2.64±1.32(1-12)) compared to 94.6% (P<0.001). The rate of patients who did not have an attack during fingolimod use was 83.1% in all patients. The mean ARR of all patients decreased from 0.61±0.5 to 0.08±0.22 before and after fingolimod by 87% (P<0.001). EDSS mean at disease onset was 1.18±0.92, 2.08 ± 1.35 at fingolimod onset and 2.28 ± 1.72 at the end of fingolimod treatment. There was a significant effect on slowing down the progression of the disability when these were compared (P=0.015). No disability progression was observed after fingolimod in 76.4% (n=109) of all patients (Fig. 1).

MRI follow-ups of 28 patients were unsuitable for

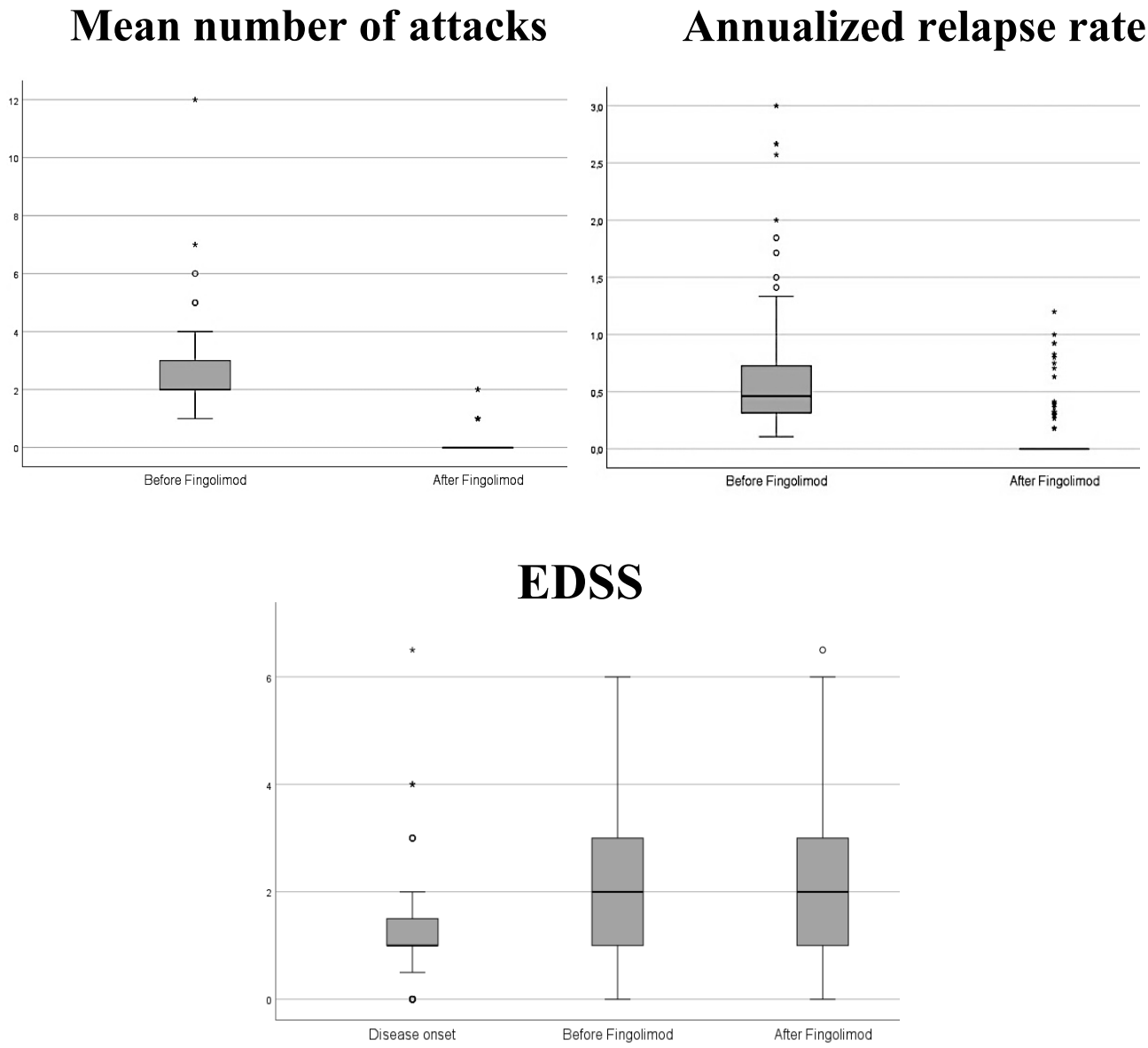

Fig. 1. Number of attacks, ARR and EDSS changes before and after fingolimod.

Table 2. **Subgroup analyzes**

		n	Annualized relapse rate Median (Minimum-Maximum)	Relapse-free % n (%)	EDSS progression-free % n (%)	MRI activity-free % n (%)	NEDA-3 % n (%)
Sex	Female	106	0.00 (0.00-1.20)	89 (84%)	80 (75.5%)	70 (83.3%)	55 (51.9%)
	Male	36	0.00 (0.00-0.80)	29 (80.6%)	29 (80.6%)	25 (83.3%)	19 (52.8%)
	P value		0.664	0.637	0.533	1.000	0.926
Disease onset age (year)	<25	40	0.00 (0.00-0.92)	35 (87.5%)	32 (80%)	25 (78.1%)	23 (57.5%)
	25-35	59	0.00 (0.00-1.20)	46 (78%)	46 (78%)	37 (78.7%)	28 (47.5%)
	>35	43	0.00 (0.00-1.00)	37 (86%)	31 (72.1%)	33 (94.3%)	23 (53.5%)
	P value		0.423	0.382	0.667	0.113	0.603
Number of previously used DMT*	1	98	0.00 (0.00-0.80)	83 (84.7%)	77 (78.6%)	66 (86.8%)	52 (53.1%)
	≥2	44	0.00 (0.00-1.20)	35 (79.5%)	32 (72.7%)	29 (76.3%)	22 (50%)
	P value		0.360	0.449	0.446	0.155	0.743
EDSS before fingolimod	<3	100	0.00 (0.00-0.92)	84 (84%)	81 (81%)	67 (84.8%)	45 (45%)
	≥3	42	0.00 (0.00-1.20)	34 (81%)	28 (66.7%)	28 (80%)	23 (54.8%)
	P value		0.518	0.658	0.065	0.525	0.288
Usage Period (months)	12-23	47	0.00 (0.00-1.20)	39 (83%)	35 (74.5%)	27 (75%)	22 (46.8%)
	24-35	30	0.00 (0.00-0.83)	25 (83.3%)	22 (73.3%)	22 (88%)	17 (56.7%)
	36-47	35	0.00 (0.00-0.32)	26 (74.3%)	26 (74.3%)	31 (93.9%)	22 (62.9%)
	≥48	30	0.00 (0.00-0.18)	28 (93.3%)	26 (86.7%)	15 (75%)	13 (43.3%)
	P value		0.270	0.243	0.551	0.109	0.344
Diagnosis-fingolimod onset time (months)	12-23	19	0.00 (0.00-0.40)	16 (84.2%)	17 (89.5%)	12 (92.3%)	9 (47.4%)
	24-47	29	0.00 (0.00-1.00)	25 (86.2%)	22 (75.9%)	25 (96.2%)	18 (62.1%)
	48-71	25	0.00 (0.00-0.92)	21 (84%)	18 (72%)	18 (81.8%)	16 (64%)
	72-95	27	0.00 (0.00-0.92)	24 (88.9%)	21 (77.8%)	13 (68.4%)	17 (63%)
	≥96	42	0.00 (0.00-1.20)	32 (76.2%)	31 (73.8%)	27 (79.4%)	14 (33%)
	P value		0.640	0.738	0.686	0.110	0.260

*Three patients who were switched to fingolimod as de-escalation therapy were excluded. (2 of these three patients did not have an attack)

evaluation. Of 114 patients, 83.3% (n=95) had no MRI activity. New/growing T2 lesions were detected in 16.4% (n=19). New Gd(+)T1 lesions were detected in 11 (10%) of them. NEDA-3 was achieved in 52.1% (n=74) of patients in terms of the number of attacks, EDSS progression, and absence of all MRI activity.
In terms of effectiveness evaluation, five parameters (ARR, relapse-free rate, EDSS progression-free rate, MRI activity-free rate, and achievement rate of NEDA-3) were evaluated in terms of five different group characteristics (sex, disease onset age, number of previously used DMTs, usage period, diagnosis-fingolimod onset time). No statistically significant difference was found in the outcome parameters specified in all subgroup analyses (Table 2).

Sustainability and Safety Implications

One hundred and nine (76.8%) patients continued the treatment. Treatment was discontinued due to side effects in 4.2%, ineffectiveness in 14.1%, both 1.4%, pregnancy in 2.1%, and patient request in 1.4% of cases. Excluding 11 patients whose treatment was changed due to ineffectiveness at follow-up up to 24 months, 80.5% of patients continued fingolimod treatment. The rates of adverse events leading to treatment discontinuation and treatment continuation were 10.6%; 61.7% at the end of the first year, 6.5%; 71.4% at the end of the second year, 4.5%; 72.3% at the end of the third year, and 4.2%; 76.8% at the end of the fourth year, respectively. Treatment non-compliance and side effects were most common in the first year. Serious adverse event rates were as follows: cardiac events 3.5% (three bradycardia, one atrioventricular arrhythmia, one acute coronary syndrome; one patient with bradycardia continued after treatment discontinuation, others discontinued), infection 1.4% (two herpes zoster infections; treatment discontinued), transient lymphopenia (<200/µL) 7% (all continued after treatment interruption), macular edema 2. 1% (treatment discontinued), transient elevation of liver transaminase levels 0.7% (three-fold or more increase from baseline) (all continued after treatment interruption), grade 2 or higher high blood pressure 2.8% (three discontinued, one continued after interruption) and other 2.8% (flushing, etc.; all discontinued). Except for two herpes zoster infections, no opportunistic infections, including progressive multifocal leukoencephalopathy (PML), were observed.

DISCUSSION

The efficacy of fingolimod treatment in MS disease has been demonstrated in randomized controlled studies [3-5]. Real-world data on fingolimod obtained after use is very instructive in clinical practice. In multicenter studies, variable cohort number of cases and fingolimod exposure time were reported. The following are examples of data on countries, case numbers and follow-up periods from a selection of studies: UK 209, 12 months; Poland 253, 42 months; Germany 4229, 7 years; Spain 804, 26.4 months; Italy 414, 22.7 months; Hungary 570, up to 5 years; Czech Republic 237, 3.5 years [6-13]. In our country, there are multicenter studies evaluating the 5-year effect on cognition, comparing natalizumab (NTZ) and ocrelizumab treatment in the first and second year, and reporting two-year efficacy and safety results [14-16].

MS most commonly affects young adults aged 20-30, with a male to female ratio of approximately 3:1 [17]. The gender distribution in our study was similar to the general distribution of the disease. The gender factor did not affect our preference towards fingolimod treatment.
DMTs used before fingolimod in our cohort were mostly IFN β (50.7%), followed by GA (30.1%) as in many other studies [6, 7, 10-12]. Some studies have evaluated the efficacy of fingolimod after induction therapy at different rates or in naive patients [10-12]. However, there were no naive patients included in this study and three patients used fingolimod after induction therapy. In our study, the rate of previous single DMT use was 69%. The most important reason for switching to fingolimod in our cohort was the ineffectiveness of previous DMTs, with a higher rate (81%) than in other studies. These rates may vary between populations, depending on regional drug reimbursement policies and the preferences of clinicians or patients. [6, 10, [12].

The rate of patients who did not relapse during fingolimod use was 83.1%, which is similar to the literature. [3][6-12] Studies with naive and post-NTZ patient groups have shown that these results are higher in naive patients and lower in post-NTZ patients [10, 12].

Compared to pre-treatment, the ARR decreased by 87%, similar to other studies (65%-95.6%) [6, 7, 9, 11, 12]. Fingolimod significantly reduces the ARR regardless of age at diagnosis, age at onset of fin-

golimod, gender, number of previous DMTs used, and duration of fingolimod exposure. ARR reduction rates increase with duration of use in studies and generally range from 74.1% to 90%. With the addition of patients who had previously received NTZ treatment, these rates were lower (65% [11], 77% [12]) and higher in naive patient groups (91.1%-95.6%) [10]. In our study, it was not possible to evaluate these rates due to the small number of patients receiving NTZ treatment and the lack of a naive patient group. However, switching to fingolimod treatment in the early stages of the disease may have been more effective in the slightly higher reduction rate in ARR compared to other studies (6.4 years).

MRI activity was absent in 83.3%. There was no significant difference between MR activity and gender, age at disease onset and other sub-parameters. Compared to other studies, the positive effect on radiologic activation in this study was slightly higher than expected [6, 10, 11, 15].

EDSS scores were slightly lower than in other studies (2.08 ± 0.2) and the proportion of patients with no increase in EDSS scores was similar (76.4%) [7, 12].

In the analysis of patients with complete MRI data, the rate of NEDA-3 was 52.1%, slightly below the literature data (52.4%-67.9%). [7, 11].

Considering reasons other than ineffectiveness (14.1%), the rate of adherence and persistence was lower than in the literature at 80.5% (81.2%-93.9%) [6-8, 10, 13]. The rate of treatment ineffectiveness has generally been reported as approximately 10% in studies, and these are usually patients who have been treated with more than one DMT previously. However, we did not detect a significant relationship between previously used DMTs and treatment ineffectiveness. The most common reasons for temporary interruption are adverse effects and patient decisions. In comparison, the reasons for permanently stopping treatment are side effects and lack of effectiveness [10, 13]. We determined the reasons for permanent discontinuation as ineffectiveness (14.1%) and side effects (4.2%). The most common side effects reported are cardiac event, infections, liver enzymes increase, and lymphopenia < 200 cells/µl. PML or macular edema are usually unspecified or minor [10, 12, 13, 18]. Side effects requiring discontinuation or interruption of treatment in our cohort were similar to the literature. Basal cell skin cancer was detected in one patient.

Our cohort is slightly above the expected range for the overall RRMS diagnosis age in terms of disease-onset distribution. However, compared to many other studies, patients in our cohort were switched to fingolimod at a younger age: 31.2 (32.6 to 42.8), had a lower EDSS before: 2.08 (2.1 to 3.6) and a shorter time from diagnosis or first clinical symptom to drug exposure: 6.4 (7.5 to 10.3) [6, 9, 10, 12, 13]. Despite all this, no significant difference was found in the outcome parameters, except for MRI activity and ARR [6, 9, 10, 12]. In addition, when the first year from the disease diagnosis was excluded, the effect did not decrease as the time from the diagnosis to fingolimod extended. The FREEDOM and FREEDOM II studies have demonstrated the importance of early initiation of therapy to protect against long-term disease-related disability [4, 5]. When comparing early fingolimod treatment with delayed treatment, there was a significant 45% reduction in ARR and a 24% reduction in the risk of confirmed disability progression. In addition, fingolimod efficacy is higher in naive patients and lower in de-escalation therapy [10-12]. Due to the variable health policies in Turkey, fingolimod treatment is not paid for the first year of diagnosis and special permission is required for its use. Therefore, it was not possible to follow a naive patient group in our study. Alongside this, since the number of patients who de-escalation was too small, this data was not included in the evaluation.

Limitations

It was not possible to evaluate NEDA-4 because the cognitive evaluation records were not complete. Since the MRIs were not optimal for 28 patients, they could not be assessed radiologically. Aside from the patients whose treatment was interrupted or discontinued, we could not reveal the complete profile because the side effect records were not detailed.

CONCLUSION

MS is a progressive disease, and starting the right DMT at the right time is very important in preventing the progression of the disease. Turkish patients across the entire cohort and across all subgroups evaluated saw significant benefits from fingolimod therapy, regardless of age, gender, or having previously used

DMTs. The most significant disease-stopping power of fingolimod is seen in untreated patients, but it was not possible to evaluate this situation in our study due to certain limitations. That being said, when considered together with other studies, there was no difference in efficacy. However, patients who had previously received different DMTs were younger, had a lower disability, or were switched to fingolimod treatment in a shorter time. This suggests that although fingolimod has the most significant disease-stopping power in naive patients, it is also effective in patients who have used other DMTs before, regardless of the number of DMTs used, age at diagnosis, and disease duration. Real-world data studies with larger subgroup analyses are required in this regard. Analysis of fingolimod adverse events in a real-world setting confirmed a long-term, favorable profile of both efficacy and safety from study start to study end. Our results support the ever-increasing evidence proving the long-term effectiveness and positive benefit/risk balance of fingolimod in RRMS in a real-life setting.

Authors' Contribution

Study Conception: FS; Study Design: FS; Supervision: ÖFT; Funding: ERK, ÖFT; Materials: FS, ERK; Data Collection and/or Processing: FS, GÖ; Statistical Analysis and/or Data Interpretation: FS, GÖ; Literature Review: FS; Manuscript Preparation: FS and Critical Review: ERK, ÖFT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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