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A 12-month, Open Label, Multicenter Pilot Study Evaluating Fingolimod Treatment in terms of Patient Satisfaction in Relapsing Remitting Multiple Sclerosis Patients - FINE Trial

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ABSTRACT

Introduction: To assess satisfaction and quality of life in patients with relapsing–remitting multiple sclerosis (RRMS) who were receiving fingolimod (0.5 mg/day) for 12 months as a second-line treatment after switching from injectable agents.

Methods: Patients aged 18–65 years with RRMS who fulfilled the eligibility criteria were enrolled from 16 centers throughout Turkey. Treatment Satisfaction Questionnaire for Medication and 36-item Short-Form Health Survey were completed at baseline and four visits to assess patient satisfaction and quality of life.

Results: Forty-two patients (62% male; mean age: 35.7±9.4 years) were eligible for inclusion. Patient satisfaction scores at the end of the study (44.7±9.9) were significantly higher than those at baseline [32.0±9.9; ($p<0.001$)]. The only significant increase in the quality of life survey was in the emotional aspect ($p=0.019$). There were 124 adverse events and none of the five serious adverse events noted was considered drug-related.

Conclusion: Large-scale comparative studies performed with disease specific quality of life instruments will allow more information on this issue.

Keywords: Multiple sclerosis, fingolimod, patient satisfaction, quality of life

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INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS). Its primary characteristics are inflammation and damage to myelin sheaths, oligodendrocytes, axons, and neurons, and it mostly affects young adults.

According to global estimates of the Multiple Sclerosis Foundation, more than 2 million people are affected by MS (1,2). Koch-Henriksen and Sørensen performed a large meta-regression analysis from the literature to investigate worldwide changes in demographic patterns of MS incidence and prevalence (2). The prevalence of the disease is higher among Caucasians and the female to male ratio of 2:1 has risen to 4:1 over recent years (3). Its etiology remains obscure; however, MS is believed to be caused through an intricate relationship between infectious agents and genetic and environmental aspects.

Multiple sclerosis presents in four forms; the most frequently seen is relapsing–remitting MS (RRMS), which is diagnosed in 85% of patients with MS at onset. RRMS is characterized by more neuroinflammation than neurodegeneration; relapses and the generation of new lesions, which are visible with magnetic resonance imaging (MRI), particularly with contrast-

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enhancing T1-weighted lesions in particular; and worsening symptoms, followed by periods of stability. Over time, residual disabilities accumulate leading to permanent disability, and approximately 50% of people with untreated RRMS show transition to secondary progressive MS within a decade of the initial diagnosis, which is distinguished by its more extensive neurodegeneration, compared with inflammation (4). The remaining two presentations are primary progressive MS, which has no clear relapses or remissions and is diagnosed in approximately 10% of patients at onset, and progressive–relapsing MS, which affects 5% of patients.

Symptoms of the disease vary in a wide spectrum. The new MS diagnostic criteria, commonly known as the McDonald criteria, are very important because they enable early diagnosis and treatment through disease-modifying drugs (DMDs), which seem most effective when started early (5). Delayed treatment could mean permanent neurologic deficiency. There is no cure for MS and drugs used are aimed at reducing relapse frequency and slow disease progression, but they do not address individual symptoms.

Disease-modifying drugs used in the treatment of MS specifically target the inflammatory and immunologic processes that underpin the pathogenesis of MS, as such their primary indication has been RRMS, but more recently, clinically isolated syndromes have also been included in the treatment profile. Interferon-β1b was the first Food and Drug Administration (FDA)-approved treatment for MS in 1993. Since then, several intravenous, intramuscular (IM), subcutaneous injection, and oral DMDs have been approved and licensed by the FDA and European Medicines Agency (4). Fingolimod (FTY720) was the first FDA-approved oral DMD for MS (6). Its therapeutic effect on the immune system is brought about through the selective downmodulation of sphingosine 1-phosphate receptors on naïve and central memory T and B cells within lymph nodes, thereby inhibiting their dissemination to other tissues including the CNS, but effector memory T cells are spared, which maintains their vital immune functions. Hence, it functions by redistributing lymphocytes to lymphatic tissues instead of destroying lymphocytes as can be observed with cytotoxic agents (7,8).

Long-term conservation of patient satisfaction and quality of life (QoL) should be considered as critical markers of clinical success in chronic debilitating diseases such as MS. Therefore, we aimed to determine patient satisfaction and QoL in patients with RRMS receiving fingolimod (0.5 mg/day) for a period of 12 months after switching from injection treatments.

METHODS

The present prospective multicenter study included patients with RRMS from 16 centers throughout Turkey who were treated with fingolimod for 1 year to investigate patient satisfaction and QoL. Ethics committee approval was obtained before commencing study procedures.

Upon signing informed consent forms, patients entered a screening phase to be evaluated for eligibility (baseline). The inclusion and exclusion criteria were as defined in the manufacturer's clinical trial that set out to establish the health outcomes of fingolimod (ClinicalTrials.gov Identifier: NCT01578330). Pregnant or nursing women were also excluded from the study. There was no randomization.

Eligible patients received their first doses and were observed during the 6-h monitoring period. Efficacy and safety evaluations were performed at weeks 4, 8, 16, 24, 36, and 52. The following information was recorded during the screening visit: patient age, sex, medical history, allergy history, weight, height, education level, employment, smoking status, and substance abuse. In addition, MS-related characteristics including year of disease onset, MS relapses, previous therapies for the treatment of the disease, concomitant treatments, and reason for inclusion in the study were also recorded. Other medications used to treat MS-related symptoms were also documented.

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) and 36-item Short-Form Health Survey (SF-36) were used to assess patient satisfaction and QoL. The TSQM-9 is a reliable and valid method for evaluating key aspects of patient satisfaction with treatment. The TSQM-9 version 1.4 consists of 14 items with a 5- to 7-point bipolar scale, which are combined to produce four summary scores: effectiveness, adverse effects, convenience, and overall satisfaction. Higher scores signify higher levels of satisfaction for all questions and summary scores (9).

Health-related QoL (HRQoL) was evaluated using the SF-36, which is a self-reported questionnaire that measures eight domains of health and has been extensively used and described elsewhere in the literature (10). Higher scores are suggestive of a better QoL. The SF-36 provides two summary scores: the Mental Component Summary and Physical Component Summary.

Statistical Analysis

Descriptive analyses including patient reported outcomes at baseline and screening visits (TSQM and SF-36) were performed for all data collected. Comparisons between baseline and follow-up visits were performed using the Chi-square test for categorical variables and t-test for continuous variables. The McNemar test was used for paired categorical outcomes, and the Wilcoxon signed-rank test was used for paired continuous outcomes. It should be noted that p-values obtained from these comparisons were used for descriptive purposes and were considered for defining a formal base for determining factors included in the statistical analysis models. Unless otherwise stated, all statistical analyses were conducted with the significance level of 0.05 against the two-sided alternative hypothesis.

RESULTS

Forty-five patients were screened from 16 centers across Turkey and 42 were eligible for the study. Among 42 enrolled patients, 5 patients were withdrawn from the study due to major protocol deviations, 2 patients were excluded due to pregnancy and candidiasis. Therefore, 35 patients completed the study.

Table 1. Baseline demographic characteristics of the study population

		Fingolimod 0.5 mg n=42
Age (years)	Mean±SD	35.7±9.4
Gender – n (%)	Male	26 (61.9%)
	Female	16 (38.1%)
Educational status – n (%)	Elementary	12 (28.6%)
	High school	11 (26.2%)
	University	19 (45.2%)
Occupational status – n (%)	Civil servant	4 (9.5%)
	Retired	2 (4.8%)
	Unemployed	18 (42.9%)
	Private sector	8 (19.0%)
	Worker	6 (14.3%)
	Self-employed	4 (9.5%)

SD: standard deviation

Patients' mean age was 35.7±9.4 years (range, 18–58 years), and male patients constituted most of the population (61.9%). Medical history revealed that all of the 42 patients was receiving treatment for MS at baseline. Forty percent of the patients had previously received interferon-β1b, 35.6% received interferon-β1a, and 24.4% received glatiramer acetate; all had discontinued medication because of inadequate efficacy. The demographic characteristics of participants are presented in Table 1.

The Treatment Satisfaction Questionnaire for Medication and SF-36 questionnaires were completed in five visits including the baseline visit. The mean TSQM-9 score at the end of the study (44.7±9.9) was significantly higher than that obtained at baseline (32.0±9.9; p<0.001). TSQM-9 scores of patients are presented in Table 2. The assessment of SF-36 scores demonstrated that a statistically significant increase was only observed with emotional role (p=0.019). Patients' SF-36 scores recorded during the study are shown in Table 3.

Overall, 124 adverse events (AEs) were documented in 31 patients. Urinary infections (12.9%), upper respiratory system infections (10.5%), and hepatic enzyme increase (7.3%) were the most frequent AEs, followed by a decrease in lymphocyte count, MS attack, and headache. Two incidences of bradycardia were noted. AEs with a frequency of >1 are given in Table 4. Two AEs were grade 3, and 21 AEs were suspected to be drug-related. Four serious adverse events (SAEs) were reported in four patients: MS aggravation, fracture, pregnancy, and middle ear surgery; none of them were suspected to be drug-related. Similarly, other safety evaluations including clinical laboratory examinations, vital signs, physical, and ophthalmological examinations revealed no risk related to the study medication. Drug was discontinued in two patients who were withdrawn from the study; one patient with oral candidiasis and the other due to pregnancy. No deaths occurred during the study.

Table 2. TSQM scores of patients during the study

	TSQM Scores Mean+SD
Baseline	32.0+9.9
Week 4	42.3+7.6
Week 16	45.4+8.3
Week 24	44.4+8.2
Week 52*	44.7+9.9

*p <0.001
TSQM: treatment satisfaction questionnaire for medication; SD: standard deviation

DISCUSSION

Multiple sclerosis is a life-long disease with an unpredictable disease course and obscure etiology that affects the physical and mental health of patients. There are no preventive measures and no cure is available; the treating physicians' main concerns are directed toward selecting the best treatment option that is efficient and safe, as well as providing the utmost patient satisfaction and QoL.

Fingolimod was shown as an effective DMD in several studies with an acceptable safety profile. Phase III, controlled clinical studies with large sample sizes and more than 1000 patients with RRMS demonstrated that fingolimod significantly reduced annualized relapse rates, MRI measures, and brain volume loss compared with placebo and IM interferon -β1a and that its beneficial properties were retained in long-term extension studies (11,12,13,14,15,16).

Table 4. Adverse events that occurred during the study*

Adverse Event	N
Urinary infection	16 (12.9)
Upper respiratory infection	13 (10.5)
Increase of hepatic enzymes	9 (7.3)
Decrease in lymphocyte count	7 (5.6)
Multiple sclerosis attack	6 (4.8)
Headache	6 (4.8)
Elevated low-density lipoprotein	4 (3.2)
Tooth abscess	3 (2.4)
Nausea	3 (2.4)
Toothache	3 (2.4)
Herpes Simplex	3 (2.4)
Incontinence	3 (2.4)
Bradycardia	2 (1.6)
Cold	2 (1.6)
Gastritis	2 (1.6)
Constipation	2 (1.6)
Vertigo dizziness	2 (1.6)
Fungal infection	2 (1.6)

*Adverse events with a frequency >1occurrence are shown in the table.

Table 3. SF-36 scores of patients during the study

Mean +SD	Physical Function	Physical Role	Pain	General Health	Vitality	Social Function	Emotional Role	Mental Health
Baseline	62.5+29.1	45.6+41.0	59.7+24.8	47.0+22.4	26.1+18.4	61.7+29.3	41.0+38.5	29.6+19.4
Week 4	59.7 +30.9	53.6+43.8	61.7+23.7	47.8+20.5	28.9+23.1	61.8+26.4	48.4+43.0	31.5+17
Week 16	67.0+25.6	58.6+43.3	63.7+23.7	50.7+21.9	36.5+22.6	63.6+29.7	51.7+42.5	35.9+18.7
Week 24	57.9+31.1	47.8+46.0	62.6+24.8	48.5+20.3	35.2+22.9	60.6+29.9	54.8+43.3	36.5+17.1
Week 52	59.5+34.3*	46.9+44.7*	65.9+23.3*	50.8+21.9*	33.1+20.0*	65.8+29.1*	52.7+46.2**	36.3+20.3*

* Not significant
**p =0.019
SD: standard deviation

Furthermore, large-scale studies in real-world settings showed that patients with RRMS who switched from injectable therapies to fingolimod had significantly lower rates of relapse or disability progression and also showed better treatment adherence than those who switched to other injectable treatments (17,18,19,20,21). Additional data exist suggesting that fingolimod is appropriate for patients who switch from natalizumab due to John Cunningham virus seroconversion, which causes progressive multifocal leukoencephalopathy and reduced response or tolerance (22,23).

Regarding safety concerns, Kappos et al. (24) reviewed the FREEDOMS study and patients who received fingolimod (n=3476) in phase II and III studies and extension studies thereof and concluded that although infrequent SAEs occurred, the risk of infections, malignancies, or serious cardiovascular events was no greater than that with placebo. Analyses of data from important phase III trials showed that fingolimod caused temporary cardiac changes, but these were largely asymptomatic. Symptomatic bradycardia or second- degree atrioventricular block have been reported in a very small minority of patients (<1% for both) with 0.5 mg fingolimod (25). Additionally, a study in 2282 patients RRMS who had cardiac conditions reported that cardiac issues observed when initiating fingolimod were similar to those in earlier controlled studies, regardless of whether patients with previous cardiac conditions were included (26).

Fingolimod is rarely, but significantly, related to the development of herpes zoster infections and their associated neurologic complications (4). Patients with no history of chickenpox or those who have not been vaccinated against varicella zoster virus (VZV) should be checked for VZV antibodies, and patients who are antibody- negative are recommended for vaccination prior to starting treatment.

In our study, no serious AEs or deaths were reported; only two patients were withdrawn from the treatment, and neither was considered treatment-related. Accordingly, fingolimod treatment was considered safe and well-tolerated. The safety profile of fingolimod provided from this study is in line with data obtained from previous studies.

Long-term conservation of HRQoL in chronic debilitating diseases such as MS should be regarded as an important landmark of therapeutic success. Poor recovery after relapse, development of new deficits, and the intensifying nature of MS inhibit daily activities and have a negative impact on patients' well-being. Several studies have identified that patients with MS have lower QoL. The value of measuring HRQoL is being increasingly appreciated in the follow-up of patients with chronic diseases, and this is especially relevant with MS (27).

Patients in the Evaluate Patient OutComes (EPOC) study reported significantly better improvements in most outcomes than those who continued with injectable DMDs after changing to fingolimod therapy for 6 months (28). In the EPOC trial, 1053 patients were randomized to change to fingolimod or remain on injectable disease-modifying treatments (iDMT). Switching to fingolimod provided superior changes in TSQM Global Satisfaction scores compared with those of patients who stayed on iDMTs ($p<0.001$). Similarly, with the exception of glatiramer acetate with TSQM adverse effects subscale ($p=0.111$), every TSQM subscale score improved after switching to fingolimod (all $p<0.001$). Moreover, SF-36 scores were better with fingolimod compared with interferon-β1b (8).

The present study also showed that there was a significant increase in the mean TSQM-9 scores after 12 months of treatment ($p<0.001$). However, the increase in emotional aspect was the only statistically significant ($p=0.019$) SF-score, which may have resulted from the small sample size.

The small sample size and absence of a comparator drug are the main limitations of the present study. Further, the use of MS-specific instruments could discern true changes in the HRQoL of patients with MS.

Future large-scale comparative studies that use disease-specific QoL instruments would allow a more comprehensive understanding of QoL and treatment satisfaction in patients with RRMS.

Ethics Committee Approval: Ethics committee approval was received for this study from Erciyes University Ethics Committee for Clinical Research (03.01.2012/decision no 2012/03).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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