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Experience with Fingolimod in Clinical Practice

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Abstract

Aim—To report experience with fingolimod in clinical practice.

Design/Methods—Patients in an academic medical center who were prescribed fingolimod from October 2010 to August 2011 were identified through the electronic medical record and followed for 12 months after fingolimod initiation. Adverse effects, clinical measures, MRI data, and quality of life measures were assessed.

Results—Three hundred seventeen patients started fingolimod. Eleven patients were treatment naïve (3.5%) and 76 (24.0%) had remote disease modifying therapy use prior to fingolimod. One hundred fifty-one (47.6%) switched because of patient preference and 79 (24.9%) switched because of breakthrough disease. About 11.6% transitioned from natalizumab. Follow-up data were available for 306 patients (96.5%) with mean follow-up time 332 days. Fingolimod was discontinued in 76 of 306 patients (24.8%) at mean 248 days after fingolimod start. Discontinuation most often was due to adverse effects (n=40) or breakthrough disease (n=22). Among patients who started fingolimod with available 12 month follow-up data, 267 (87.3%) remained relapse free and 256 (83.7%) had no relapses or gadolinium enhancement. Time to first relapse occurred at mean 282 days after fingolimod initiation. Quality of life measures remained stable at follow-up.

Conclusions—Fingolimod was discontinued at a higher rate in clinical practice than in clinical trials. Discontinuation was primarily due to adverse effects or breakthrough disease. Disease activity was adequately controlled in most patients who started fingolimod. This clinical practice

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cohort is consistent with efficacy data from phase 3 trials and describes the most common tolerability issues in clinical practice.

Keywords

Multiple Sclerosis; Fingolimod; Clinical Practice; Disease Activity; Tolerability

Introduction

Fingolimod (FTY720, Gilenya® Novartis pharmaceuticals) was the first oral disease modifying therapy (DMT) approved by the U.S. Food and Drug Administration (FDA) to reduce relapses and disability progression in relapsing forms of multiple sclerosis (MS). Fingolimod is a sphingosine 1-phosphate receptor (S1PR) modulator that inhibits lymphocyte egress from lymph nodes, presumably interrupting the recirculation of autoreactive T- and B-lymphocytes to the central nervous system (CNS). These immunologic effects are thought to account for the benefits in MS (1–3), though other mechanisms may also exist. Three phase 3 clinical trials demonstrated the efficacy of fingolimod, measured by decreased annualized relapse rate (ARR) and MRI measures of disease activity, as compared to placebo (4, 5) and intramuscular (IM) interferon (IFN) beta 1-a (6).

Adverse effects (AEs) observed in patients receiving fingolimod during phase 3 clinical trials included elevation of liver function tests (LFT), headache, decreased resting heart rate and slowing of the atrioventricular (AV) conduction, herpes infections, and macular edema. A reduction of circulating lymphocytes is expected in fingolimod-treated patients. The FDA made several recommendations for the safe use of fingolimod in MS patients with revised recommendations for cardiovascular monitoring in May 2012 (7). Baseline complete blood count (CBC), LFT panel, and ophthalmological evaluation were recommended for all patients starting fingolimod. Additionally, a six-hour observation period was recommended to monitor for signs and symptoms of bradycardia following the first dose, including hourly heart rate and blood pressure measurements for all patients starting fingolimod. An electrocardiogram (EKG) was recommended before dosing and at the end of the observation period. Extended monitoring for patients at higher risk for bradycardia includes continuous EKG monitoring overnight. Varicella zoster virus (VZV) vaccination was recommended for patients without a history of VZV infection or immunization, or with negative VZV serology.

Phase 3 clinical trials are the standard for regulatory approval of new agents for MS. However, clinical trials occur in highly regimented environments, and many patients are excluded because of strict inclusion and exclusion criteria to limit potential toxicity of investigational drugs. As a result, some AEs are only recognized after approval of MS therapies (8, 9). The efficacy and safety of newly approved agents must be confirmed in clinical practice where agents are used in a broader population with less regimented safety supervision. We describe the 12 month experience with fingolimod in clinical practice in a large academic MS center as an extension of data published previously (10).

Materials and Methods

Fingolimod start-up procedures

A formal protocol for fingolimod pre-testing, first dose observation, and follow-up based on FDA recommendations was prospectively implemented by a consensus of clinicians at the Mellen Center when fingolimod was first approved in September 2010. Patients who were prescribed fingolimod had a routine CBC and LFT panel collected and underwent a 12-lead EKG screen with cardiologist interpretation. Anti-VZV IgG antibody titers were drawn for patients without past medical history of VZV infection or immunization. If the titers were negative, patients completed vaccination with Varivax® prior to fingolimod start. Patients also underwent a baseline ophthalmological evaluation and/or optical coherence tomography (OCT), specifically evaluating for macular edema. The treating neurologist approved initiation of fingolimod after the patient met all criteria based on the clinical history and pre-treatment investigations.

First dose observation (FDO) was conducted as a shared medical visit, in which two to ten patients received instructions, ingested the medication under the supervision of a medical assistant, and were subsequently observed in a group setting. Patients were interviewed individually by advanced practice clinicians, and medications and MS disease history were reviewed. Heart rate (HR) and blood pressure (BP) were measured at baseline and three and six hours after fingolimod ingestion, and any AEs were recorded in the medical chart. Patients were subsequently evaluated at three- and twelve-month follow-up visits.

Data collection

Following institutional review board (IRB) approval, all patients prescribed fingolimod at the Mellen Center between October 2010 and August 2011 were identified. Review of the electronic medical record was conducted to determine baseline demographic data; MS clinical history (i.e. date of onset, disease course, disease modifying therapy (DMT) history, reason for DMT switch to fingolimod, and John Cunningham virus [JCV] serology); fingolimod screening procedures; dates of medication prescription and insurance approval; AEs at three and twelve months of fingolimod therapy; and disease activity measured by the number of clinical relapses and new gadolinium enhancing (GdE) lesions on brain MRI at 12 months. Clinical measures, including number of relapses and Timed 25 Foot Walk (T25FW, a quantified measure of walking ability), and quality of life (QOL) measures were also assessed. MRI studies during follow-up were recorded as being conducted on or off fingolimod. GdE lesions were manually counted from each MRI scan by one of the authors (CH).

Clinical relapses, defined as new or worsening symptoms attributable to MS that lasted for at least 24 hours, were documented in the chart by the treating neurologist. T25FW (11) and QOL measures including the Multiple Sclerosis Performance Scale (MSPS, an assessment tool of vision, hand function, sensation, spasticity, mobility, fatigue, cognition, and bladder and bowel control) (12), Patient Health Questionnaire-9 (PHQ-9, a standardized depression scale) (13), and European Quality of Life-5 dimensions (EQ5D, a standardized assessment of quality of life) (14), were measured at the three and twelve month follow-up

appointments. Absolute lymphocyte counts three and twelve months after fingolimod initiation were also collected.

Statistical analysis

Data were entered into a secure electronic spreadsheet and analyzed using R Version 2.11.1 (Copyright 2010 R Statistical Software). Descriptive statistical methods were applied to the entire dataset. The paired *t*-test was used to compare measures of disease severity and QOL measures at baseline and month 12. The PHQ-9 was dichotomized at a score of 10 or above and a change in the proportion of patients meeting this criterion was analyzed over time. The proportion of patients with a 20% change in T25FW over time was also calculated. Patients who continued fingolimod and those who discontinued the medication were compared. Significance for all tests was defined as $p<0.05$.

Results

Demographic data and disease history of the 317 patients who started fingolimod are summarized in Table 1. Fingolimod was used as initial therapy in 11 patients (3.5%); most were previously treated with another agent. Patients starting fingolimod used a mean of 2.0 agents (median: 2.0; interquartile range: 1.0, 3.0; SD: 1.12) before fingolimod initiation. The majority of patients switched from IFN beta or glatiramer acetate, but a sizable percentage of patients also switched from natalizumab. Most patients switched therapies because of intolerance or breakthrough disease. The majority of patients who switched from natalizumab had positive JCV serology (n= 20/37), with risk of PML contributing to the decision to switch therapy. Most of the remaining patients in this sub-group (n=10/37) switched DMT due to ease of oral administration.

Twelve month follow-up data were available for 306 patients, as presented in Table 2. Seventy-six patients (24.8%) discontinued fingolimod at mean 248 days (SD: 151) after starting therapy. Discontinuation most often was due to AEs (n=40; 13.1%) or breakthrough disease (n=22; 7.2%). Patients who continued fingolimod were previously treated with an average of 1.95 agents prior to fingolimod start, as compared to 2.04 agents among patients who discontinued the medication. AEs of mild-moderate severity occurred in approximately 25.8% of patients who were available for 12 month follow-up.

Clinical and radiographic data are summarized in Table 3. At 12 months, GdE lesions were observed in 7.8% (n=24) of the entire study population. Only 6.1% of patients who continued fingolimod had GdE lesions (n=14), and the majority of those only had one GdE lesion (n=10). In contrast, 13.1% of patients discontinuing fingolimod had GdE lesions (n=10). Among patients who continued fingolimod, 209 were relapse free (90.9%), 216 were GdE lesion free (93.9%), and 202 remained relapse and GdE lesion free (87.8%) at 12 months.

A total of 41 relapses in 39 patients were observed over the study follow-up with 21 relapses occurring in patients who continued fingolimod and 18 relapses in patients who discontinued treatment (Table 3). The majority of patients who continued fingolimod and had any relapses had only one clinical relapse (n=20 of 21). Similarly, of the 76 patients

who discontinued fingolimod, most had only one relapse (n=17 of 18). No patient experienced more than two clinical relapses. Mean time to first relapse across the entire population was 282 days (median: 336; interquartile range 120.8, 423.8; SD: 171).

The most common AEs leading to fingolimod discontinuation were infection (n=8), headache (n=5), cardiac side effects (n=4), and pulmonary side effects (n=4). The majority of infections were of mild severity and included urinary tract infection (UTI) (n=4), upper respiratory tract infection (URI) (n=3), and local yeast infection (n=3); but only one case of URI led to discontinuation of the drug. Other AEs included macular edema of mild-moderate severity (n=3), bradyarrhythmia of mild-moderate severity (n=3), sepsis from pneumonia of severe severity (n=1), and herpes virus infection of mild severity (n=1). Only one case each of macular edema and bradyarrhythmia led to drug discontinuation, as the other cases were mild and improved without intervention. There were no deaths.

Reflecting fingolimod's mechanism of action, absolute lymphocyte counts (ALC) were decreased at the time of 12 month follow-up (mean ALC 525.0, SD: 313.0; three month mean ALC 484.6, SD: 237.3). In most cases, lymphopenia was not associated with neutropenia, and one patient discontinued the medication due to an infection while neutropenic.

T25FW and QOL measures (MSPS, PHQ-9, and EQ5D) are presented in Table 4. Overall, there were no statistically significant differences in T25FW (n=253), MSPS (n=187), PHQ-9 (n=208), and EQ5D (n=238) at follow-up compared to baseline (all $p>0.1$).

Approximately equal proportions of patients who demonstrated active disease while on fingolimod were directly switched from IFN beta (14.4%), glatiramer acetate (10.3%), or natalizumab (13.5%). The distribution of relapses based on previous disease therapy is presented in Appendix Table A.1. About half of patients who discontinued fingolimod were subsequently started on an alternate DMT within the 12 month follow-up period, and the agent most commonly used was natalizumab. The remaining patients who relapsed were continued on fingolimod due to early time to first relapse (<3 months from time of fingolimod initiation). Of the 34 patients who switched therapy, 13 patients relapsed after switching off fingolimod. The majority who relapsed were switched either to natalizumab (n=6) or mycophenolate mofetil (n=4), suggesting more active baseline disease in this group. The distribution of alternate therapies used with subsequent clinical relapses is summarized in Appendix Table A.2.

Conclusions

In the present study, fingolimod was mostly used in patients with relapsing-remitting MS who were previously treated with at least one other DMT. A large proportion of patients switched from one of the injectable therapies to fingolimod due to ease of oral administration.

A large number of patients started fingolimod at our center with the vast majority available for follow-up. Most patients continued fingolimod after 12 months with generally good disease control with a large proportion of patients achieving disease-free status as measured

by GdE lesion free and relapse free rates. For all patients who started fingolimod, relapse free rate and MRI lesion free rate were similar to phase 3 trial results in the TRANSFORMS (relapse free: 82.6%, MRI GdE lesion free: 90.1%) (6) and FREEDOMS (relapse free: 70.4%, MRI GdE lesion free: 89.7%) trials (4).

Most patients who switched from natalizumab to fingolimod overall had stable disease course. Clinical relapses were observed in 13.5% (n=5/37), and new GdE lesions were observed in 5.4% (n=2/37) at 12 month follow-up. Of patients who remained disease activity free, the mean washout period between natalizumab and fingolimod treatment was 3.2 months, and the mean washout for those who experienced a relapse or GdE lesions was 3.6 months (washout period for all natalizumab switchers- median: 3.0 months; interquartile range: 2.0, 4.0). Recent studies showed similar results. One study assessing the impact of washout duration between natalizumab and fingolimod on the occurrence of MS relapses showed that eight patients (50%) had at least one relapse if treatment was delayed by three months or more (n=16), compared to three patients (7%) who were treated within three months of natalizumab discontinuation (n=43) (p=0.02) (15). Similarly, in a double-blinded, placebo-controlled trial, patients switching from natalizumab to fingolimod with shorter washout periods had lower risk of clinical and MRI disease recurrence by the time of 32 week follow-up (GdE lesion and relapse free rates: 8 week washout- 75% and 96%, respectively; 12 week washout- 61.3% and 95.2%, respectively; 16 week washout- 47.5% and 86%, respectively) without increased risk of infections or other treatment-related AEs (16). A large French observational study also showed decreased risk of disease reactivation during a shorter washout period of less than three months (OR=0.23, p-value<0.001) (17).

Discontinuation rate at 12 months was higher (24.8%) than in clinical trials (TRANSFORMS discontinuation rate: 12.4%; FREEDOMS discontinuation rate: 18.8%) (4, 6) and was most often due to AEs (13.1%). The AEs observed in patients receiving fingolimod were similar to those seen in previous clinical studies (4, 6). In our investigation, discontinuation was related to expected AEs; and infections, namely URI and UTI, and headache were the most frequent causes of discontinuation. These findings reflected the relatively high incidence of mild infections and headache in clinical trials (18). Elevated alanine and aspartate aminotransferase levels greater than three times the upper limit of the normal range occurred in 3.8% of patients, which was similar compared to the results in phase 3 clinical trials (4, 6).

Macular edema occurred in a total of 3 patients (0.9%) by the time of 12 month follow-up, which was similar to the percentage seen in clinical trials: macular edema occurred in 0.5% of subjects in the fingolimod 0.5mg treatment arm and 1% of subjects in the 1.25mg treatment arm (6). The emergence of herpes virus infection was slightly lower than expected (0.3%) compared to that in the 0.5mg groups in the FREEDOMS (8.7%) (4) and TRANSFORMS (2.1%) (6) trials. The incidence of bradyarrhythmia in our experience (0.3%) was similar to that in patients who were treated with 0.5mg fingolimod (0.5%) in TRANSFORMS study (6) and slightly lower compared to patients treated with 0.5mg fingolimod (2.1%) in FREEDOMS trial (4). Importantly, our data showed no unexpected AEs in clinical practice.

Another main contributor to fingolimod discontinuation was breakthrough disease (7.2%) as measured by clinical relapses and/or active disease activity on cranial MRI (new GdE lesions). Approximately equal proportions of patients who demonstrated active disease while on fingolimod were directly switched from IFN beta, glatiramer acetate, or natalizumab. This observation suggests that the natalizumab switchers did not experience a robust increase in disease activity after starting fingolimod as compared to those who switched from the other agents.

The data from the current study support the effectiveness of fingolimod in clinical practice, albeit with more frequent tolerability issues leading to drug discontinuation as compared to phase 3 clinical trials (4, 6). The study may be limited in that the authors analyzed a cohort of patients followed in a large academic MS referral center that may not be representative of the general MS population. The current study is also limited by a relatively short duration of follow-up. Thus, rare or late-appearing AEs may not have been detected. Missing clinical, MRI, or QOL data at month 12 are also a limitation that potentially could bias the results. Only 12 month MRI data were reviewed and analyzed; imaging completed outside of this time period was not included in the analysis since the authors felt the results would not be comparable. Fifty-four patients (17%) did not undergo brain MRI at the time of 12 month follow-up, and these figures were treated as missing data in the analysis. The number of patients missing clinical data including T25FW (17%), PHQ-9 (32%), MSPS (22%), and EQ5D (22%) was substantial, illustrating one of the limitations of “real world” observational studies.

Our study supports the use of fingolimod for patients with relapsing-remitting MS due to clinical effectiveness and ease of oral administration. Discontinuation due to AEs appears to be relatively common. Proactive measures to anticipate or address AEs are warranted. Longer follow-up studies are needed to comment on long-term tolerability and effectiveness in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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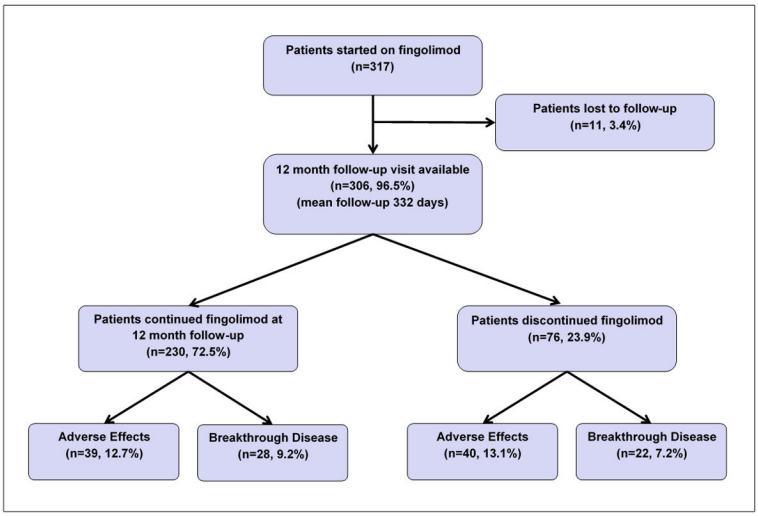

Figure 1.
Fingolimod 12 month follow-up.

Table 1

Baseline characteristics

	Total	Directly switched due to intolerance, risk, or convenience	Directly switched due to breakthrough disease
Number total	317		
Number available for follow-up	306		
Number switched directly from other DMT*	230	151	79
Female	223 (70.3%)	104 (68.8%)	53 (67.1%)
Age (years, SD)	43.6 (9.3)	44.1 (8.8)	42.7 (9.6)
Disease Course			
Relapsing remitting	256 (80.8%)	127 (84.7%)	66 (83.5%)
Secondary progressive with relapses	32 (10.1%)	15 (9.9%)	5 (6.3%)
Secondary progressive without relapses	19 (6.0%)	6 (4.0%)	5 (6.3%)
Primary progressive	5 (1.6%)	2 (1.3%)	1 (1.3%)
Clinically isolated syndrome	1 (0.3%)	0	0
Disease duration (years, SD)	12.1 (7.9)	12.2 (7.8)	10.9 (7.2)
Fingolimod used without prior DMT	11 (3.5%)	0	0
Previous DMT use	306 (96.5%)	151 (100%)	79 (100%)
Remote DMT use	76 (24.0%)	0	0
Switched directly from other DMT	230 (72.6%)	151 (100%)	79 (100%)
Medication Switched			
Interferon	90 (28.3%)	57 (37.7%)	33 (41.8%)
Glatiramer acetate	77 (24.2%)	49 (32.5%)	28 (35.4%)
Natalizumab	37 (11.6%)	30 (19.8%)	7 (8.9%)
Other	21 (6.6%)	15 (9.9%)	11 (13.9%)
MRI available 3 months prior to fingolimod start	113 (35.6%)	52 (34.4%)	34 (43.0%)
Gadolinium enhancement	31/113 (27.4%)	4/52 (7.6%)	17/79 (21.5%)

Abbreviations: DMT, disease modifying therapy.

*A total of 317 patients started fingolimod with eleven lost to follow-up. Eleven patients started fingolimod without prior DMT use, and 76 patients had remote DMT use. Of the 230 patients who directly switched from prior DMT to fingolimod, 151 patients switched because of intolerability, risk, or convenience; and 79 patients switched because of breakthrough disease.

Table 2

Twelve-month follow-up data

N Total	317
Follow-up data available	306 (96.5%)
Time to follow-up (mean days)	332.9 (SD: 129)
Total Adverse Effects	79 (25.8%)
Infection	23 (7.5%)
Headache	16 (5.2%)
Fatigue	6 (2.0%)
Cardiac side effects	5 (1.6%)
Elevated transaminases	5 (1.6%)
Pulmonary side effects	4 (1.3%)
Dizziness	4 (1.3%)
Leukopenia	4 (1.3%)
Nausea	4 (1.3%)
Macular edema	3 (1.0%)
Edema	2 (0.7%)
Alopecia	2 (0.7%)
Allergic reaction	1 (0.3%)
Fingolimod discontinued	76 (24.8%)
Mean time to discontinuation (days)	248.2 (SD: 151)
Reason for discontinuation	
Adverse Effects	40 (13.1%)
Infection	8 (2.6%)
Headache	5 (1.6%)
Cardiac side effects	4 (1.3%)
Pulmonary side effects	4 (1.3%)
Elevated liver enzymes	3 (1.0%)
Leukopenia	3 (1.0%)

Macular edema	2 (0.7%)
Back pain	2 (0.7%)
Breakthrough Disease	22 (7.2%)
Relapse/Disease Progression	19 (6.2%)
MRI Disease Activity	3 (1.0%)
Insurance	4 (1.3%)
Pregnancy	3 (1.0%)
Diagnosis of NMO	2 (0.7%)
Surgery	2 (0.7%)
Allergy	1 (0.3%)
Stem cell transplant	1 (0.3%)

Abbreviations: NMO, neuromyelitis optica.

Table 3

Measures of disease activity

	Total	Remained on Fingolimod	Stopped Fingolimod
Number available for follow-up	306	230	76
No prior DMT	9	6 (2.6%)	3 (3.9%)
Switched due to patient preference	147	116 (50.4%)	31 (40.8%)
Switched due to breakthrough disease	76	58 (25.2%)	18 (23.7%)
Remote DMT use	74	50 (21.7%)	24 (31.6%)
Mean time on fingolimod (days)	317 (SD:119)	355 (SD:114)	248 (SD:151)
MRI Data			
Number of patients with GdE Lesions	24 (7.8%)	14 (6.1%)	10 (13.1%)
1 GdE Lesion	14 (4.6%)	10 (4.3%)	4 (5.2%)
2 GdE Lesions	5 (1.6%)	2 (0.8%)	3 (3.9%)
3 GdE Lesions	4 (1.3%)	1 (0.4%)	3 (3.9%)
4 GdE Lesions	1 (0.3%)	1 (0.4%)	
Number of patients with relapses	39 (12.7%)	21 (9.1%)	18 (23.6%)
Number of relapses on fingolimod			
1 Relapse	37 (12.1%)	20 (8.7%)	17 (22.3%)
2 Relapses	2 (0.7%)	1 (0.4%)	1 (1.3%)
Time to Relapse	282 days (SD: 171)	330 days (SD: 146)	280 days (SD: 153)
Disease Freedom			
Relapse Free	267 (87.3%)	209 (90.9%)	58 (76.3%)
GdE Lesion Free	282 (92.2%)	216 (93.9%)	66 (86.8%)
Relapse/GdE Lesion Free	256 (83.7%)	202 (87.8%)	54 (71.1%)

Abbreviations: DMT, disease modifything therapy; GdE, gadolinum enhancing; SD, standard deviation.

Table 4

T25FW and quality of life measures

Baseline and 12 month T25FW and quality of life measures in all patients			
	Baseline	**Follow-up**	**P value**
T25FW seconds (SD) n=253	9.1 (17.2)	9.2 (17.7)	0.99
PHQ-9 score (SD) n=208	7.3 (5.7)	6.9 (5.3)	0.37
MSPS score (SD) n=187	11.9 (8.2)	11.7 (7.4)	0.57
EQ5D score (SD) n=238	0.74 (0.19)	0.75 (0.19)	0.54
Baseline and 12 month T25FW and quality of life measures in patients remaining on fingolimod			
T25FW seconds (SD) n=203	7.7 (15.3)	8.3 (15.8)	0.05
PHQ-9 score (SD) n=165	6.7 (5.1)	6.0 (4.6)	0.07
MSPS score (SD) n=149	11.5 (8.6)	10.7 (7.1)	0.21
EQ5D score (SD) n=195	0.77 (0.16)	0.77 (0.19)	0.85
Baseline and 12 month T25FW and quality of life measures in patients who discontinued fingolimod			
T25FW seconds (SD) n=50	10.3 (15.5)	13.7 (23.5)	0.06
PHQ-9 score (SD) n=43	6.6 (6.7)	8.1 (6.4)	0.08
MSPS score (SD) n=38	12.3 (7.1)	13.3 (7.3)	0.13
EQ5D score (SD) n=43	0.71 (0.21)	0.68 (0.22)	0.13

Abbreviations: EQ5D, European quality of life- 5 dimensions; MSPS, MS performance scale; PHQ-9, patient health questionnaire, T25FW, timed 25 foot walk.