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Early Tolerability and Safety of Fingolimod in Clinical Practice

Daniel Ontaneda, MD¹, Claire Hara-Cleaver, RN MSN¹, Richard A. Rudick, MD¹, Jeffrey A. Cohen, MD¹, and Robert A. Bermel, MD¹

¹Mellen Center, Department of Neurology, Cleveland Clinic, Cleveland, OH, USA

Abstract

Background—Fingolimod is approved by the U.S. Food and Drug Administration to reduce relapses and disability progression in relapsing forms of MS. Several screening studies and a first-dose observation (FDO) period are recommended due to adverse effects observed in clinical trials.

Objective—To describe the early experience with fingolimod, including startup, tolerability and safety in a large academic multiple sclerosis (MS) center.

Methods—Patients prescribed fingolimod from September 2010 to July 2011 were identified through electronic medical records. Demographics, MS disease history, pre-treatment screening studies, FDO experience during shared medical visits and three month follow-up data were analyzed.

Results—Three hundred ninety-one patients were prescribed fingolimod of whom 317 started the medication and were included in the analysis. Fingolimod was most frequently used in relapsing remitting MS (n = 256, 80.8%) and was prescribed as a first-line agent in 11 cases (3.5%). FDO was uneventful in 308 patients (96.8%). Adverse events during FDO were self limited and included symptomatic bradycardia (n = 3), chest tightness (n = 2) and hypertension (n = 1). Fingolimod was discontinued in 30 patients (9.5%) at three months. Adverse effects leading to discontinuation by more than one patient included headache (n = 4), macular edema (n = 3), nausea (n = 3) and hypertension (n = 2).

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Corresponding author: Daniel Ontaneda MD, Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic Foundation, 9500 Euclid Avenue, U-10, Cleveland, OH, USA, Tel: 216-445-0151, Fax: 216-445-7013, ontaneda@ccf.org.

Author contributions:

Dr. Ontaneda was responsible for study design, data collection, statistical analysis, manuscript drafting and revision. Claire Hara-Cleaver was responsible for study design, data collection and manuscript revising. Dr. Rudick was responsible for study design, analysis and manuscript revision. Dr. Cohen was responsible for study design, analysis and manuscript revision.

Dr. Bermel was responsible for study design, data collection, analysis, manuscript drafting and revision.

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Conclusions—Fingolimod was well tolerated during FDO and adverse events were self limited. The shared medical visit is an appropriate setting for FDO. Adverse effects were similar to those described in clinical trials but discontinuation rate was higher.

Keywords

multiple sclerosis; disease modifying agents; fingolimod; clinical practice; adverse effects; tolerability

1. Introduction

Fingolimod (FTY720) is the first oral disease-modifying therapy (DMT) approved by the U.S. Food and Drug Administration (FDA) for relapsing forms of multiple sclerosis (MS). Fingolimod-phosphate is a sphingosine 1-phosphate (S1P) analog which inhibits lymphocyte egress from lymph nodes.^{1,2} The efficacy of fingolimod in MS was demonstrated by two phase III clinical trials^{3,4} in which fingolimod decreased the annualized relapse rate and several MRI measures of disease compared to placebo³ and IM interferon (IFN) beta-1a.⁴

Certain organ-specific adverse events (AEs), including elevation of liver function tests (LFT), headache, decreased resting heart rate and slowing of atrioventricular (AV) conduction (observed after first-dose), herpes infections and macular edema were observed in patients receiving fingolimod during clinical trials. Reduction of circulating lymphocytes is expected in fingolimod-treated patients. The FDA made several recommendations for the safe use of fingolimod.⁵ Baseline ophthalmologic evaluation, complete blood count (CBC) and LFT were recommended for all patients starting fingolimod. A 12 lead EKG was recommended for patients with risk factors for bradyarrhythmia, and a six-hour observation period was recommended in all patients to monitor for signs/symptoms of bradycardia following the first-dose. Varicella zoster virus (VZV) vaccination was also recommended in patients without a history of VZV infection/immunization as well as those with negative VZV serology.

The safety and tolerability of fingolimod in the general MS patient population is of interest. We present our initial experience prescribing fingolimod to 391 patients in an academic MS clinic in the U.S.

2. Methods

2.1 Fingolimod start-up procedures

A protocol for fingolimod pre-testing and first dose observation was decided by consensus of clinicians at our center when fingolimod was first approved. Patients for whom fingolimod was prescribed routinely had a screening 12 lead EKG with cardiologist interpretation, CBC and LFT. Patients with abnormal screening EKG or cardiac history (syncope, presyncope, structural heart disease, or arrhythmia) were referred for cardiology consultation at the discretion of the treating neurologist. For patients without a past history of VZV infection or VZV immunization, anti VZV IgG antibody titers were drawn. If VZV IgG titers were negative, patients completed vaccination one month prior to starting fingolimod with subcutaneous live attenuated VZV vaccine given at two doses 4–8 weeks apart. Patients also had a baseline ophthalmologic evaluation and/or optical coherence tomography (OCT) specifically looking for macular edema. Ordering clinicians recorded test results in a chart note as “normal”, “abnormal but acceptable” (if testing was abnormal but not a contraindication for fingolimod use) or “abnormal” (if testing indicated a potential contraindication to fingolimod use requiring clearance through a cardiologist, hepatologist, hematologist, or ophthalmologist). Once patients satisfied all criteria based on history and

pre-treatment investigations, the treating neurologist approved the medication and recorded the date of pre-treatment testing approval. Insurance approval dates were also recorded in the medical record

After pre-treatment testing and insurance approval were complete, patients were scheduled for first-dose observation (FDO). FDO was conducted as a shared medical visit in which 2–10 patients received first dose instruction, took the first dose and were observed in a group setting. Patients were interviewed individually by advanced practice clinicians, MS disease history was reviewed and medications were reconciled. Fingolimod was administered by a medical assistant. Heart rate (HR) and blood pressure (BP) were monitored at baseline, three hours and six hours after fingolimod ingestion and any AEs were recorded. A rapid response acute care team was available for medical stabilization, advanced cardiac life support and transportation to the emergency department if needed. The six hour observation period was also used to provide educational material to patients. Patients had a three month follow-up with repeat CBC, LFT and OCT scheduled at completion of FDO.

2.2 Data collection

After institutional review board approval, all patients prescribed fingolimod between October 2010 and July 2011 were identified. A retrospective electronic medical record review was conducted to determine demographics; MS clinical history (date of onset, clinical course, DMT history, reason for DMT switch to fingolimod, John Cunningham virus [JCV] serology); fingolimod screening procedures and dates of medication prescription and insurance approval. FDO data extracted from the medical record included vital signs, AEs and interventions. Measurements of disease severity obtained at the time of fingolimod prescription and at three month follow-up included the timed 25 foot walk (T25FW),⁶ multiple sclerosis performance scale (MSPS),⁷ patient health questionnaire 9 (PHQ-9)⁸ and EQ5D.⁹ Absolute lymphocyte counts three months after fingolimod initiation were recorded.

2.3 Statistical Analysis

Data were entered into an electronic database 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 quality of life at baseline and three month follow-up. A mixed effect model was used to examine the effect of abnormal EKG screening on heart rate changes during FDO. Linear mixed effect models with and without the effect of screening EKG results were compared using the analysis of variance test. Significance for all tests was defined as $p < 0.05$.

3. Results

A total of 391 patients were prescribed fingolimod (Figure 1). Seventy-four patients did not start fingolimod due to patient preference ($n=27$, 36.5%), failure to complete screening tests ($n=25$, 33.8%), insurance denial ($n=10$, 13.5%), cardiac contraindication ($n=8$, 10.8%), melanoma ($n=1$, 1.4%), pregnancy ($n=1$, 1.4%), neutropenia ($n=1$, 1.4%) and abnormal pulmonary function tests ($n=1$, 1.4%).

Demographics and disease history of the 317 patients who started fingolimod are summarized in Table 1. Mean disease duration was 12.1 years (SD 7.9 years, range <1–39 years). Fingolimod was used as a second line agent in 132 patients (41.6%), as a third line agent in 95 patients (30.0%) and as a fourth line agent in 54 patients (17.0%). Patients starting fingolimod used a mean of 1.9 agents (SD 1.12, range: 1–7) before fingolimod. MRI of the brain within three months prior to fingolimod prescription was available in 113

patients and approximately one-third showed gadolinium enhancement. A small number of patients used concomitant medications that potentially slow AV nodal conduction.

The results of pre-fingolimod screening studies are summarized in Table 2. Screening CBC and LFT were normal in most patients. Two patients required VZV immunization; the remaining patients had either positive serology or history of VZV infection. Abnormal EKG results were found in 79 patients (24.9%). The most common abnormality was sinus bradycardia. Cardiology consultation was sought in 33 patients (10.4%) and fingolimod use was approved in all. Two hundred eighty one patients (88.6%) had a baseline ophthalmological exam with OCT; 35 patients (11.0%) had OCT alone. No patient had macular edema at baseline.

The mean interval after prescription date was 33.6 days (SD 34.6 days) for insurance approval and 49.4 days (SD 33.4 days) for pre-treatment testing approval. The interval between pre-treatment testing approval and FDO was 40.7 days (SD 25.1 days). On average, patients were dosed with fingolimod 90.2 days (SD 39.1 days) after prescription of the medication; however there was a progressive decrease in this interval over time. Comparing prescriptions made during the fourth quarter of 2010 and the first and second quarter of 2011, progressive decreases in time to insurance approval, pre-treatment testing approval and FDO were observed (Figure 2).

First-dose observation was uneventful in 310 patients (97.7%) (Table 3). Three patients experienced symptomatic bradycardia, however all AEs were self limited, and none required intervention. Significant decreases in HR were observed three hours after first dose (−11.5 bpm; $p<0.001$; 95%CI: −12.6 to −10.3) and at six hours (−12.0 bpm; $p<0.001$; 95%CI: −13.2 to −10.9) (Figure 3). Systolic BP dropped at three hours (−1.8 mmHg; $p=0.021$; 95%CI: −3.4 to −0.2) and at six hours (−1.8 mmHg; $p=0.011$; 95%CI: −3.5 to −0.5). Diastolic blood pressure (DBP) also dropped at three hours (−3.3 mmHg; $p<0.001$; 95%CI: −4.3 to −2.3) and at 6 hours (−3.7 mmHg; $p<0.001$; 95%CI: −4.8 to −2.6). A total of 27 patients had DBP below 60 during FDO, only 4 of whom had DBP <60 before starting fingolimod and only one of those patients became symptomatic.

All patients experiencing symptomatic bradycardia during FDO had an abnormal screening EKG showing sinus bradycardia. To examine the effect of an abnormal EKG on HR change, linear mixed effect models were compared with and without abnormal EKG as an effect variable. Analysis of variance revealed no significant difference between the models ($p=0.16$), suggesting an abnormal screening EKG does not predict a different HR response to fingolimod.

Follow-up data were available for 307 patients (96.8%) with mean follow-up of 98 days (Table 3). Thirty patients (9.5%) discontinued fingolimod, most often due to AEs. AEs leading to discontinuation by more than one patient included headache ($n=4$), macular edema ($n=3$), nausea ($n=3$) and hypertension ($n=2$). There were no significant differences in T25FW ($n=194$), PHQ-9 ($n=142$), MSPS ($n=139$) or EQ5D ($n=164$) at follow-up compared to baseline (all $p>0.1$). Absolute lymphocyte count at follow up was 0.485 k/ul (SD 0.237, range 0.126–1.9 k/ul).

4. Discussion

In our early experience, fingolimod was mostly used in patients with relapsing remitting MS as a second line agent. Patients used an average of two disease modifying medications prior to starting fingolimod. The lack of long term safety with fingolimod was the likely contributing factor for clinicians not to use the medication as a first line agent. The majority of patients switched from interferon beta or glatiramer acetate, but a sizable amount of

patients switched from natalizumab (n=37). More than half of the patients who switched from natalizumab had positive JCV serology (20/37), with risk of PML contributing to the decision to change therapy. Ten patients previously on natalizumab switched despite negative JCV serology, and in these patients ease of administration was the likely reason. Screening studies were obtained in almost all patients, and few patients had absolute contraindications to fingolimod. The majority of patients prescribed fingolimod who did not start the medication did so as the result of a decision to not start medication or obtain screening tests rather than a contraindication found on screening. In some patients, fingolimod was prescribed to expedite screening tests although a final decision to start the medication was pending.

On average there was a 90 day delay between fingolimod prescription and FDO. This was the result of the time needed for screening testing, insurance approval and FDO scheduling. The delay between prescription and FDO decreased over time due to more efficient pretreatment testing (same-day on-demand access to OCT, EKG and blood draw at our institution) and insurance approval. In contrast, the interval between pre-treatment testing approval and first dose observation increased over time, because demand for FDO visits exceeded available appointments. Despite this delay the time from prescription to FDO still dropped over time and in the last quarter of the study was 76 days. The lengthy delay in starting fingolimod is of some concern, especially in patients with active disease. For patients switching to fingolimod from other disease modifying treatments, the anticipated delay in starting fingolimod should be considered when planning discontinuation of the current treatment.

A large number of patients (n=317) started fingolimod at our center and the medication was generally well tolerated. Fingolimod discontinuation at three months was 9.5% and, as expected, this was higher than what was observed in clinical trials.^{3,4} Discontinuation was related to expected AEs and headache was the most frequent cause of discontinuation, reflecting the incidence of headache in clinical trials.¹⁰ We did not formally collect compliance data in this study, though inconsistent compliance with MS disease modifying treatment remains an important issue.

From a cardiovascular standpoint, fingolimod was safe in our population and no serious AEs occurred. There was a significant drop in HR, maximal at 6h after initial dose (mean -12.0 bpm at 6h). This is similar to results from a combined safety analysis of the phase III trials of fingolimod in MS where a mean heart rate drop of 11 bpm and 8 bpm was observed for the 0.5mg and 1.25 mg doses respectively.¹¹ Only a minority of patients experienced symptomatic bradycardia in our study, which was similar to that observed in the phase II and phase III trials.^{3,4,10} The three cases of symptomatic bradycardia occurred in patients with abnormal screening EKG showing sinus bradycardia. However, a mixed effect model did not show that an abnormal screening EKG predicted a larger change in heart rate after fingolimod first dose. Thus, although patients with pre-treatment bradycardia may be at increased risk, the majority of patients with abnormal EKGs had uneventful first dose observations (73/76). The FDA identified risk factors for slowing of AV conduction and bradycardia during fingolimod use, including patients with a low heart rate, history of syncope, sick sinus syndrome, second degree or higher conduction block, ischemic heart disease, congestive heart failure or those who receive class Ia or class III antiarrhythmics, beta blockers or calcium channel blockers.⁵ Patients with these characteristics were excluded from clinical trials. Several patients with heart disease and resting bradycardia in our study tolerated fingolimod without problems. Additionally patients using beta blockers, calcium channel blockers or digitalis tolerated fingolimod and had uneventful first dose observations. However, caution should be used with concomitant medications that affect AV

conduction as serious AEs have been reported.¹² Typically, these medications are held the day of FDO.

Changes in BP after first dose were of a small magnitude and unlikely to result in symptoms; this was similar to what has been observed previously.¹¹ Effect on cardiovascular risk due to the mild chronic elevation in BP expected with long-term fingolimod use remains unknown. Four patients in our study had SBP greater than 180 mmHg during FDO (all were asymptomatic), likely related to coexisting chronic hypertension. Our results suggest that first dose observation is likely to be uneventful in patients with normal baseline heart rates, a normal screening EKG, no prior cardiac history, who do not use medications causing bradycardia or AV slowing.

Macular edema occurred in 0.9% of patients at three month follow-up, similar to the rate of 0.3% of patients on 0.5 mg fingolimod and 1% of patients on 1.25 mg of fingolimod in MS phase III clinical trials,^{4,13} and was asymptomatic in all cases. In clinical trials, macular edema typically occurred during the first four months of fingolimod use and caused visual symptoms in approximately half the cases. The precise mechanism of fingolimod-associated macular edema is unknown, but may relate to interaction with S1P receptors on macular vascular endothelial cells.¹⁴ Macular edema appears to occur at higher rates in patients with comorbid diabetes mellitus, uveitis and with increasing age.^{15–17} and for this reason patients with diabetes were excluded from phase III MS trials. In our study 3.8% of patients had diabetes mellitus, but one of the three patients who developed macular edema had diabetes mellitus. All patients who developed macular edema were over the age of fifty. All patients were asymptomatic at the time of detection, highlighting the need for routine screening for macular edema at 3–4 months. Periodic additional ophthalmologic follow-up may be reasonable in patients with diabetes mellitus and age over fifty years given potential for increased risk in this patient population. Absolute lymphocyte counts dropped predictably at three month follow-up. In most cases lymphopenia was not associated with neutropenia and no patients discontinued the medication due to infectious complications. Screening CBC did not identify patients at risk for neutropenia. There were no severe or serious infections in this cohort, but follow-up was short. The incidence of infectious complications with longer term fingolimod use remains a key unknown issue.

The inclusion of patients with comorbid conditions that may increase the risk of fingolimod-related complications (hypertension, diabetes, bradycardia, AV slowing medications, abnormal LFT/CBC) in this study did not seem to result in a significant increase incidence of serious AEs compared to clinical trials. Although our study was not intended to measure clinical efficacy it appears there was no worsening in disease severity measures at three month follow-up. This included stability of patient reported outcomes, which may be impacted by medication side effects.

The use of a shared medical visit appears to be an efficient and effective setting for FDO. Vital signs (HR and BP) measured at three hour intervals identified patients with asymptomatic bradycardia. Continuous real time monitoring of vital signs during first dose observation was not used and would have been unlikely to identify AEs or change outcomes significantly in this population. Although a substantial time commitment from patients is needed for FDO, the shared medical visit setting provides a unique opportunity for patient education.

These data support the short term safety and tolerability of fingolimod in clinical practice. These results are of interest as some patients included in our study would have been excluded from fingolimod clinical trials due to systemic diseases including diabetes mellitus, cardiac disease, asthma and chronic obstructive pulmonary disease. Patients with

these comorbidities tolerated fingolimod and the medication appeared to be safe. The long-term safety of fingolimod in these patients, however, is still unknown and needs further evaluation. Discontinuation of disease modifying therapies when switching to fingolimod should be delayed to account for the time required to initiate fingolimod. Fingolimod is attractive to patients given the oral route of administration, however discontinuation and non compliance due to adverse effects needs to be monitored by clinicians. The current study is limited by a short duration of follow-up and by a relatively small sample size, however the number of patients in this study is similar to the 0.5mg fingolimod arms from phase III clinical trials.^{3,4}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Chun J, Hartung HP. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. *Clin Neuropharmacol.* 2010; 33:91–101. [PubMed: 20061941]
2. Brinkmann V, Davis MD, Heise CE, Albert R, Cottens S, Hof R, Bruns C, Prieschl E, Baumruker T, Hiestand P, Foster CA, Zollinger M, Lynch KR. The immune modulator FTY720 targets sphingosine 1-phosphate receptors. *J Biol Chem.* 2002; 277:21453–7. [PubMed: 11967257]
3. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, Selmaj K, Agoropoulou C, Leyk M, Zhang-Auberson L, Burtin P. FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med.* 2010; 362:387–401. [PubMed: 20089952]
4. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, Pelletier J, Capra R, Gallo P, Izquierdo G, Tiel-Wilck K, de Vera A, Jin J, Stites T, Wu S, Aradhye S, Kappos L. TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med.* 2010; 362:402–15. [PubMed: 20089954]
5. NDA 02257 FDA Approved Labeling Text for Gilenya (fingolimod) capsules. 2010. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022527s000lbl.pdf
6. Rudick RA, Cutter G, Reingold S. The multiple sclerosis functional composite: a new clinical outcome measure for multiple sclerosis trials. *Mult Scler.* 2002; 8:359–65. [PubMed: 12356200]
7. Schwartz CE, Vollmer T, Lee H. North American Research Consortium on Multiple Sclerosis Outcomes Study Group. Reliability and validity of two self-report measures of impairment and disability for MS. *Neurology.* 1999; 52:63–70. [PubMed: 9921850]
8. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001; 16:606–13. [PubMed: 11556941]
9. The EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* 1990; 16:199–208. [PubMed: 10109801]
10. Collins W, Cohen J, O'Connor P, de Vera A, Zhang-Auberson L, Jin FJ, Kappos L. Long-term safety of oral fingolimod (FTY720) in relapsing multiple sclerosis: integrated analyses of phase 2 and 3 studies (P843). *Mult Scler.* 2010; 16:S295.
11. DiMarco JP, O'Connor P, Cohen JA. First-dose effect of fingolimod: pooled safety data from two phase 3 studies (TRANSFORMS and FREEDOMS) (P830). *Mult Scler.* 2010; 16:S290.
12. Espinosa PS, Berger JR. Delayed fingolimod-associated asystole. *Mult Scler.* 2011; 17:1387–9. [PubMed: 21652609]

13. Kappos L, Antel J, Comi G, Montalban X, O'Connor P, Polman CH, Haas T, Korn AA, Karlsson G, Radue EW. FTY720 D2201 Study Group. Oral fingolimod (FTY720) for relapsing multiple sclerosis. *N Engl J Med*. 2006; 355:1124–40. [PubMed: 16971719]
14. Horga A, Castillo J, Montalban X. Fingolimod for relapsing multiple sclerosis: an update. *Expert Opin Pharmacother*. 2010; 11:1183–96. [PubMed: 20367536]
15. Salvadori M, Budde K, Charpentier B, Klempnauer J, Nashan B, Pallardo LM, Eris J, Schena FP, Eisenberger U, Rostaing L, Hmissi A, Aradhye S. FTY720 0124 Study Group. FTY720 versus MMF with cyclosporine in de novo renal transplantation: a 1-year, randomized controlled trial in Europe and Australasia. *Am J Transplant*. 2006; 6:2912–21. [PubMed: 17061999]
16. Tedesco-Silva H, Szakaly P, Shoker A, Sommerer C, Yoshimura N, Schena FP, Cremer M, Hmissi A, Mayer H, Lang P. FTY720 2218 Clinical Study Group. FTY720 versus mycophenolate mofetil in de novo renal transplantation: six-month results of a double-blind study. *Transplantation*. 2007; 84:885–92. [PubMed: 17984842]
17. Hoitsma AJ, Woodle ES, Abramowicz D, Proot P, Vanrenterghem Y. on behalf of the FTY720 Phase II Transplant Study Group. FTY720 combined with tacrolimus in de novo renal transplantation: 1-year, multicenter, open-label randomized study. *Nephrol Dial Transplant*. 2011; 26:3802–5. [PubMed: 21911597]

Figure 1.
Fingolimod initiation

Figure 2. Time from fingolimod prescription to insurance approval, clinician approval and first dose observation by quarter of prescription.

Table 1

Baseline characteristics

N total	317
Female	223 (70.3%)
Age (years, SD)	43.6 (9.3)
Disease Course	
Relapsing remitting	256 (80.8%)
Secondary progressive with relapses	32 (10.1%)
Secondary progressive without relapses	19 (6.0%)
Primary progressive	5 (1.6%)
Clinically isolated syndrome	1 (0.3%)
Disease duration (years, SD)	12.1 (7.9)
Fingolimod used as first line agent	11 (3.5%)
Previous DMT use	306 (96.5%)
Remote DMT use	76 (24.0%)
Switched directly from other DMT	230 (72.6%)
Medication Switched	
Interferon	90 (28.3.1%)
Glatiramer acetate	77 (24.2%)
Natalizumab	37 (11.6%)
Other	21(6.6%)
Reason for switch	
Intolerance/convenience/risk	151 (47.7%)
Breakthrough disease	79 (24.9%)
Not Switched	87 (27.4%)
MRI available 3 months prior to fingolimod start	113 (35.6%)
Gadolinium enhancement	31/113 (27.4%)
Hypertension	30 (9.5%)
Diabetes Mellitus	12 (3.8%)
Asthma	11 (3.5%)
Cardiac disease	8 (2.5%)
Beta blocker	12 (3.8%)
Calcium channel blocker	9 (2.8%)
Digoxin	2 (0.6%)

Table 2

Fingolimod screening studies

Complete blood count	
Normal	245 (77.3%)
Abnormal but acceptable	68 (21.5%)
Abnormal	2 (0.6%)
None	2 (0.6%)
Liver function tests	
Normal	295 (93.1%)
Abnormal but acceptable	20 (6.3%)
Abnormal	1 (0.3%)
None	1 (0.3%)
Varicella Zoster immune status	
History of Varicella zoster	256 (80.8%)
Positive VZV IgG titers	56 (17.7%)
VZV vaccination	2 (0.6%)
None	3 (0.9%)
EKG	
Normal	220 (69.4%)
Abnormal but acceptable	72 (22.7%)
Abnormal	7 (2.2%)
None	18 (5.7%)
Cardiology Consultation	
Reason for cardiology consult	33 (10.4%)
Abnormal screening EKG	28 (8.8%)
Co-morbid cardiac history	4 (1.3%)
History of syncope/presyncope	1 (0.3%)
Ophthalmologic screening	
Normal	214 (67.5%)
Abnormal but acceptable	101 (31.9%)
Abnormal	1 (0.3%)
None	1 (0.3%)
Ophthalmologist consultation and OCT	281 (88.6%)
OCT alone	35 (11.0%)

OCT = optical coherence tomography, VZV = varicella zoster virus

Table 3

First dose observation and three month follow-up data

Fingolimod Started	317 (100%)
Difficulty with receiving continued supply of fingolimod	3 (0.9%)
First dose observation (n=317)	
First dose monitoring uneventful	310 (97.8%)
Symptomatic bradycardia	3 (0.9%)
Chest tightness	2 (0.6%)
Hypertension	1 (0.3%)
Sensory symptoms	1 (0.3%)
Follow up available after first dose observation	306 (96.5%)
Mean follow-up time, days (SD)	98 (32.1)
Fingolimod discontinued	30 (9.5%)
Reasons for discontinuation	
Adverse effects	26 (8.2%)
Disease activity	2 (0.6%)
Financial	1 (0.3%)
Pregnancy	1 (0.3%)
Adverse effects leading to discontinuation	
Headache	4 (1.3%)
Nausea	3 (0.9%)
Macular edema	3 (0.9%)
Hypertension	2 (0.6%)
Blurred vision	1 (0.3%)
Shortness of breath/wheezing	1 (0.3%)
Back pain	1 (0.3%)
Alopecia	1 (0.3%)
Leukopenia	1 (0.3%)
Prostate infection	1 (0.3%)
Irregular heart rate	1 (0.3%)
Fatigue	1 (0.3%)
Hives	1 (0.3%)
Paresthesias	1 (0.3%)
Weakness	1 (0.3%)
Edema	1 (0.3%)
Dizziness	1 (0.3%)
Diaphoresis	1 (0.3%)
Mean absolute lymphocyte count at follow-up k/ul (SD) *	0.485 (0.237)
Median absolute lymphocyte count at follow-up k/ul (range)	0.450 (0.126–1.900)

* Absolute lymphocyte count normal range: 1.0–4.0 k/ul