The effect of oral immunomodulatory therapy on treatment uptake and persistence in multiple sclerosis

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Keywords: Relapsing/remitting, Disease modifying therapies, Multiple sclerosis

Abstract:

Objective
To analyse the effect of the introduction of fingolimod, the first oral disease modifying therapy, on treatment utilisation and persistence in an international cohort of patients with multiple sclerosis.

Methods
MSBASIS, a prospective, observational sub-study of the MSBase registry, collects demographic, clinical and paraclinical data on patients followed from MS onset (n=4718). We conducted a multivariable conditional risk set survival analysis to identify predictors of treatment discontinuation and assess if the introduction of fingolimod has altered treatment persistence.

Results
A total of 2640 patients commenced immunomodulatory therapy. Following the introduction of fingolimod, patients were more likely to discontinue all other treatments (hazard ratio 1.64, $p<0.001$) while more patients switched to fingolimod than any other therapy (42.3% of switches). Patients switched to fingolimod due to convenience. Patients treated with fingolimod were less likely to discontinue treatment compared to other therapies ($p<0.001$). Female sex, country of residence, younger age, a high EDSS and relapse activity were all independently associated with higher rates of treatment discontinuation.

Conclusion
Following the availability of fingolimod, patients were more likely to discontinue injectable treatments. Those who switched to fingolimod were more likely to do so for convenience. Persistence was improved on fingolimod compared to other medications.

TITLE PAGE

Title

The effect of oral immunomodulatory therapy on treatment uptake and persistence in multiple sclerosis

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keywords

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Abstract

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MSBASIS, a prospective, observational sub-study of the MSBase registry, collects demographic, clinical and paraclinical data on patients followed from MS onset (n=4718). We conducted a multivariable conditional risk set survival analysis to identify predictors of treatment discontinuation and assess if the introduction of fingolimod has altered treatment persistence.

Results

A total of 2640 patients commenced immunomodulatory therapy. Following the introduction of fingolimod, patients were more likely to discontinue all other treatments (hazard ratio 1.64, p<0.001) while more patients switched to fingolimod than any other therapy (42.3% of switches). Patients switched to fingolimod due to convenience. Patients treated with fingolimod were less likely to discontinue treatment compared to other therapies (p<0.001). Female sex, country of residence, younger age, a high EDSS and relapse activity were all independently associated with higher rates of treatment discontinuation.

Conclusion

Following the availability of fingolimod, patients were more likely to discontinue injectable treatments. Those who switched to fingolimod were more likely to do so for convenience. Persistence was improved on fingolimod compared to other medications.

Introduction

Disease modifying therapies (DMT) are moderately effective at reducing relapse rates, slowing disability progression, decreasing brain lesion accumulation and delaying conversion of clinically isolated syndrome (CIS) to relapsing-remitting multiple sclerosis (RRMS).[1, 2] Patients who persist on therapy have been reported to undergo fewer hospital admissions and to incur lower MS related healthcare costs when compared to patients who discontinue or never initiate a DMT.[3]

Until recently, the injectable compounds IFNβ-1a IM, IFNβ-1a SC, IFNβ-1b and glatiramer acetate were the only DMTs available. Despite evidence from controlled studies supporting their efficacy, the uptake of, and persistence on, these therapies has been limited by their parenteral route of administration, side effects and a perceived lack of efficacy on the part of the patient brought about by the unpredictable, intermittent nature of relapses.[4, 5] Studies have shown that persistence on injectable DMTs is surprisingly short. It has been reported that between 4% and 57% of patients discontinue treatment within 12 months of DMT initiation, with average persistence on therapy ranging from approximately 0.6 to 2.8 years and significant differences existing across countries and between nationalities.[5-11]

Fingolimod, the first widely available orally administered DMT, has been shown to be superior to both placebo and IFNβ-1a IM in reducing relapse activity and brain lesion accumulation.[12-14] Given it lacks some of the tolerability issues inherent in the injectable therapies, the introduction of fingolimod brings with it the prospect of improved treatment tolerance, increased treatment persistence and, potentially, improved patient outcomes. However, no large prospective studies have assessed patterns of treatment utilisation and switching since the introduction of fingolimod. The few published studies that have are retrospective in nature, with limited follow-up.[15, 16]

This study aims to characterise how the introduction of fingolimod has affected treatment persistence, treatment utilisation and predictors of treatment discontinuation in an international, prospective, observational cohort of patients with CIS and early RRMS.

Methods

Ethics Statement

The MSBase registry[17] (registered with WHO ICTRP, ID ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee. Human Research Ethics Committee approval, or exemptions according to local regulations, as well as written informed consent from patients to participate in the MSBase Registry, was obtained at each participating site.

Database

The MSBase Incident Study (MSBASIS) is an international, observational cohort study of patients seen from CIS onset, from 69 treatment centres across 19 countries (see Supplementary Table 1). The study commenced in December 2004. Data extraction took place on the 20th of January 2015. MSBASIS requires a minimum baseline dataset of MS related outcomes to be recorded at first visit, as well as a minimum dataset to be provided at each follow-up visit, which must occur at least annually. Patient datasets were recorded in near real-time using the iMed electronic patient record system.

Patients and Procedures

A patient was considered eligible for the study if a participating neurologist confirmed the diagnosis of CIS within 12 months of CIS onset using the 2005 or 2010 McDonald diagnostic criteria as per the year of diagnosis. Patients were excluded from the study if they had a diagnosis of primary progressive MS, were prescribed fingolimod as part of a clinical trial or were prescribed mitoxantrone or an oral DMT other than fingolimod (the latter exclusion being due to insufficient commencements per therapy for statistical analysis). The minimum baseline dataset included date of CIS onset, clinical presentation, Kurtzke Expanded Disability Status Scale (EDSS) and Functional System scores, and a cerebral magnetic resonance imaging

(MRI) scan available within 12 months of CIS onset. The minimum dataset collected at each follow-up appointment included date of visit, date of onset and duration of any relapses, DMT commencement and cessation dates, glucocorticoid therapy for relapses and EDSS scores including functional system scores. Reasons for treatment discontinuation were recorded for a proportion of treatment cessations. Online EDSS competency certification was required at each participating centre. The quality assurance procedures are described elsewhere.[4] For the purpose of this analysis, the start of the post-oral treatment epoch was determined for each country as the date of the first fingolimod initiation outside a clinical trial in patients within MSBASIS. Duration of each treatment within either of these epochs was specified, with left- and right-side censoring introduced to categorise the treatment extending across both epochs.[18]

Definitions

A relapse was defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for >24 hours, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse. Baseline annualised relapse rate (ARR) was calculated as the number of relapses experienced prior to treatment divided by the years between CIS onset and treatment commencement. The number of relapses in the 6 months preceding treatment discontinuation or censoring was noted. Change in EDSS was defined as the difference in EDSS scores between the earliest and latest visits within the treatment period. Treatment cessation was defined as a period of 90 or more days without treatment after a DMT was initiated. Treatment switch was defined as any DMT commencement following a previously discontinued therapy. A delayed continuation was defined as stopping a DMT for more than 90 days only to reinitiate the same DMT.

Statistical Analysis

In order to analyse treatment duration, patient data were censored at the most recent visit date. Treatment persistence for all initiation events was visualised using the Kaplan-Meier method. The formal statistical evaluation of the effect of treatment epoch and other predictors of treatment persistence was conducted with a two-step conditional risk set model, with the final multivariable model built based on the outcomes of a series of univariable models.[19] A variation of the Andersen-Gill model (a proportional hazards model with robust variance estimation), the conditional risk set model allows for multiple events and adjusts for the event dependence (such as the individual propensity to treatment discontinuations). Hazard proportionality was assessed in both the univariable and multivariable models by analysis of scaled Schoenfeld residuals. Interactions between epoch and all other variables were tested to determine whether the introduction of fingolimod had altered predictors of treatment discontinuation. Fisher's exact test was used to test for differences in the recorded reasons for treatment discontinuation between DMTs. All reported p-values are two-tailed and $p<0.05$ was considered significant for each analysis. All analyses were performed using Stata version 12.0 (StataCorp, College Station, Texas).

Results

Patient Demographics and Treatment Characteristics

A total of 4111 patients were included in the study, Figure 1 summarises patient disposition in relation to treatment epoch and exclusion criteria. Of these, a total of 2640 patients were prescribed at least one DMT over a median follow-up period of 4.8 years (Interquartile range (IQR): 2.4, 7.1), with 71.4% of first treatment commencements occurring prior to the introduction of oral therapies and 28.6% occurring after fingolimod became available. Baseline characteristics for patients at first treatment commencement for each DMT are summarised in Table 1. Patients initiating therapy with natalizumab appeared younger at symptom onset and treatment start, had higher relapse and MRI activity and were less likely to start therapy during

CIS when compared to patients on other treatments. Conversely, patients were more likely to start therapy during CIS with IFNβ-1a IM.

We recorded 1617 subsequent treatment commencements by 1102 patients, comprising 1399 treatment switches and 218 delayed continuations, resulting in 4257 total treatment starts over 12878 patient years of follow-up. Of these, 1204 treatments (28.3%) occurred exclusively in the pre-oral epoch, 1781 (41.8%) occurred exclusively in the post-oral epoch and 1272 treatments (29.9%) crossed over between the two epochs.

----Figure 1-----

----Table 1----

Treatment Persistence

One year after treatment commencement, 19.7% of all treatments had been discontinued. When analysing each DMT individually at one year after commencement, 22.6% of glatiramer acetate treatments, 18.9% of IFNβ-1a IM treatments, 21.0% of IFNβ-1b treatments, 19.7% of IFNβ-1a SC treatments, 21.2% of natalizumab treatments and 10.5% of fingolimod treatments had been discontinued. Table 2 summarises the treatment discontinuation events by sex, location, DMT identity, EDSS at treatment start and baseline MRI results.

Predictors of Treatment Discontinuation

Univariable analyses revealed that sex, location, treatment identity, pre-/post-oral epoch, age at treatment start, relapse activity and EDSS step at treatment start were all associated with changes in treatment discontinuation rates and were therefore included in the multivariable model. The multivariable analysis revealed that patients were significantly more likely to discontinue treatment in the post-oral epoch (figure 2a) (hazard ratio (HR): 1.64 $p<0.001$). However, while patients had an overall greater risk of discontinuing therapy in the post-oral

epoch, those patients who commenced fingolimod had a significantly lower risk of treatment discontinuation when compared to patients on all other therapies (figure 2b) (HR: 0.46, p<0.001 when compared to IFNβ-1a SC).

The multivariable model also demonstrated that male sex was predictive of a decreased risk of treatment discontinuation (Figure 2c), as was older age at treatment start. An EDSS of greater than 4 at treatment start when compared to an EDSS score of zero was associated with a greater risk of treatment discontinuation. Patients who discontinued therapy were more likely to have experienced relapses within the six months preceding treatment discontinuation, while patients being treated in all locations except for the Netherlands and Canada had a lower risk of treatment discontinuation when compared to patients in Australia. Table 2 provides detailed results of univariable and multivariable analyses. None of the tested interactions between epoch and other variables reached statistical significance.

----Figure 2----

----Table 2----

Treatment Switches

Before the introduction of oral therapies, the cohort recorded 2476 treatment commencements, including 519 treatment switches. The majority of patients switched to glatiramer acetate (28.5%), IFNβ-1a SC (26.2%) or natalizumab (26.4%). In the post-oral epoch, a total of 3053 treatments, including 882 switches, took place. Switching behaviour changed dramatically in the post-oral epoch, with the majority of switches being to fingolimod (42.3%), while 15.8% of switches were to glatiramer acetate, 13.0% were to IFNβ-1a SC and 21.1% were to natalizumab. Patient switching behaviours before and after the introduction of fingolimod are summarised in Table 3 and Table 4, respectively.

----Table 3----

----Table 4----

Reasons for Treatment Discontinuation and Switching

Recording of categorically described reasons for treatment discontinuation is not a mandatory part of the MSBASIS observational protocol, but the data was available for 54.8% of discontinuations. Table 5 reports the reasons for treatment discontinuation across all therapies, showing that an adverse event or lack of tolerance was the most common reason for treatment discontinuation amongst patients on IFNβ-1a SC, IFNβ-1b and glatiramer acetate (31.0 – 36.0% of recorded discontinuations) while patients on IFNβ-1a appeared more likely to discontinue treatment due to a lack of improvement (30.2%). Patients on fingolimod most commonly discontinued therapy due to either a lack of tolerance or lack of improvement (26.4% and 28.3% respectively). Patients on natalizumab most commonly discontinued due to a scheduled stop (45.0%), a category that was often used in association with positive John Cunningham virus serology.

When examining the reasons recorded for switching treatments after the introduction of oral therapies (see Table 6), a relatively larger proportion of patients switching to fingolimod did so for convenience (10.7%) compared to patients switching to natalizumab (2.6%) or other injectables (6.4%). Patients who stopped their previous therapy due to a lack of improvement, persistence of relapses or progression of disease made up the largest proportion of patients who subsequently commenced natalizumab. Patients were relatively less likely to switch to natalizumab after stopping their previous therapy due to an adverse event or lack of tolerance and a comparatively small proportion of patients switching to oral therapies switched after pregnancy compared to patients switching to natalizumab or to other injectables.

----Table 5----

----Table 6----

Discussion

In this analysis of prospectively collected data from the MSBase registry seen-from-onset cohort, we have shown that patients were more likely to discontinue immunomodulatory therapy once fingolimod became available, while their treatment persistence improved if treated with fingolimod compared to all other DMTs.

We found that 10.5% of patients prescribed fingolimod and between 18.9% and 22.6% of patients prescribed injectable DMTs discontinued treatment within 12 months of initiation. These results are in keeping with discontinuation rates of injectable DMTs reported by other studies. Retrospective American studies have reported 12-month discontinuation rates between 26% and 57%.[8, 9] Prospective European studies investigating long term adherence to injectable therapies have reported discontinuation rates between 4% over 12 months and 46% over 4.2 years.[10, 11] Given that the MSBase registry is composed of patients from treatment centres across a range of countries around the world, it is important to note that indications for fingolimod prescription differ between countries. While fingolimod is available as a first line therapy in countries such as Australia, the United States, Switzerland and Kuwait, in all other European Union member countries, including Italy and Spain, fingolimod, similar to natalizumab, is prescribed primarily as a second line therapy, with first line indication only for patients with very active disease. Prior MSBase studies, which investigated treatment persistence on two dosages of IFNβ-1a SC reported annualised discontinuation rates of 25% and 20% for the lower and higher doses, respectively.[4] While another study, which used the MSBASIS cohort to examine first treatment persistence, found that between 31% and 44% of patients discontinued injectable therapy over a median follow-up period between 2.3 years and 3.0 years.[20] To date, the only available study investigating adherence to fingolimod in a real world setting was published by Agashivala and colleagues. This study used a retrospective

pharmaceutical claims dataset with 12 months of follow-up. Among patients living in the United States with previous DMT experience, 26% of those prescribed fingolimod and between 37% and 57% of those prescribed injectable DMTs had discontinued therapy over 12 months of follow-up. These results are in agreement with our observation that patients on fingolimod discontinue treatment at a slower rate than patients on injectable DMTs.[15]

We have shown that an adverse event or lack of tolerability was the most common reason provided for treatment discontinuation across most of the injectable therapies, the exception being IFNβ-1a IM for which a lack of improvement was the most common reason provided. This finding is consistent with other studies.[5, 21, 22] Agashivala et al. suggested that the better persistence on fingolimod may be attributed to the once daily oral administration and lack of side effects frequently encountered with injectable DMTs, such as influenza-like symptoms and injection site reactions.[15] In our study, the proportion of patients who reported lack of tolerance/adverse event as a reason for fingolimod discontinuation was in the range of that for the injectable DMTs. Here we report that a significantly higher proportion of patients switched to fingolimod, and perhaps persisted on treatment, for convenience (10.7%) when compared to patients switching to injectable therapies or natalizumab. However, this result is limited by the small number of patients who discontinued fingolimod over the follow-up period (71 patients, of whom 53 provided reasons for discontinuation). The most common reason for switching to fingolimod was a lack of improvement on a previous therapy. Given that fingolimod has a second line indication in a majority of the countries included in this study, this result is not unexpected.

Our study demonstrated that the introduction of fingolimod has changed treatment switching patterns. In the pre-oral epoch, 73.6% of patients who switched therapies switched to one of the injectable DMTs, while 26.4% of switching patients escalated therapy to natalizumab. These results are consistent with retrospective studies that have looked at treatment switching patterns in MS prior to fingolimod introduction, which found that around 25% of patients on injectable therapies escalated to natalizumab.[16, 23] Treatment switching behaviour was altered

considerably in the post-oral epoch, with switching to fingolimod largely replacing the switching between IFN/GA preparations from the pre-oral epoch. Once it became available, 42.3% of switching patients switched to fingolimod, accounting for almost 90% of all fingolimod treatment initiations in our cohort. This reduced the proportion of patients switching to other injectables or natalizumab to 36.6% and 21.1%, respectively when compared to their pre-oral epoch share. The relatively smaller decrease in the proportion of patients switching to natalizumab may reflect its higher efficacy, which predisposes it for use in active disease.[24-26] We have supported this notion by showing that a relatively higher proportion of patients escalated therapy to natalizumab due to ongoing disease activity despite treatment (73.0%). Female sex, Australian residence, younger age at treatment start, a high EDSS at treatment commencement and on-treatment relapse activity were additional, independent, predictors of a shorter time to treatment discontinuation. Our finding that country of residence is closely related to treatment persistence, and that females are at a higher risk of discontinuing treatment, replicates and extends prior MSBasis cohort study results.[20] The propensity for females to discontinue therapy at a greater rate than males may be related to childbearing, with a planned or confirmed pregnancy accounting for between 8.5% and 13.4% of all recorded reasons for treatment discontinuation among female patients. This highlights a need for appropriate support and counselling of women planning pregnancy to ensure that they re-engage with treatment as soon as practicable post-pregnancy to guard against disability worsening.[27] We further confirmed the findings of prior studies showing that a high EDSS at treatment commencement is associated with treatment discontinuation.[5, 8] However, here we found that relapse rate on treatment, rather than increasing EDSS on treatment is associated with a significantly increased risk of treatment discontinuation

The prospective, observational nature of this study allowed us to follow a well-defined patient cohort representative of clinical practice at tertiary MS centres, over an extended period of follow-up. However, it is important to acknowledge that our data was incomplete in some areas, with a relative lack of MRI data and non-mandatory reporting of reasons for

discontinuation. There was also a discrepancy in the proportion of reasons for discontinuation recorded for patients on fingolimod (74.6%) as compared to injectables (52.8%), which could potentially bias our results. Similarly, data on comorbid conditions, which have been shown to affect treatment adherence,[28] is not collected as a mandatory part of the MSBASIS dataset and thus any potential effect could not be assessed. While our analysis had sufficient power to assess our primary endpoint, analysis of the interaction between epoch and other variables may have been underpowered. The observed variability in the length of follow up between treatment groups is due to their differing periods of availability, similarly, the observed variability in follow up between countries is due to the differing periods of involvement of the various treatment centres within the MSBASIS study (eTable 1).

In this study, we have shown that patients with early multiple sclerosis, treated at tertiary MS centres, are more likely to discontinue non-oral therapy in the post-oral epoch, while patients who switch to or initiate fingolimod tend to persist on therapy longer in comparison to patients on injectable DMTs. We speculate that this increased discontinuation rate may be driven by a large proportion of patients finding injectable treatment regimens relatively onerous and subsequently switching to oral DMTs due to their perceived improved tolerability and more convenient route of administration. In this study, we assessed how treatment behaviours have changed with the introduction of the first oral DMT. However further analyses are required to determine whether persistence on fingolimod is superior to that of other oral DMTs once they become more widely available and prescribed. While it is encouraging to see improved treatment persistence in patients taking fingolimod, it remains to be shown if this improved persistence will be associated with improvements in patient outcomes such as disability progression, relapse rate and MRI activity.

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Conflict of Interest Statement

Alessandra Lugaresi is a Bayer Schering, Biogen Idec, Genzyme, Merck Serono Advisory Board Member. She received travel grants and honoraria from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi/Genzyme and Teva, research grants from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi and Teva, travel and research grants from the Associazione Italiana Sclerosi Multipla.

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Jose Antonio Cabrera-Gomez did not declare any competing interests.

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Table 1

Baseline characteristics at first treatment initiation by DMT identity

Variable	All DMTs	IFNβ-1a IM	IFNβ -1a SC	IFNβ -1b	GA	NAT	FTY
Patients – n (%)	2640 (100)	812 (30.8)	792 (30.0)	520 (19.7)	403 (15.3)	68 (2.6)	45 (1.7)
Sex – n (%)							
Female	1857 (70.3)	561 (69.1)	545 (68.8)	368 (70.8)	308 (76.4)	42 (61.8)	33 (73.3)
Location – n (%)							
Australia	265 (10.0)	40 (4.9)	58 (7.3)	84 (16.1)	52 (12.9)	15 (22.1)	16 (35.6)
Canada	288 (10.9)	75 (9.2)	89 (11.2)	39 (7.5)	68 (16.9)	14 (20.6)	3 (6.7)
Italy	509 (19.3)	164 (20.2)	217 (27.4)	45 (8.7)	76 (18.9)	6 (8.8)	1 (2.2)
Spain	388 (14.7)	77 (9.5)	123 (15.5)	103 (19.8)	62 (15.4)	10 (14.7)	13 (28.9)
Netherlands	211 (8.0)	33 (4.1)	92 (11.6)	40 (7.7)	44 (10.9)	2 (2.9)	0 (0.0)
Other	979 (37.1)	423 (52.1)	213 (26.9)	209 (40.2)	101 (25.1)	21 (30.9)	12 (26.7)
Age at symptom onset – mean (SD)	31.7 (9.6)	31.1 (9.5)	31.2 (9.6)	31.8 (9.3)	34.1 (9.9)	29.0 (9.7)	31.5 (10.6)
Age at treatment start – mean (SD)	32.9 (10.0)	32.0 (9.6)	32.4 (9.6)	33.0 (9.4)	35.7 (9.9)	30.2 (10.0)	33.8 (11.3)
Follow-up (years) – median (IQR)	4.8 (2.4, 7.1)	5.4 (2.9, 7.2)	4.6 (2.3, 6.9)	4.8 (2.6, 7.0)	4.2 (2.0, 7.0)	3.0 (1.8, 4.5)	2.6 (1.7, 4.9)
Epoch – n (%)							
Pre-oral	1884 (71.4)	658 (81.0)	560 (70.7)	382 (73.5)	265 (65.8)	19 (27.9)	0 (0.0)
Post-oral	756 (28.6)	154 (19.0)	232 (29.3)	138 (26.5)	138 (34.2)	49 (72.1)	45 (100)
EDSS at treatment start – median (IQR)	2 (1, 2.5)	1.5 (1, 2)	2 (1, 2.5)	2 (1, 2.5)	2 (1, 2.5)	2.5 (1.5, 4)	2 (1.0, 2.5)
Baseline ARR – median (IQR)	0.3 (0, 1.5)	0 (0, 0.7)	0.9 (0, 1.9)	0.2 (0, 1.4)	0.6 (0, 1.6)	1.7 (0.7, 2.4)	0.5 (0, 1.4)
Disease course– n (%)							
CIS	678 (27.6)	375 (46.2)	99 (12.5)	136 (26.2)	61 (15.1)	3 (4.4)	4 (8.9)
RRMS	1959 (74.2)	437 (53.8)	692 (87.4)	382 (73.5)	342 (84.9)	65 (95.6)	41 (91.1)
SPMS	3 (0.1)	0 (0.0)	1 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
T2 hyperintense lesions – n (% of available)							
MRI available	1810 (68.8)	460 (56.7)	575 (72.6)	357 (68.7)	289 (71.7)	47 (69.1)	36 (80.0)
≥ 9	672 (37.1)	164 (35.2)	200 (33.7)	149 (41.7)	104 (34.7)	37 (64.9)	18 (50.0)
< 9	1138 (62.9)	302 (64.8)	394 (66.3)	208 (58.3)	196 (65.3)	20 (35.1)	18 (50.0)
Contrast enhancing lesions – n (% of available)							
MRI Available	1476 (55.9)	380 (46.8)	507 (64.0)	288 (55.4)	230 (57.1)	44 (64.7)	27 (60.0)

≥ 1	405 (27.4)	89 (23.4)	149 (29.4)	79 (27.4)	47 (20.4)	27 (61.4)	14 (51.9)
0	1071 (72.6)	291 (76.6)	358 (70.6)	209 (72.6)	183 (79.6)	17 (38.6)	13 (48.1)

Abbreviations: n, number; DMT, Disease modifying therapy; IFN, Interferon; GA, Glatiramer Acetate; NAT, Natalizumab; FTY, Fingolimod; SD, Standard deviation; IQR, Interquartile range; EDSS, Expanded disability status scale; ARR, Annualised relapse rate; CIS, Clinically isolated syndrome; RRMS, Relapsing remitting multiple sclerosis; MRI, Magnetic resonance imaging.

Table 2

Predictors of treatment discontinuation in the MSBasis cohort

Predictor	Level	Discontinuations / total treatments (% of level)	Discontinuation rate per annum	Univariable HR (95% CI)[α]	P	Multivariable HR (95% CI)[α#]	P
Sex	Female	1572/3095 (50.8)	0.21	Reference		Reference	
	Male	486/1162 (41.8)	0.16	**0.73 (0.67, 0.82)**	**<0.001**	**0.72 (0.63, 0.82)**	**<0.001**
Location	Australia	322/533 (60.4)	0.29	Reference		Reference	
	Canada	318/536 (59.3)	0.21	0.76 (0.65, 0.88)	<0.001	0.86 (0.67, 1.1)	0.2
	Italy	399/838 (47.6)	0.18	**0.63 (0.55, 0.73)**	**<0.001**	**0.67 (0.54, 0.84)**	**<0.001**
	Spain	232/582 (39.9)	0.14	**0.51 (0.43, 0.60)**	**<0.001**	**0.49 (0.38, 0.63)**	**<0.001**
	Netherlands	165/315 (52.4)	0.25	0.86 (0.71, 1.05)	0.2	0.85 (0.62, 1.18)	0.3
	Other	622/1453 (42.8)	0.18	**0.64 (0.56, 0.74)**	**<0.001**	**0.68 (0.55, 0.85)**	**0.001**
Treatment	IFNβ-1a SC	567/1115 (50.1)	0.20	Reference	-	Reference	-
	IFNβ-1a IM	520/964 (53.9)	0.19	0.98 (0.87, 1.10)	0.7	1.1 (0.93, 1.28)	0.3
	IFNβ-1b	349/626 (55.8)	0.21	1.10 (0.96, 1.24)	0.2	1.03 (0.86, 1.23)	0.7
	GA	374/718 (52.1)	0.23	1.13 (0.99, 1.28)	0.1	1.04 (0.87, 1.25)	0.6
	NAT	177/408 (43.4)	0.21	0.93 (0.78, 1.10)	0.4	1.05 (0.82, 1.34)	0.7
	FTY	71/426 (16.7)	0.11	**0.44 (0.35, 0.57)**	**<0.001**	**0.46 (0.33, 0.66)**	**<0.001**
Epoch	Pre-oral	857/2476 (34.6)	0.18	Reference		Reference	
	Post-oral	1201/3053 (39.3)	0.21	**1.22 (1.11, 1.35)**	**<0.001**	**1.64 (1.44, 1.86)**	**<0.001**
Age at treatment start	Per 10 years	-	-	**0.88 (0.84, 0.93)**	**<0.001**	**0.80 (0.74, 0.85)**	**<0.001**
EDSS at treatment start	0	235/449 (52.3)	0.22	Reference	-	Reference	

	1 - 3.5	1328/2804 (47.4)	0.18	0.83 (0.72, 0.95)	0.008	1.06 (0.87, 1.29)	0.6
	≥ 4	231/416 (55.5)	0.26	1.17 (0.97, 1.41)	0.1	**1.50 (1.14, 1.97)**	**0.004**
	Missing*	264/588 (44.9)	0.23	-	-	-	-
Change in EDSS	Per EDSS step	-	-	1.06 (1.01, 1.10)	0.01	1.04 (0.99, 1.10)	0.08
Relapses in the final 6 months of observation or treatment	Per relapse	-	-	**1.86 (1.74, 1.98)**	**<0.001**	**2.27 (2.07, 2.50)**	**<0.001**
MRI – T2 hyperintense lesion	≥ 9	498/1073 (46.4)	0.22	1.10 (0.99, 1.23)	0.08	-	-
	< 9	911/1833 (49.7)	0.20	Reference		-	
	Missing	649/1351 (48.0)	0.18	-	-	-	-
MRI – Gadolinium enhancing lesion	≥ 1	281/628 (44.7)	0.20	1.01 (0.89, 1.16)	0.8	-	-
	0	887/1758 (50.4)	0.19	Reference		-	-
	Missing	890/1871 (47.6)	0.20	-	-	-	-

Scaled Schoenfeld residuals test (global) for the final multivariable model: p=0.15.

Abbreviations: n, number; HR, Hazard Ratio; CI, Confidence Interval; IFN, Interferon; IM, Intramuscular; SC, Subcutaneous; GA, Glatiramer Acetate; NAT, Natalizumab; FTY, Fingolimod; EDSS, Expanded disability status scale; MRI, Magnetic resonance imaging.

[α]Conditional risk set model, a variation of the Andersen-Gill proportional hazards model, adjusted for even dependence, with time to discontinuation measured from study entry.

[#]Multivariable conditional risk set model was adjusted for sex, location, treatment, age at treatment start, EDSS at treatment start, change in EDSS over treatment duration, number of relapses in the 6 months leading up to treatment cessation or final visit and baseline.

*No EDSS score available at treatment start.

Table 3

Treatment switching behaviour in the pre-oral therapy epoch

	Initial DMT					
	IFNβ-1a IM	**IFNβ-1a SC**	**IFNβ-1b**	**GA**	**NAT**	**Total**
Total Switches / Total Treatments	194/733	143/716	94/446	76/423	12/158	519/2476
Subsequent DMT						
IFNβ-1a IM	-	16 (11.2)	16 (17.0)	18 (23.7)	1 (8.3)	51 (9.8)
IFNβ-1a SC	95 (49.0)	-	15 (16.0)	23 (30.3)	3 (25.0)	136 (26.2)
IFNβ-1b	29 (15.0)	9 (6.3)	-	8 (10.5)	1 (8.3)	47 (9.1)
GA	42 (21.6)	66 (46.1)	33 (35.1)	-	7 (58.3)	148 (28.5)
NAT	28 (14.4)	52 (36.4)	30 (31.9)	27 (35.5)	-	137 (26.4)

Table refers to a subset of the study cohort, those patients who discontinued therapy and commenced a different therapy prior the introduction of oral therapies.

Abbreviations: IFN, Interferon; IM, Intramuscular; SC, Subcutaneous; GA, Glatiramer Acetate; NAT, Natalizumab

Table 4

Treatment switching behaviour in the post-oral therapy epoch

	Initial DMT						
	IFNβ-1a IM	**IFNβ-1a SC**	**IFNβ-1b**	**GA**	**NAT**	**FTY**	**Total**
Total Switches / Total Treatments	172/593	245/787	145/386	177/516	103/347	40/426	882/3053
Subsequent DMT							
IFNβ-1a IM	-	13 (5.3)	11 (7.6)	17 (9.6)	2 (1.9)	1 (2.5)	44 (5.0)
IFNβ-1a SC	69 (40.1)	-	7 (4.8)	28 (15.8)	7 (6.8)	4 (10.0)	115 (13.0)
IFNβ-1b	9 (5.2)	5 (2.0)	-	8 (4.5)	2 (1.9)	1 (2.5)	25 (2.8)
GA	23 (13.4)	61 (24.9)	33 (22.8)	-	21 (20.4)	1 (2.5)	139 (15.8)
NAT	20 (11.6)	59 (24.1)	33 (22.8)	41 (23.2)	-	33 (82.5)	186 (21.1)
FTY	51 (29.7)	107 (43.7)	61 (42.1)	83 (46.9)	71 (68.9)	-	373 (42.3)

Table refers to a subset of the study cohort, those patients who discontinued therapy and commenced a different therapy after the introduction of oral therapies.
Abbreviations: DMT, Disease modifying therapy; IFN, Interferon; IM, Intramuscular; SC, Subcutaneous; GA, Glatiramer Acetate; NAT, Natalizumab; FTY, Fingolimod

Table 5

Reasons for treatment discontinuation for all treatment commencements

	IFNβ-1a IM	IFNβ-1a SC	IFNβ-1b	GA	NAT	FTY	P#
Commencements – n	964	1115	626	718	408	426	
Discontinuations – n	520	567	349	374	177	71	
Recorded reasons for discontinuation – n (%)	311 (59.8)	284 (50.1)	171 (49.0)	189 (50.5)	120 (67.8)	53 (74.6)	
Reasons recorded – n (%)*							
Adverse event/lack of tolerance	69 (22.2)	94 (33.1)	53 (31.0)	69 (36.0)	18 (15.0)	14 (26.4)	**<0.001α**
Lack of improvement	94 (30.2)	73 (25.7)	34 (19.9)	43 (22.8)	13 (10.8)	15 (28.3)	**0.001α**
Persistence of relapse	18 (5.8)	7 (2.5)	10 (5.8)	5 (2.6)	0 (0.0)	5 (9.4)	**0.003α**
Progression of disease	27 (8.7)	16 (5.6)	8 (4.7)	14 (7.4)	5 (4.2)	1 (1.9)	0.3α
MRI activity	13 (4.2)	1 (0.4)	1 (0.6)	4 (2.1)	0 (0.0)	2 (3.8)	**0.02α**
Pregnancy	40 (12.9)	38 (13.4)	18 (10.5)	16 (8.5)	14 (11.7)	7 (13.2)	0.6α
Convenience	26 (8.4)	26 (9.2)	22 (12.9)	20 (10.6)	12 (10.0)	6 (11.3)	0.7α
Non-adherence	6 (1.9)	8 (2.8)	2 (1.2)	5 (2.6)	4 (3.3)	2 (3.8)	0.7α
Scheduled Stop	18 (5.8)	21 (7.4)	23 (13.5)	13 (6.9)	54 (45.0)	1 (1.9)	**<0.001α**

Abbreviations: n, number; IFN, Interferon; GA, Glatiramer Acetate; NAT, Natalizumab; MRI, Magnetic resonance imaging

*Percentage of recorded reasons

#p-value between treatment groups

αFisher's exact test.

Table 6

Reasons for switching to injectable therapies, fingolimod or natalizumab in the post-oral therapy epoch

	Injectable	Natalizumab	Fingolimod	P#
Switches to subsequent DMT - n	323	186	373	
Recorded reasons for switch – n (%)	235 (72.8)	115 (61.8)	214 (57.4)	
Reasons recorded – n (%)*				
Adverse event/lack of tolerance	62 (26.4)	8 (7.0)	51 (23.8)	**<0.001α**
Lack of improvement	50 (21.3)	52 (45.2)	67 (31.3)	**<0.001α**
Persistence of relapse	6 (2.6)	17 (14.8)	8 (3.7)	**<0.001α**
Progression of disease	11 (4.7)	15 (13.0)	9 (4.2)	**0.007α**
MRI activity	8 (3.4)	2 (1.7)	4 (1.9)	0.6α
Pregnancy	51 (21.7)	13 (11.3)	9 (4.2)	**<0.001α**
Convenience	15 (6.4)	3 (2.6)	23 (10.7)	**0.020α**
Non-adherence	8 (3.4)	2 (1.7)	4 (1.9)	0.6α
Scheduled Stop	24 (10.2)	3 (2.6)	39 (18.2)	**<0.001α**

Abbreviations: n, number; MRI, Magnetic resonance imaging

*Percentage of recorded reasons

#p-value between treatment groups

αFisher's exact test.

Pregnancy refers to mothers who recommenced a different therapy after having children.

Figure Legends

Figure 1

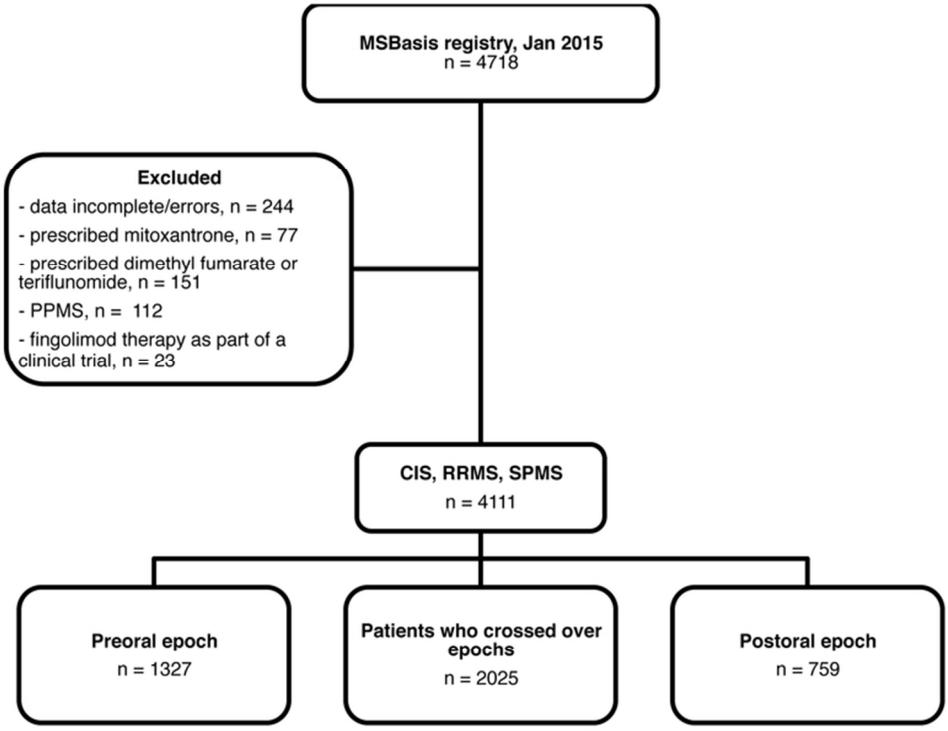
CONSORT flowchart of patient disposition.

Abbreviations: n, number; CIS, Clinically isolated syndrome; RRMS, Relapsing remitting multiple sclerosis; SPMS, Secondary progressive multiple sclerosis; PPMS, Primary progressive multiple sclerosis.

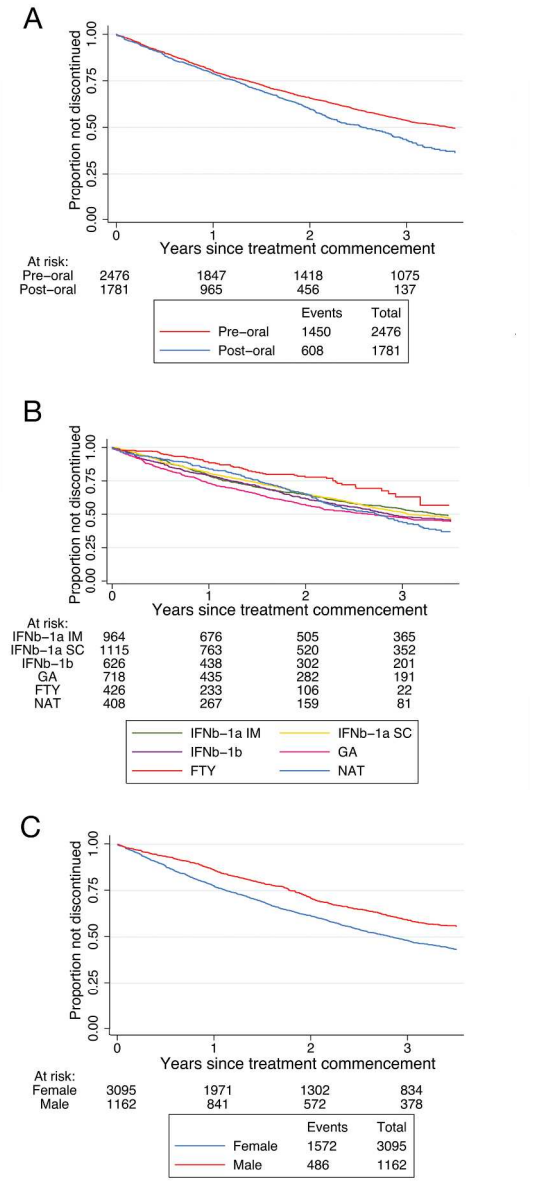
Figure 2

Kaplan-Meier estimates of treatment discontinuation.

A: Treatment discontinuation by treatment epoch; B: Treatment discontinuation by DMT identity; C: Treatment discontinuation by patient sex.
Kaplan Meier curves were derived from treatment data not clustered by patient ID, with time to discontinuation measured from treatment start.



CONSORT flowchart of patient disposition
69x52mm (300 x 300 DPI)



Kaplan-Meier estimates of treatment discontinuation
203x458mm (300 x 300 DPI)

eTable 1: **Number of eligible patients per centre**

Centre	Country	Eligible patients	Cumulative follow up (years)
FLENI	Argentina	87	165.5
Hospital Italiano	Argentina	50	150.7
INEBA	Argentina	31	84.6
The Royal Melbourne Hospital	Australia	120	635.8
Box Hill Hospital	Australia	88	418.6
John Hunter Hospital	Australia	79	291.4
Flinders Medical Centre	Australia	26	109.3
BMRI	Australia	22	107.8
Geelong Hospital	Australia	18	50.2
St Vincent's Hospital	Australia	16	117.4
Cliniques Universitaires Saint-Luc	Belgium	46	231.6
Neuro Rive-Sud	Canada	187	936.0
CHUM – Hospital Notre Dame	Canada	108	667.2
Hotel-Dieu de Levis	Canada	95	639.2
Jewish General Hospital	Canada	38	189.7
CIREN	Cuba	97	519.7
General Teaching Hospital	Czech Republic	381	1936.8
Aarhus University Hospital	Denmark	93	216.7
Hopital Tenon	France	152	99.7
Al-Zahra Hospital	Iran	4	2.6
University of Bari	Italy	285	1497.4
University 'G. d'Annunzio'	Italy	249	850.0
Ospedali Riuniti di Salerno	Italy	146	295.0
Generale Provinciale Macerata	Italy	92	473.6
National Neurological Institute C. Mondino	Italy	35	173.7
University of Florence	Italy	22	47.8
Amiri Hospital	Kuwait	180	335.3
Clinic of Neurology Clinical Center	Macedonia	41	164.7
Mater Dei Hospital	Malta	30	83.0
University Hospital Nijmegen	Netherlands	109	123.5
Orbis Medicle Center	Netherlands	107	505.7
Groene Hart Ziekenhuis	Netherlands	68	320.5
Hospital Universitario Virgen Macarena	Spain	360	1630.5
Hospital Universitario La Paz	Spain	157	446.0
Hospital Universitario Virgen de Valme	Spain	97	519.7
Hospital Donostia	Spain	9	18.3
Universitatsspital Basel	Switzerland	3	6.4
Farabi Hospital, Karadeniz Technical University	Turkey	204	559.7
19 Mayis University, Medical Faculty	Turkey	116	223.9
The Walton Centre for Neurology and Neurosurgery	United Kingdom	13	13.6
Craigavon Area Hospital	United Kingdom	11	48.3
New York University Langone Medical Center	United States	39	98.1

STROBE Statement—checklist of items that should be included in reports of observational studies

Title: "The effect of oral immunomodulatory therapy on treatment uptake and persistence in multiple sclerosis"

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8-9
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig 1
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-11
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	9-10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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