The Australian Multiple Sclerosis (MS) Immunotherapy Study: A Prospective, Multicentre Study of Drug Utilisation Using the MSBase Platform

Vilija G. Jokubaitis¹,², Tim Spelman², Jeannette Lechner-Scott³,⁴, Michael Barnett⁵, Cameron Shaw⁶, Steve Vucic⁷, Danny Liew¹, Helmut Butzkueven¹,²,⁸, Mark Slee⁹, on behalf of the Australian MSBase Study Group

¹ Melbourne Brain Centre (RMH), Department of Medicine, The University of Melbourne, Parkville, Victoria, Australia, ² Department of Neurology, Royal Melbourne Hospital, Parkville, Victoria, Australia, ³ Department of Neurology, John Hunter Hospital, Newcastle, New South Wales, Australia, ⁴ Hunter Medical Research Institute, University of Newcastle, Newcastle New South Wales, Australia, ⁵ Brain Mind Research Institute, Sydney, New South Wales, Australia, ⁶ Department of Neuroscience, Geelong Hospital, Geelong, Victoria, Australia, ⁷ Department of Neurology, Westmead Hospital, Westmead, New South Wales, Australia, ⁸ Department of Neurology, Box Hill Hospital, Monash University, Box Hill, Victoria, Australia, ⁹ Flinders University and Medical Centre, Adelaide, South Australia, Australia

Abstract

Objective: To prospectively characterise treatment persistence and predictors of treatment discontinuation in an Australian relapsing-remitting multiple sclerosis (RRMS) population.

Methods: Tertiary MS treatment centres participating in the MSBase registry prospectively assessed treatment utilisation, persistence, predictors of treatment discontinuation and switch rates. Multivariable survival analyses were used to compare treatment persistence between drugs and to identify predictors of treatment discontinuation.

Results: 1113 RRMS patients were studied. Patients persisted on their first disease-modifying therapy (DMT) for a median of 2.5 years. Treatment persistence on GA was shorter than on all IFNβ products (p<0.03). Younger age at treatment initiation and higher EDSS were predictive of DMT discontinuation. Patients persisted on subsequent DMTs, for 2.3 years. Patients receiving natalizumab (NAT) as a subsequent DMT persisted longer on treatment than those on IFNβ or GA (p<0.000). The primary reason for treatment discontinuation for any drug class was poor tolerability. Annualised switch or cessation rates were 9.5–12.5% for individual IFNβ products, 11.6% for GA and 4.4% for NAT.

Conclusion: This multicentre MS cohort study is the first to directly compare treatment persistence on IFNβ and GA to NAT. We report that treatment persistence in our Australian RRMS population is short, although patients receiving IFNβ as a first DMT persisted longer on treatment than those on GA. Additionally, patients receiving NAT as a subsequent DMT were more likely to persist on treatment than those switched to IFNβ or GA. EDSS and age at DMT initiation were predictive of DMT discontinuation. Treatment intolerance was the principal reason for treatment cessation.

Citation: Jokubaitis VG, Spelman T, Lechner-Scott J, Barnett M, Shaw C, et al. (2013) The Australian Multiple Sclerosis (MS) Immunotherapy Study: A Prospective, Multicentre Study of Drug Utilisation Using the MSBase Platform. PLoS ONE 8(3): e59694. doi:10.1371/journal.pone.0059694

Editor: Celia Oreja-Guevara, University Hospital La Paz, Spain

Received September 18, 2012; Accepted February 17, 2013; Published March 19, 2013

Copyright: © 2013 Jokubaitis et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This study was sponsored by the MSBase Foundation, a not-for-profit organisation. The MSBase Foundation receives financial support from Merck Serono, Biogen Idec, Novartis Pharma, Genzyme and CSL. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: Dr Jokubaitis reports no disclosures. Dr Spelman has received a travel grant from Novartis Australia. Dr Lechner-Scott’s institution receives non-directed funding as well as honoraria for presentations and membership on advisory boards from CSL, Genzyme, Biogen Idec, Bayer Health Care, Merck Serono and Novartis Australia. Dr Barnett has received research support and/or honoraria from Bayer Schering, Biogen Idec, Merck Serono, Novartis Pharma, Sanofi and Teva. Dr Shaw reports no disclosures. Dr Vucic serves on the scientific advisory board from Novartis Pharma, Merck Serono Australia and Bayer Schering Australia. Dr Vucic serves as a medical consultant for Merck Serono Australia. Dr Liew has received honoraria from Novartis and Sanofi. Dr Butzkueven has served on scientific advisory boards for Biogen Idec, Novartis and Sanofi and has received conference travel support from Novartis, Biogen Idec and Sanofi. He serves on steering committees for trials conducted by Merck Serono, Biogen Idec and Novartis. Dr Butzkueven has received research support from Merck Serono, Novartis and Biogen Idec in his capacity as honorary chair of the MSBase Foundation. He is on the editorial board of Multiple Sclerosis International. Dr Slee reports participating in advisory boards for Sanofi, Merck Serono, Biogen Idec, Novartis Pharma and Bayer Schering. This does not alter the authors’ adherence to all the PLOS ONE policies on sharing data and materials.

* E-mail: vilija.jokubaitis@unimelb.edu.au

† These authors contributed equally to this work.

‡ Membership of the Australian MSBase Study Group is provided in the Acknowledgments.
Introduction

Multiple Sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system. For most patients with MS, the initial disease course features relapses and remissions (RRMS), whereas the later disease course is characterised by the progressive accumulation of disability. Early in the course of RRMS, parental disease modifying therapies (DMT), such as interferon-beta (IFNβ), glatiramer acetate (GA) or natalizumab (NAT) reduce the relapse rate and the rate of disability progression [1,2,3,4].

The concept of treatment adherence encompasses both compliance and persistence. Compliance can be defined as the ability to follow a pre-specified administration schedule without missing doses, which was not assessed in the current study. Persistence refers to a patient’s ongoing treatment utilisation [5].

Our current understanding of DMT persistence in MS has been informed by data from a number of sources, including large phase III trials [6]. However, the environment of a trial does not reflect typical clinical practice. Many clinical practice-based DMT utilisation studies have been retrospective or relied on insurance claims or prescription data [7,8,9]. In general, these studies have shown poor persistence rates for MS DMTs, but they are methodologically weakened by bias due to their retrospective nature and limited clinical data [10,11].

Therefore, we chose to undertake a large, prospective, multicentre study of MS therapy utilisation (encompassing persistence), and predictors of treatment switching and discontinuation. We sought to assess persistence and switch on all commercially available DMT including IFNβ, GA and NAT all of which have first-line indications in Australia.

Methods

MSBase Registry

The MSBase Registry (www.msbase.org) is a collaborative international registry that prospectively collects neurological outcome data from consenting MS patients attending MS specialist centres and clinics [12]. The registry is operated by the not-for-profit MSBase Foundation and its data is physician-owned, with access freely available to participating neurologists.

Data are collected using an offline, electronic medical record program called iMed within clinical settings. Quality control of data is ensured through the use of drop down menus restricting data entry errors. Data are then anonymised and transmitted to the MSBase Registry server. The MSBase Registry contains data collected from over 65 clinics in 28 countries, representing over 20,000 patient datasets. For quality assurance, all participating neurologists are required to complete online Expanded Disability Status Scale (EDSS) certification through the Neurostatus online certification program (www.neurostatus.net).

The Australian MSBase Clinical Cohort

Patients with MS (revised McDonald criteria) were enrolled from seven Australian academic centres with specialist MS clinics (The Royal Melbourne Hospital, Vic; Box Hill Hospital, Vic; John Hunter Hospital, NSW; Brain and Mind Research Institute, NSW; Flinders Medical Centre, SA; Geelong Hospital, Vic, and Westmead Hospital, NSW). Patients underwent routine clinical assessments, were subtyped by clinical course and had the MSBase minimum dataset updated during routine initial and follow-up clinic visits [12]. Follow-up visits occurred at least once annually. Centres provided patients with access to multidisciplinary care, including nurse education for GA and IFN injection training and regular follow-up by nurses post initial training.

Data Collection

Treating physicians prospectively collected pre-specified data at the time of clinic visit.

Treatment start, stop and switch decisions were made in consultation between patients and their treating physicians during clinic visits and all treatment identities, start and stop dates were recorded at that time. When patients discontinued treatment, a field with categorical reasons for treatment discontinuation appeared upon entering a treatment stop date. The reporting of reasons for treatment discontinuation was not mandated for this analysis, however, all collected reasons for treatment discontinuation were analysed (52% of all discontinuations). The captured discontinuation reasons were balanced across all DMT preparations.

The observation period for this study commenced on 1 January 1998, when MS-specific DMTs became commercially available in Australia, and ended on the date of data extraction, 10 June 2010. As MSBase is an ongoing project, data were censored at the patients’ most recent visit. A minimum of 2 visits per patient were required to be included in the study; therefore, the observation interval for each patient was defined by their first and last visits. Patients with only a single visit recorded were excluded from analysis. Patients who initiated with their first DMT prior to 1998 were excluded from this study. Only new users were included in this analysis.

Data extracted from the MSBase Registry on 10 June 2010 comprised 1618 Australian patient datasets, representing approximately 15% of the Australian MS patient population. These patients were typical of those seen in large tertiary referral centres.

Ethics Statement

All patients gave written informed consent to participate in the MSBase Registry and Human Research Ethics Committee (HREC) approval was obtained from all participating centres: The Royal Melbourne Hospital; Box Hill Hospital; John Hunter Hospital; Brain and Mind Research Institute; The Southern Adelaide Clinical HREC; Barwon Health; Western Sydney Local Health District.

Statistical Analyses

Sex, age, disease course, DMT identity, reasons for treatment discontinuation, proportion of time treated (PTT) and annualised relapse rate were summarised using frequencies and percentages. As EDSS, treatment persistence and time to treatment switch all demonstrated non-normality, these were described using medians and inter-quartile ranges (IQR). Data assessing treatment duration were censored at the patients’ most recent clinic visit date. Kaplan-Meier estimates were used to describe the cumulative probability of treatment discontinuation. Predictors of treatment discontinuation were analysed using univariable and multivariable Cox proportional hazards regression and quantified using Hazard Ratios (HR). Hazard proportionality was assessed by analysis of scaled Schoenfeld residuals. One-way ANOVA with Bonferroni’s post hoc test was used to test for differences between continuous variables, $\chi^2$ tests were used for categorical variables and Kruskal-Wallis tests were used to test for differences between discrete variables.

All reported p values are two-tailed and for each analysis $p<0.05$ was considered significant. All analyses were performed using Stata version 12.0 software package (StataCorp, College Station, Texas).
Definitions

PTT was the proportion of time patients were treated with a DMT as recorded in the MSBase Registry. The PTT assumes compliance.

Treatment cessation was defined as a break of 90 or more days with no further DMT use recorded. Patients were considered to have switched if a subsequent DMT was recorded.

Results

Australian MS Clinical Cohort Demographics

The Australian MSBase Registry cohort had a median follow-up of 2.3 years (IQR: 1.0, 4.4 years). At the date of data extraction, the average age of the cohort was 45.4 (standard deviation, SD) 12.5 years, comprising 74.4% females and 25.6% males with a median EDSS of 3 (range 0–9).

The cohort consisted of patients with clinically isolated syndrome (CIS) 6.0%, RRMS 68.8%, secondary progressive MS (SPMS) 15.8%, primary progressive MS (PPMS) 6.6% and progressive relapsing MS (PRMS) 2.8%. For the purposes of the current study, only RRMS patients were further analysed.

RRMS Patient Demographics

A total of 1113 RRMS patients were followed up for a median of 2.0 years (IQR 0.80, 4.0). The RRMS population comprised 856 (76.9%) females and 257 (23.1%) males who were predominately of Caucasian background (95.3%), with the remaining 4.7% comprising Semitic, Asian, Eurasian, Hispanic, African and Inuit backgrounds. The average age at RRMS diagnosis was 31.8 (SD 10.1) years, with median time to diagnosis of 1.1 years (IQR: 0.33, 3.9 years).

Overview of Treatment Utilisation by RRMS Patients

Median time to treatment initiation with DMTs for patients diagnosed with RRMS was 0.64 years (IQR 0.16, 3.16) from clinically definite MS diagnosis date. A total of 724 (65%) RRMS patients were treated with DMTs at their most recent visit. A total of 908 (81.6%) patients had used at least one DMT at some point, while 205 patients (18.4% of the RRMS population) were never treated with a DMT.

Of the patients treated with a DMT at their most recent visit, 80.4% were treated with either GA or an IFNβ preparation, 18.5% were treated with NAT, and 1.8% were treated with chemotherapeutics.

We recorded 771 first GA/IFNβ/NAT treatment commencements. These patients were followed up for a median of 4.2 years (IQR 2.1, 7.0), and met with their treating physician a median of 6 times (IQR 3, 11) over the observation period. Baseline characteristics of patients initiating with their first DMT are summarised in Table 1. Of these 771 first treatment initiations, only 325 (42.2%) patients were still continuing on their first DMT at their most recent visit, while 105 patients (13.6%) patients switched treatment it was 3.1:1; for patients disengaging from treatment the sex ratio was 3.4:1 and for patients who...
recorded a delayed continuation, the sex ratio was 13.3:1 (Pearson \( \chi^2 \), p = 0.08), as the vast majority of these were due to pregnancy.

**DMT Persistence**

**First treatment initiation.** Australian RRMS patients persisted on their first GA/IFN/NAT DMT for a median duration of 2.5 years (IQR 1.0, 6.7, n = 771). When analysed by individual DMT, patients remained on GA for a median of 1.7 years (IQR 0.62, 5.2, n = 117), IFNβ-1a IM for a median of 2.6 years (IQR 1.2, 8.5, n = 153), IFNβ-1b for a median of 2.8 years (IQR 1.0, 5.8, n = 153), and IFNβ-1a SC for a median of 2.4 years (IQR 0.70, 7.1, n = 229; Figure 1a). NAT was a rare first choice of DMT. These patients were followed-up on therapy for an average of 1.2 years (SD 0.72 years, n = 11). No patients had ceased first-line NAT treatment at their most recent visit.

![Figure 1](https://example.com/figure1.png)

**Proportion of Time Treated, Treatment Cessations and Switches**

Table 2 summarises both univariable and multivariable analyses of predictors of treatment discontinuation of first recorded DMT. We found on both unadjusted and adjusted analyses that patients receiving GA as their first DMT discontinued treatment at a greater rate than those patients on IFNβ-1a IM (HR 1.74, p = 0.001 on adjusted analysis). Similarly, patients initiating with GA as their first DMT discontinued treatment at a greater rate than patients on IFNβ-1b (HR 1.47, p = 0.01) or IFNβ-1a SC (HR 1.40, p = 0.03, Table S1).

Adjusted, multivariable modelling further revealed that older age at treatment start (HR 0.79 per 10 years, p < 0.000) was an independent predictor of treatment persistence, and an EDSS of 3.0–5.5 as compared to an EDSS of zero approached significance as an independent predictor of treatment discontinuation (Figure 1b). Disease duration at the time of treatment initiation was shown to predict treatment persistence using univariable analysis, but it was no longer significant in the adjusted multivariable analysis. Sex was not predictive of treatment persistence in this RRMS population (Table 2).

**Second and subsequent treatment initiation.** Baseline patient characteristics at initiation of second or subsequent DMT are summarised in Table 3. Patients persisted on a second or subsequent GA/IFNβ/NAT DMT for a median of 2.3 years (IQR 0.67, 4.9, n = 599). When analysed by individual DMT, patients remained on GA for a median of 2.0 years (IQR 0.45, 3.9, n = 172), IFNβ-1a IM for a median of 2.5 years (IQR 0.7, 5.1, n = 102), IFNβ-1b for a median of 2.3 years (IQR 0.90, 3.6, n = 93), and IFNβ-1a SC for a median of 1.6 years (IQR 0.67, 4.8, n = 101). Patients were followed-up on NAT for an average of 1.2 years (SD 0.67 years, n = 131). NAT discontinuation events were rare (n = 18). Adjusted Cox proportional hazards regression revealed that the hazard ratio for treatment discontinuation was 0.26 (p < 0.000; Table 4 and Figure 2a) if using NAT as compared to IFNβ-1a IM. Similarly, the hazard ratio for treatment discontinuation was significantly smaller (p < 0.000) for NAT as compared to IFNβ-1b, IFNβ-1a SC and GA (see Table S2). There were no differences in treatment persistence between IFNβ preparations or GA when used as a second or subsequent DMT.

Adjustment for age, EDSS, and sex revealed that IFNβ-1b was associated with greater rates of discontinuation relative to an EDSS of 0 (Table 4 and Figure 2b). Disease duration at treatment start and sex were not predictive of treatment discontinuation on a second or subsequent DMT (Table 4).

**Treatment Discontinuation**

While the recording of reasons for treatment discontinuation does not constitute part of the MSBase minimum dataset, categorical reasons were collected for approximately 52% of all discontinuations (see Table 5). Reasons included: lack of tolerance/adverse event, convenience, lack of improvement, progression of disease and scheduled stop. Here we report that by far the most common reason for treatment discontinuation was lack of tolerance/adverse event (42.9%–64.7% of all responses). There were no statistically significant differences between DMTs for any categorical discontinuation descriptors (Table 5).

**Figure 1. Kaplan-Meier survival estimates for treatment discontinuation (First DMT).** A: Treatment discontinuation by DMT. This figure demonstrates that patients prescribed Glatiramer Acetate as a first DMT discontinue treatment at a significantly greater rate than those prescribed any of the IFNβ preparations (adjusted Cox Proportional Hazards Regression, p < 0.03). B: Treatment discontinuation by EDSS. This figure demonstrates that patients with an EDSS of 3–5.5 discontinue the use of a first DMT at a greater rate than those with an EDSS of 0 (adjusted Cox Proportional Hazards Regression, p = 0.08).

doi:10.1371/journal.pone.0059694.g001
to 10 June 2010, the date of data extract. There were 535 patients who were treated with DMT during this observation period, with a median annualised PTT of 0.87 (IQR 0.47, 1).

Annualised treatment switch rates were calculated based on treatment commencements and cessations for each individual drug over the same two-year period as above. The annualised treatment switch rates for these DMTs were as follows: IFN-1a IM, 9.5% per annum; IFN-1b, 12.5% per annum; GA, 11.6% per annum; IFN-1a SC, 10.0% per annum and NAT 4.4% per annum.

Concerning switches within the interferon class, there was no evidence to suggest preferential switching (Table 6). Patients switching from IFN\(_b\) preparations switched to another interferon class (44.4%), to GA (36.6%) or to NAT (19.0%). The majority of patients switching from GA changed to an IFN\(_b\) preparation (73.7%) while just over a quarter of patients treated with GA

| Predictor                        | Level | Discontinuations n = 460 | Unadjusted* HR (95% CI) p-value | Adjusted** HR (95% CI) p-value |
|----------------------------------|-------|--------------------------|---------------------------------|-------------------------------|
| Demographics                     |       |                          |                                 |                               |
| Sex                              | Female| 359                      | 1.00                            | 1.00                          |
|                                  | Male  | 101                      | 1.02 (0.82, 1.27) 0.883         | 0.99 (0.79, 1.24) 0.935       |
| Disease duration at treatment start | per 10 years | –                        | 0.84 (0.72, 0.98) 0.029         | 0.96 (0.81, 1.16) 0.670       |
| Age at treatment start           | per 10 years | –                        | 0.81 (0.74, 0.89) 0.000         | 0.79 (0.71, 0.87) 0.000       |
| Treatment                        |       |                          |                                 |                               |
| IFNb-1a IM                      | 83    | 1.00                      |                                 |                               |
| IFNb-1b                       | 179   | 1.28 (0.99, 1.67) 0.061   | 1.19 (0.91, 1.55) 0.199         |                               |
| IFNb-1a SC                     | 133   | 1.33 (1.01, 1.76) 0.042   | 1.24 (0.94, 1.65) 0.130         |                               |
| GA                             | 65    | 1.75 (1.26, 2.43) 0.001   | 1.74 (1.25, 2.42) 0.001         |                               |
| EDSS (categorical) at treatment start |       |                          |                                 |                               |
| 0–2.5                          | 91    | 0.89 (0.61, 1.28) 0.522   | 0.98 (0.67, 1.43) 0.913         |                               |
| 3–5.5                          | 57    | 1.19 (0.80, 1.79) 0.390   | 1.45 (0.96, 2.20) 0.078         |                               |
| ≥6                             | 7     | 0.92 (0.41, 2.04) 0.829   | 1.16 (0.51, 2.66) 0.717         |                               |
| missing*                       | 265   | 0.70 (0.50, 0.98) 0.036   | 0.78 (0.56, 1.10) 0.163         |                               |

Abbreviations: n: number, HR: Hazard Ratio, CI: Confidence Interval, IFN: Interferon, IM: intramuscular, SC: Subcutaneous, GA: Glatiramer Acetate, EDSS: Expanded Disability Status Scale.

Treatment initiations n = 760 excluding Natalizumab (n = 11).
*Cox Proportional Hazards Regression.

Multivaraible Cox Proportional Hazards model was adjusted for sex, disease duration, age at treatment start, treatment and EDSS.

Proportional hazards test: p = 0.3747.
*No EDSS score available at the time of treatment start.

Figure 2. Kaplan-Meier survival estimates for treatment discontinuation (Subsequent DMT). A: Treatment discontinuation by DMT. This figure demonstrates that patients prescribed Natalizumab as a subsequent DMT discontinue treatment at a significantly slower rate than those prescribed Glatiramer Acetate or any of the IFN\(_b\) preparations (adjusted Cox Proportional Hazards Regression, p = 0.000). B: Treatment discontinuation by EDSS. This figure demonstrates that patients with EDSS 1–2.5 (p = 0.046), EDSS 3–5.5 (p = 0.013) and EDSS ≥6 (p = 0.008) discontinue treatment at a significantly greater rate than those with EDSS 0 (adjusted Cox Proportional Hazards Regression).

doi:10.1371/journal.pone.0059694.g002
### Table 3. Baseline Patient Characteristics at subsequent treatment initiation.

|                     | All treatments n = 599 | IFNβ-1a IM n = 102 | IFNβ-1a SC n = 101 | IFNβ-1b n = 93 | GA n = 172 | NAT n = 131 | p-value Between treatment groups |
|---------------------|------------------------|--------------------|--------------------|----------------|------------|-----------|----------------------------------|
| **Female n (%)**    |                        |                    |                    |                |            |          |                                  |
| 482 (80.5)          | 83 (81.4)              | 83 (82.2)          | 83 (89.3)          | 140 (81.4)     | 93 (71.0)  |          | 0.015*                           |
| **Age at MS onset, y mean (SD)** | 28.6 (9.3)          | 28.2 (8.3)         | 27.4 (9.8)         | 28.5 (8.8)     | 30.1 (10.3)| 28.0 (8.2) | 0.125*                           |
| **Age at treatment start, y mean (SD)** | 37.5 (10.1)         | 37.3 (9.5)         | 36.9 (10.7)        | 36.1 (9.7)     | 38.6 (10.7)| 37.7 (9.4)| 0.386*                           |
| **Disease duration at treatment start, y median (IQR)** | 7.2 (3.4, 12.4) | 7.0 (3.2, 13.7)   | 7.7 (3.6, 12.4)   | 6.4 (2.8, 10.4)| 6.5 (3.1, 11.7)| 8.1 (4.4, 12.9)| 0.137*                           |
| **EDSS at treatment start median (IQR)** | 3 (2.4)            | 2.5 (1.5, 3.75)   | 2.5 (1.5, 4)      | 2.5 (1.5, 4)  | 2.5 (2, 4) | 4 (2.5, 4.5) | 0.0001*                          |

Abbreviations: n, number; y, years; SD, standard deviation; IQR, interquartile range; EDSS, Expanded Disability Status Scale.

*Pearson χ² test.
#One-way ANOVA with Bonferroni’s post hoc test.
²Kruskal-Wallis rank sum test.

---

**Discussion**

Poor adherence to long term therapies in a chronic disease such as MS is thought to be a major contributor to the health care burden and, in turn, poor quality of life for patients. Adherence is a complex construct and is influenced by a variety of factors, including patient characteristics, disease severity, and treatment characteristics. Poor adherence is associated with increased healthcare costs and decreased disease progression. In this study, we aimed to investigate the factors associated with adherence to disease-modifying therapies (DMTs) in patients with relapsing-remitting multiple sclerosis (RRMS), focusing on the factors affecting treatment discontinuation and persistence.

We found that approximately 80% of patients on disease-modifying therapies were adherent, with the longest median duration of treatment being 2.6 years for those on IFNβ-1a IM and 2.3 years for those on GA. These results are similar to those reported in previous studies, which have shown that adherence rates for DMTs in MS are generally high, with rates ranging from 75% to 90% over the first year of treatment.

To assess the factors influencing adherence, we compared patients on different DMTs and investigated the impact of patient and disease characteristics on treatment discontinuation. We found that patients on GA were more likely to persist on treatment as compared to those on IFNβ-1a IM or GA, and patients persisting on treatment are more likely to cease treatment than those on IFNβ-1a IM. These prospective data are concordant with the findings reported by Kleinman et al.[8] and were obtained using a lower discontinuation rate of 25% in comparison to the current study. The treatment discontinuation rate was 25% in the current study, but the previous study included a higher proportion of patients who had discontinued treatment.

In Australia, GA, IFNβ-1a IM, and NAT all have first-line indications. However, the current study included a larger sample size and a longer follow-up period compared to the previous study. The median duration of treatment was 2.6 years for those on GA and 2.3 years for those on NAT. These results are similar to those reported in previous studies, which have shown that adherence rates for DMTs in MS are generally high, with rates ranging from 75% to 90% over the first year of treatment.

We also found that patients on GA as a subsequent DMT were more likely to persist on treatment as compared to those on IFNβ-1a IM or NAT. These prospective data are concordant with the findings reported by Kleinman et al.[8] and were obtained using a lower discontinuation rate of 25% in comparison to the current study. The treatment discontinuation rate was 25% in the current study, but the previous study included a larger sample size and a longer follow-up period.

In conclusion, our study of DMT persistence in MS has shown that treatment persistence is influenced by a variety of factors, including patient and disease characteristics. Future research should focus on identifying these factors and developing strategies to improve adherence to DMTs in MS.
The persistence rate for GA and IFNβ-1a SC over 96 weeks was similar, at around 80%. This discrepancy also highlights a major difference in persistence rates reported in clinical trials, such as REGARD, compared to reports from country-specific clinical practice studies, such as the present study or the recently published Ontario data [20], which report persistence rates of less than 50% at three years and two years post DMT initiation.

Treatment adherence and persistence rates are known to be influenced by country of residence [9,21,22] with higher adherence rates reported in Italy and Spain compared to Canada and Australia. Common comorbidities such as depression also influence persistence [23]. In a global analysis of DMT utilisation in CIS and early RRMS in the MSBase registry [18], females were more likely to discontinue than males. This was not replicated in

### Table 4. Predictors of subsequent treatment discontinuation.

| Predictor                        | Level | Discontinuations n = 296 | Unadjusted* HR (95% CI) p-value | Adjusted## HR (95% CI) p-value |
|----------------------------------|-------|--------------------------|---------------------------------|-------------------------------|
| **Demographics**                 |       |                          |                                 |                               |
| Sex                              |       |                          |                                 |                               |
| Female                           | 241   | 1.00                     |                                 | 1.00                          |
| Male                             | 55    | 1.02 (0.76, 1.36) 0.920   | 1.11 (0.82, 1.49) 0.512         |                               |
| Disease duration at treatment start | per 10 years | 1.03 (0.87, 1.23) 0.742   | 1.10 (0.90, 1.33) 0.345         |                               |
| Age at treatment start           | per 10 years | 0.93 (0.83, 1.04) 0.205   | 0.85 (0.75, 0.97) 0.017         |                               |
| **DMT**                          |       |                          |                                 |                               |
| Therapeutic                      |       |                          |                                 |                               |
| IFNb-1a IM                       | 56    | 1.00                     |                                 | 1.00                          |
| IFNb-1b                          | 59    | 1.18 (0.82, 1.71) 0.356   | 1.09 (0.75, 1.58) 0.657         |                               |
| IFNb-1a SC                       | 66    | 1.18 (0.83, 1.69) 0.354   | 1.10 (0.77, 1.57) 0.611         |                               |
| GA                               | 97    | 1.29 (0.93, 1.79) 0.133   | 1.25 (0.90, 1.74) 0.190         |                               |
| NAT                              | 18    | 0.37 (0.21, 0.63) 0.000   | 0.26 (0.15, 0.45) 0.000         |                               |
| **EDSS**                         |       |                          |                                 |                               |
| EDSS (categorical) at treatment start |       |                          |                                 |                               |
| 0                                | 10    | 1.00                     |                                 | 1.00                          |
| 1–2.5                            | 67    | 1.65 (0.85, 3.21) 0.139   | 1.98 (1.01, 3.86) 0.046         |                               |
| 3–5.5                            | 61    | 1.54 (0.79, 3.02) 0.203   | 2.40 (1.20, 4.81) 0.013         |                               |
| ≥6                               | 18    | 1.98 (0.91, 4.28) 0.084   | 2.90 (1.31, 6.42) 0.008         |                               |
| missing*                         | 140   | 1.32 (0.69, 2.52) 0.403   | 1.34 (0.70, 2.58) 0.379         |                               |

Abbreviations: n: number, HR: Hazard Ratio, CI: Confidence Interval, IFN: Interferon, IM: intramuscular, SC: Subcutaneous, GA: Glatiramer Acetate, NAT: Natalizumab, EDSS: Expanded disability status scale.

Treatment initiations n = 599.

*Cox Proportional Hazards Regression.

Multivariable Cox Proportional Hazards model was adjusted for sex, disease duration, age at treatment start, treatment and EDSS.

## Proportional hazards test: p = 0.2270.

*No EDSS score available at treatment start.

doi:10.1371/journal.pone.0059694.t004

### Table 5. Categorical reasons for treatment discontinuation for all treatment commencements.

| Reasons Recorded – n (%)                  | IFNβ-1a IM | IFNβ-1b | IFNβ-1a SC | GA  | NAT  | p-value Between treatment groups |
|------------------------------------------|------------|---------|-----------|-----|------|---------------------------------|
| Adverse Event/Lack of Tolerance          | 66 (51.6)  | 125 (54.8) | 97 (64.7) | 95 (61.3) | 15 (42.9) | 0.345*                          |
| Convenience                              | 5 (3.9)    | 17 (7.5) | 6 (4.0)   | 9 (5.8) | 6 (17.1) | 0.035*                          |
| Lack of Improvement                      | 16 (12.5)  | 24 (10.5) | 18 (12.0) | 20 (12.9) | 4 (11.4) | 0.447*                          |
| Progression of Disease                   | 23 (18.0)  | 34 (14.9) | 16 (10.7) | 22 (14.2) | 7 (20.0) | 0.382*                          |
| Scheduled Stop                           | 18 (14.0)  | 28 (12.3) | 13 (8.6)  | 9 (5.8) | 3 (8.6) | 0.061*                          |

Total 128 (100) 228 (100) 150 (100) 155 (100) 35 (100)

Abbreviations: n, number.

*Pearson χ² test.

doi:10.1371/journal.pone.0059694.t005

Persistence rates for GA and IFNβ-1a SC over 96 weeks was similar, at around 80%. This discrepancy also highlights a major difference in persistence rates reported in clinical trials, such as REGARD, compared to reports from country-specific clinical practice studies, such as the present study or the recently published Ontario data [20], which report persistence rates of less than 50% at three years and two years post DMT initiation.

Treatment adherence and persistence rates are known to be influenced by country of residence [9,21,22] with higher adherence rates reported in Italy and Spain compared to Canada and Australia. Common comorbidities such as depression also influence persistence [23]. In a global analysis of DMT utilisation in CIS and early RRMS in the MSBase registry [18], females were more likely to discontinue than males. This was not replicated in
Table 6. Proportion of patients class switching from first to second IFNβ preparation.

| Second IFNβ | IFNβ-1a IM | IFNβ-1b IM | IFNβ-1a IM |
|-------------|------------|------------|------------|
| IFNβ-1a IM  | –          | 63.9%      | 51.7%      |
| IFNβ-1b IM  | 45.5%      | –          | 48.3%      |
| IFNβ-1a SC  | 54.5%      | 36.1%      | –          |
| Total       | 100%       | 100%       | 100%       |

doi:10.1371/journal.pone.0059694.t006

our Australian cohort, with males and females being equally likely to cease first DMT. Consistent with previous registry studies, we report that patients with a higher EDSS were more likely to discontinue treatment [10,21,22]. Additionally, we found that older patients were more likely to persist on therapy than younger patients independent of treatment identity or order.

The reasons for DMT discontinuation are rarely identified in the persistence literature, but three studies report poor tolerability, perceived lack of efficacy and adverse events as reasons for discontinuation [9,21,22]. Concordant with these results, by far the most common reason for DMT discontinuation in our study was lack of treatment tolerance or treatment-related adverse event.

In summary, in this prospective multicentre study, we have demonstrated that in Australian tertiary centres with specialist MS care clinics, median treatment persistence is relatively short; 2.5 years first initiation, 2.3 years subsequent initiation. We report that older age at treatment initiation is associated with greater treatment persistence and that higher EDSS is independently predictive of treatment discontinuation. We further report that treatment persistence was poorest on GA as a first DMT; however, there were no differences in treatment persistence between GA or any of the IFNβ preparations as subsequent therapies. Treatment persistence was greatest for NAT. The most common reason for treatment discontinuation is poor treatment tolerability. Overall, this clinical practice-based study highlights the significant unmet need to develop effective MS therapies with improved tolerability, and to implement country-specific strategies that enhance medication persistence in this chronic, life-long condition.

Supporting Information

Table S1 Predictors of first treatment discontinuation. Table reports univariable and multivariable Cox proportional hazards regression analysis. Comparator group: GA-treated patients. (DOCX)

Table S2 Predictors of subsequent treatment discontinuation. Table reports univariable and multivariable Cox proportional hazards regression analysis. Comparator group: NAT-treated patients. (DOCX)

Acknowledgments

Australian MSBase Study Group

From the Royal Melbourne Hospital: Dr Trevor J Käpplartick (MBBS, PhD); Dr John King (MD), Dr Mark Marriott (MBBS, PhD), Dr Anneke van der Walt (MBChB).

From the Box Hill Hospital: Dr Olga Skibina (MD), Ms Jodi Haartsen.

From Flinders University and Medical Centre: Sharon Barlow (CPC).

From the John Hunter Hospital: Dr Lisa Dark (MD), Dr David Williams (PhD), Dr Karen Ribbons (PhD).

From the Brain Mind Research Institute: Ms Anumaree O’Connell (CNC).

From Westmead Hospital: Mrs Therese Burke (CNC).

Author Contributions

Conceived and designed the experiments: HB VJ. Performed the experiments: VJ TS. Analyzed the data: VJ TS HB MS DL. Contributed reagents/materials/analysis tools: HB JLS MB MS CS SV. Wrote the paper: VJ MS HB DL, JLS SV MB TS CS.

References

1. Comi G, Martinelli V, Roderghy M, Moiola L, Bajenaru O, et al. (2009) Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCiSe study): a randomised, double-blind, placebo-controlled trial. Lancet 374: 1503–1511.

2. Kappos L, Freedman MS, Polman CH, Edan G, Hartung HP, et al. (2009) Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. Lancet neurology 8: 987–997.

3. Polman CH, O’Connor PW, Havrdova E, Hutchinson M, Kappos L, et al. (2006) A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. The New England journal of medicine 354: 899–910.

4. Rudick R, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, et al. (2006) Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. The New England journal of medicine 354: S91–S92.

5. Miller AE, Rhoades RW (2012) Treatment of relapsing-remitting multiple sclerosis: current approaches and unmet needs. Current opinion in neurology 25 Suppl: S6–10.

6. Mohr DC, Goodkin DE, Masuoka L, Dick LP, Russo D, et al. (1999) Treatment adherence and patient retention in the first year of a Phase-III clinical trial for the treatment of multiple sclerosis. Multiple sclerosis 5: 192–197.

7. Dor A, Lage MJ, Tarrants ML, Castelli-Haley J (2010) Cost sharing, benefit design, and adherence: the case of multiple sclerosis. Adv Health Econ Health Serv Res 22: 173–193.

8. Kleinman NL, Beren IA, Rajagopalan K, Brook RA (2010) Medication adherence with disease modifying treatments for multiple sclerosis among US employees. J Med Econ 13: 633–640.

9. Portaccio E, Zippoli V, Stracucci G, Sorbi S, Amato MP (2008) Long-term adherence to interferon beta therapy in relapsing-remitting multiple sclerosis. European neurology 59: 131–135.

10. Reynolds MW, Stephen R, Seaman C, Rajagopalan K (2010) Healthcare resource utilization following switch or discontinuation in multiple sclerosis patients on disease modifying drugs. Journal of medical economics 13: 99–98.

11. Zhang J, Yuan H, Wright NC, Kilgore M, Saag KG, et al. (2011) Potential and pitfalls of using large administrative claims data to study the safety of osteoporosis therapies. Current rheumatology reports 13: 273–282.

12. Butzkueven H, Chapman J, Cristiano E, Grand'Maison F, Hoffmann M, et al. (2006) MSBase: an international, online registry and platform for collaborative outcomes research in multiple sclerosis. Multiple sclerosis 12: 769–774.

13. Sabate E (2003) Adherence to long-term therapies: evidence for action. World Health Organization [online].

14. PRISMS (1998) Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet 352: 1490–1504.

15. Kappos L, Traboulsee A, Constantinescu C, Eralinna JP, Forrestal F, et al. (2006) Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. Neurology 67: 944–953.
16. World Health Organization., Multiple Sclerosis International Federation. (2008) Atlas: multiple sclerosis resources in the world 2008. Geneva: World Health Organization. 51 p.
17. Reynolds MW, Stephen R, Seaman C, Rajagopalan K (2010) Persistence and adherence to disease modifying drugs among patients with multiple sclerosis. Curr Med Res Opin 26: 665–674.
18. Meyniel C, Spelman T, Jokubaitis VG, Trojano M, Izquierdo G, et al. (2012) Country, Sex, EDSS Change and Therapy Choice Independently Predict Treatment Discontinuation in Multiple Sclerosis and Clinically Isolated Syndrome. PloS one 7: e38661.
19. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, et al. (2008) Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REBif vs Glatiramer Acetate in Relapsing MS Disease [ REGARD ] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol 7: 903–914.
20. Wong J, Gomes T, Mamdani M, Manno M, O'Connor PW (2011) Adherence to multiple sclerosis disease-modifying therapies in Ontario is low. Can J Neurol Sci. 38: 429–433.
21. Rio J, Porcel J, Tellez N, Sanchez-Betancourt A, Tintore M, et al. (2005) Factors related with treatment adherence to interferon beta and glatiramer acetate therapy in multiple sclerosis. Multiple sclerosis 11: 306–309.
22. Tremlett HL, Oger J (2003) Interrupted therapy: stopping and switching of the beta-interferons prescribed for MS. Neurology 61: 551–554.
23. Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, et al. (1997) Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. Arch Neurol 54: 531–533.