Discontinuing disease-modifying therapy in MS after a prolonged relapse-free period: a propensity score-matched study

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ABSTRACT

Background Discontinuation of injectable disease-modifying therapy (DMT) for multiple sclerosis (MS) after a long period of relapse freedom is frequently considered, but data on post-cessation disease course are lacking.

Objectives (1) To compare time to first relapse and disability progression among ‘DMT stoppers’ and propensity-score matched ‘DMT stayers’ in the MSBase Registry; (2) To identify predictors of time to first relapse and disability progression in DMT stoppers.

Methods Inclusion criteria for DMT stoppers were: age ≥18 years; no relapses for ≥5 years at DMT discontinuation; follow-up for ≥3 years after stopping DMT; not restarting DMT for ≥3 months after discontinuation. DMT stayers were required to have no relapses for ≥5 years at baseline, and were propensity-score matched to stoppers for age, sex, disability (Expanded Disability Status Score), disease duration and time on treatment. Relapse and disability progression events in matched stoppers and stayers were compared using a marginal Cox model. Predictors of first relapse and disability progression among DMT stoppers were investigated using a Cox proportional hazards model.

Results Time to first relapse among 485 DMT stoppers and 854 stayers was similar (adjusted HR, aHR=1.07, 95% CI 0.84 to 1.37; p=0.584), while time to confirmed disability progression was significantly shorter among DMT stoppers than stayers (aHR=1.47, 95% CI 1.18 to 1.84, p=0.001). The difference in hazards of progression was due mainly to patients who had not experienced disability progression in the prebaseline treatment period.

Conclusions Patients with MS who discontinued injectable DMT after a long period of relapse freedom had a similar relapse rate as propensity score-matched patients who continued on DMT, but higher hazard for disability progression.

INTRODUCTION

The therapeutic effect of starting injectable disease-modifying therapies (DMTs)—Interferon β and Glatiramer Acetate—on multiple sclerosis (MS) has been investigated extensively,1 but little is known about the effect of stopping these drugs.2 Discontinuing Interferon β (IFNβ) in patients with ongoing relapses leads to disease reactivation to pretreatment levels,3-5 but could injectable DMTs be safely stopped after a prolonged period of relapse freedom? A definitive answer to this question requires an adequately powered clinical trial in which some patients are randomised to continue treatment and others—to placebo.6 Such trials have been successfully carried out in oncology7 8 and other areas of medicine, but not in MS. In the absence of a randomised discontinuation trial, clinicians can take recourse in observational studies that utilise a propensity score-matching technique.9 Such an approach has been used in the MS field to assess long-term treatment effect of IFNβ therapy;10 impact of IFNβ-neutralising antibodies;11 and effectiveness of therapy switches.12 In the present work, we make use of propensity score-matching to address the question of whether the clinical course among patients with MS who stopped injectable DMT after being relapse-free over the prior 5 years (‘stoppers’) differs from that of patients who continued on injectable DMT (‘stayers’). We also identify predictors of relapses and disability progression among DMT stoppers.

MATERIALS AND METHODS

The MSBase Registry

The MSBase Registry is a global collaborative research group that prospectively collects outcomes data from MS treatment centres, using an internet-based, physician owned and operated system (http://www.msbase.org).13 Each centre enters patient data in the offline iMed local electronic database during routine clinic visits and intermittently uploads anonymised data sets to the MSBase server. Physicians record clinical information such as date of MS onset, diagnostic criteria used, Expanded Disability Status Score (EDSS) and relapse characteristics. Records are classified as complete and eligible for analyses if they meet a minimum required set of data. Informed consent from all patients according to local laws is required for participation in MSBase and the project holds Human Research Ethics Committee approval or exemption at each contributing centre.
Quality assurance
The use of the iMed electronic database and minimum data set requirements for inclusion into MSBase ensures a unified approach. Cases fulfil either the Poser\textsuperscript{14} or McDonald\textsuperscript{15} criteria for MS and clinical information, including relapse data, which are collected in ‘real time’. The data set includes details on patient demographics (sex, birth date, MS onset date), disability assessments (visit date, EDSS), relapses and treatment (name of disease-modifying therapy, dates of the start and discontinuation). Quality assurance is maintained with inbuilt data quality checking in the iMed local record system, which was applied to key dates and data in the minimum data set. In order to ensure EDSS competency, all participating neurologists completed the Neurostatus certification (http://www.neurostatus.net) or provided evidence of prior completion.

Inclusion criteria for DMT stoppers
Centres that consented to participate in this study, and contributed more than 20 eligible patients, were included in the analysis. Twenty-eight clinical centres across 15 countries contributed eligible patients for matched analysis. Inclusion criteria for ‘DMT stoppers’ were: diagnosis of MS by Poser or McDonald criteria; age 18 years or older at DMT discontinuation (‘baseline’); no relapses for ≥5 years prior to baseline; continuous treatment with injectable DMT (IFNβ or Glatiramer) for ≥3 years prior to baseline; ≥3 years of follow-up after baseline; no restart of a DMT for ≥3 months after baseline (such early re-starters were excluded because they were considered ‘treatment switchers’ rather than ‘treatment stoppers’). We identified 426 DMT stoppers in the MSBase who satisfied our inclusion criteria. None of these patients recorded a pregnancy during the follow-up period.

Propensity score matching of DMT stayers
Patients with MS who stayed on DMT and were eligible for matching were required to have had no relapses for ≥5 years prior to baseline, and to have been continuously treated with an injectable DMT (IFNβ or Glatiramer) for ≥3 years prior to baseline and ≥3 years afterwards. We identified 1133 such patients in the MSBase registry. We then used a logistic regression model in which stopping DMT was the outcome variable, and the baseline and prebaseline characteristics (sex, age, disease duration, baseline EDSS, prebaseline DMT exposure and country) formed the explanatory variables in order to calculate the propensity score for DMT stayers. The propensity score matching technique used a 5-to-1 digit matching algorithm, as described in more detail in our prior publications,\textsuperscript{12,16} which allowed us to successfully match 1:2 each of the DMT stoppers (n=426) to DMT stayers (n=852). The baseline for the DMT stayers was the date of a contemporaneous EDSS assessment that was propensity matched for index year and disease course, and activity to a corresponding DMT stopper. Success of matching was assessed using paired tests and analysis of standardised differences. Wilcoxon rank-sum and a χ\textsuperscript{2} tests were used to compare unmatched baseline characteristics, while Wilcoxon signed-rank and McNemar tests were used to compare matched characteristics.

Outcome measures
The primary end points were time to first relapse and time to first 3-month confirmed disability progression. Relapses and disability (EDSS) were recorded by a treating neurologist. Confirmed disability progression events were defined as a minimum one-point increase in EDSS score above a baseline EDSS of 1–5.5, confirmed at repeat assessment at least 3 months later. Baseline EDSS scores of zero required a confirmed 1½ point increase, and baseline EDSS scores ≥6 required a half-point increase above baseline confirmed at least 3 months later. EDSS scores recorded within 30 days of a relapse were excluded.

Statistical analyses
Categorical variables were summarised using frequency and percentage. Continuous variables were summarised using mean and standard deviation (SD), or median and interquartile range (IQR). Comparison of post-baseline relapse and confirmed disability progression hazards among DMT stoppers and propensity score-matched stayers was carried out using a marginal Cox model. Stoppers were censored at the point of restarting treatment, where applicable. Post hoc Rosenbaum sensitivity analyses across all outcomes were conducted to test the sensitivity of our propensity matched stayers versus stoppers models to unobserved heterogeneity secondary to baseline characteristics that were either not collected or incompletely observed.\textsuperscript{17–20} For all such models, no evidence for a significant influence of unmeasured confounding was observed. A subgroup analysis, of stoppers only, was conducted using a Cox Proportional Hazards regression. For all analyses p<0.05 was considered significant. All analyses were conducted using Stata V13 (StataCorp, College Station, Texas, USA).

RESULTS
Characteristics of DMT stoppers and stayers
Demographic and disease-related characteristics of DMT stoppers (n=426) and propensity score-matched stayers (n=852) are shown in table 1. The two groups were successfully matched by age, sex, disease duration, EDSS, number of prebaseline DMT starts and proportion of prebaseline disease duration on treatment. The discontinued therapy among stoppers was IFNβ in 88.3% and Glatiramer acetate in 11.7%. The main reason for DMT discontinuation was recorded for 40% of DMT stoppers as medication intolerance (26.2%); lack of improvement (23.8%); adverse event (13%) and disease progression (11%).

| Table 1 Baseline characteristics of DMT stoppers and stayers |
|----------------------|----------------------|----------------------|
| Baseline characteristic | Stoppers n=426 | Stayers n=852 | p Value |
| Age, years, median (IQR) | 45.1 (37.0, 51.6) | 43.8 (37.1, 51.3) | 0.29 |
| Female sex, n (%) | 305 (71.6) | 599 (70.3) | 0.63 |
| Disease duration, years, median (IQR) | 13.7 (9.2, 20.1) | 13.1 (9.1, 18.4) | 0.05 |
| EDSS, median (IQR) | 3.5 (2, 5.5) | 3.5 (2, 5.5) | 0.12 |
| # prebaseline DMT starts—median (IQR) | 1 (1, 2) | 1 (1, 2) | 0.1 |
| Proportion disease duration on DMT—median (IQR) | 0.6 (0.4, 0.8) | 0.6 (0.4, 0.8) | 0.26 |
| # prebaseline DMT starts/ disease duration—mean (SD) | 0.1 (0.1) | 0.1 (0.1) | 0.2 |
| Duration of follow-up period, years, median (IQR) | 4.85 (3.75, 6.86) | 5.02 (3.81, 6.96) | |
| Index DMT | | |
| IFNβ preparation, n (%) | 376 (86%) | 688 (80.7%) | <0.05 |
| Glatiramer acetate, n (%) | 50 (11.7%) | 164 (19.3%) | <0.05 |

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IFNβ, Interferon β.
DMT was restarted by 198 (46%) of DMT stoppers after a mean of 0.93 (1.6) years. Reasons for restarting were not recorded. Mean post-discontinuation follow-up for stoppers was 4.85 (3.75, 6.86) years. Among DMT stayer, the continued therapy was IFNβ in 80.7% and Glatiramer acetate 19.3%. Mean post-baseline follow-up for stayer was 5.02 (3.81, 6.96) years.

Time to first relapse and confirmed disability progression among DMT stoppers and stayers

Of the 426 stoppers, 155 (36.4%) reported a relapse during follow-up. The median (IQR) time to first relapse among stoppers was 1.81 years (0.67, 2.92). Of the 852 stayer, 322 (37.8%) recorded a relapse post baseline, with a similar median (IQR) time to first relapse of 2.01 years (0.88, 3.42). Survival time to first relapse among stoppers and stayer was nearly identical (adjusted HR, aHR=1.07, 95% CI 0.84 to 1.37; p=0.584) (figure 1A), as were mean annualised relapse rates (ARR): 0.27 (±0.57) for stoppers and 0.25 (±0.51) for stayer, p=0.503. However, survival time to confirmed disability progression, shown in figure 1B, was significantly shorter among DMT stoppers than stayer (aHR=1.47, 95% CI 1.18 to 1.84, p<0.001).

We further investigated whether hazards of confirmed disability progression differed among DMT stoppers and stayer according to their prebaseline disability progression status. Among patients who were progression-free prior to baseline, that is, with no change in EDSS for 5 years or more, the DMT stoppers had a higher hazard of progression compared to stayer (aHR=1.58, 95% CI 1.19 to 2.08; p<0.001). Among patients with prebaseline disability progression, hazard of post-baseline progression was similar in stoppers and stayer (aHR=1.32, 95% CI 0.91 to 1.91; p=0.151).

Predictors of relapses and 3-month confirmed disability progression among DMT stoppers

At least one relapse was recorded following discontinuation in 155 of 426 DMT stoppers (36.4%). Significant predictors of relapse risk among stoppers were younger age (25% reduction in relapse risk ratio for every 10 years older at baseline, aHR=0.75, 95% CI 0.62 to 0.92, p=0.005) and lower baseline disability (13% decreased risk of relapse for every 1-point increase in EDSS, aHR=0.87, 95% CI 0.80 to 0.95; p<0.001). Sex, disease duration, number of prebaseline DMT starts, proportion of disease duration on treatment and the identity of index DMT were not associated with post-discontinuation relapse hazard (table 2).

Confirmed 3-month disability progression during follow-up was recorded for 131 of the 391 DMT stoppers (33.5%) for whom sufficient data were available. The only variables significantly associated with increased hazard of confirmed progression in the multivariable model were older age (32% increase in hazard of confirmed disability progression for every 10 years older at baseline, aHR=1.32, 95% CI 1.08 to 1.62; p<0.008) and prior IFN β1b-use (aHR=2.10 (1.19 to 3.72), 0.011). Sex, disease duration, baseline disability, disability progression prior to baseline, number of prebaseline DMT starts and proportion of disease duration on treatment were not associated with post-discontinuation disability progression among DMT stoppers (table 2).

DISCUSSION

In the cohort of patients with MS from the large international MSBase Registry who were relapse-free for 5 years or more, 36.4% DMT stoppers and 37.8% DMT stayer experienced a relapse during (median) 5-year follow-up. The time to first relapse was nearly identical in patients who stopped DMT and propensity score-matched patients who continued on DMT. Thus, stopping DMT after a prolonged relapse-free period was not associated with an increased risk of relapse. The risk of post-DMT relapses among DMT stoppers was higher in younger and less disabled patients, consistent with natural history studies that document an inverse relationship between age and risk of relapse.21 In contrast, risk of disability progression increased with age among DMT stoppers, in agreement with the well-known observation that older patients are more likely to have progressive disease.22

Interestingly, hazard of confirmed disability progression was almost 50% higher in DMT stoppers relative to stayer. The higher risk was largely due to a subset of previously stable stoppers with no prebaseline disability progression, who had significantly shorter time to progression relative to stable stayer. One interpretation of this result is that stable DMT-treated patients are ‘true responders’, that is, their lack of disability progression is due, in some measure, to ongoing DMT exposure. Stopping DMT in the stable patients increases their risk of entering the progressive phase, while patients with prebaseline progression have already entered the secondary progressive phase where injectable DMTs are of little or no efficacy.23 An alternative explanation is that patients who begin to experience...
deterioration of their condition—even if it is not yet reflected in change of EDSS score—are more likely to stop their DMT. Among the strengths of our study are the prospective nature of the data acquisition (though not of analyses) and the size of the registry from where participants were drawn, which allowed us to select sufficient numbers of DMT stoppers and stayers to enable meaningful propensity score matching. The limitations relate to the biases attendant to observational studies,24 including selection bias, confounding by unmeasured variables (ie, lesion burden on MRI at baseline) and lack of data completeness for some variables. Demographic and disability data were available for all patients, while ‘reasons for DMT discontinuation’ is currently not a required field in the MSBase minimum data set and was not recorded for most of the stoppers. MRI data were of insufficient density to be included in the final models, which may in part reflect clinical practice of not obtaining routine MRI on non-relapsing patients. Our study focused exclusively on ‘first-line’ injectable therapies, since the required three (or more) years of post-discontinuation follow-up was only available for these older therapies. The data on the post-injectable DMT disease course may not be generalisable to the newer agents. It is important to emphasise that, by design, we focused only on ‘inactive’ patients (no relapses for ≥5 years). The conclusions of our study need not (and probably do not) apply to younger patients with frequent relapses in whom DMT discontinuation is generally not advisable.3–5

In our study, stopping immunomodulatory therapy in patients who were relapse-free and progression-free for an extended period of time did not adversely affect relapse outcomes, but was associated with a 50% increase in risk of disability progression. It remains to be determined whether DMT can be safely discontinued in subsets of relapse-free patients, such as older patients who already entered the progressive phase, without increasing risk of disability progression. To definitively answer the question about safety of DMT discontinuation in this patient subset, a randomised trial is required. The first randomised DMT discontinuation trial in MS is scheduled to start recruitment in 2016.25 This trial should help clinicians answer the question often heard in the clinic: “Doctor, when can I stop my MS therapy?”

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18Competing interests IK served on the scientific advisory board for Biogen Idec and Genentech, and received research support from Guthy-Jackson Charitable Foundation, National Multiple Sclerosis Society, Biogen-Idec, Serono, Genzyme and Novartis. TS received compensation for serving on scientific advisory boards, honoraria for consultancy and funding for travel from Biogen Idec; and speaker honoraria from Novartis. RA received honoraria from Bayer, Biogen, Biologix, Genzyme, Genpharm, GSK, Merck Serono and Novartis, and served on advisory boards for Bayer, Biogen, Biologix, Genzyme, Genpharm, Merck Serono and Novartis. JL-S has accepted travel compensation from Biogen, Biogen and Merck Serono. Her institution receives the honoraria for talks and advisory board commitment, and also clinic support as well as research grants from Bayer Health Care, Biogen Idec, CSL, Genzyme Sanofi, Merck Serono and Novartis. HB took part in collection, analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content and study supervision. RA, JL-S, PD, FGM, MS, AL, MB, PG, GI, RH, EP and MT were involved in collection, analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; HB took part in collection, analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content and study supervision.

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### Table 2

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Time to first relapse</th>
<th>Time to confirmed disability progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aHR (95% CI) p value</td>
<td>aHR (95% CI) p value</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.89 (0.62 to 1.29) 0.550</td>
<td>1.36 (0.94 to 1.99) 0.106</td>
</tr>
<tr>
<td>Age (units=10 years)</td>
<td>0.75 (0.62 to 0.92) 0.005</td>
<td>1.32 (1.08 to 1.62) 0.008</td>
</tr>
<tr>
<td>EDSS</td>
<td>0.87 (0.80 to 0.95) 0.001</td>
<td>1.04 (0.95 to 1.13) 0.400</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>1.00 (0.96 to 1.03) 0.862</td>
<td>1.00 (0.97 to 1.03) 0.886</td>
</tr>
<tr>
<td>Number of prebaseline DMT starts</td>
<td>1.02 (0.87 to 1.20) 0.772</td>
<td>1.09 (0.93 to 1.27) 0.273</td>
</tr>
<tr>
<td>Proportion disease duration on treatment</td>
<td>0.49 (0.19 to 1.25) 0.133</td>
<td>0.35 (0.12 to 1.01) 0.052</td>
</tr>
<tr>
<td>DMT stopped: Avonex (IFNb 1a IM)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Betaseron (IFNb 1b)</td>
<td>1.51 (0.92 to 2.46) 0.101</td>
<td>2.10 (1.19 to 3.72) 0.011</td>
</tr>
<tr>
<td>Copaxone (Glatiramer acetate)</td>
<td>1.28 (0.73 to 2.25) 0.393</td>
<td>1.50 (0.71 to 3.17) 0.283</td>
</tr>
<tr>
<td>Rebif (IFNb 1a SC)</td>
<td>1.41 (0.87 to 2.28) 0.162</td>
<td>1.49 (0.82 to 2.73) 0.192</td>
</tr>
</tbody>
</table>

The number of DMT stoppers with post-baseline relapse was 155 (36.4%) and that for post-baseline confirmed disability progression was 131 (30.8%).

DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; IFNb, Interferon β; IM, intramuscular; SC, subcutaneous.

### Table 3

| Number of prebaseline DMT starts 1.02 (0.87 to 1.20) 0.772 | 1.09 (0.93 to 1.27) 0.273 |
| Proportion disease duration on treatment | 0.49 (0.19 to 1.25) 0.133 | 0.35 (0.12 to 1.01) 0.052 |
| DMT stopped: Avonex (IFNb 1a IM) | Reference | Reference |
| Betaseron (IFNb 1b) | 1.51 (0.92 to 2.46) 0.101 | 2.10 (1.19 to 3.72) 0.011 |
| Copaxone (Glatiramer acetate) | 1.28 (0.73 to 2.25) 0.393 | 1.50 (0.71 to 3.17) 0.283 |
| Rebif (IFNb 1a SC) | 1.41 (0.87 to 2.28) 0.162 | 1.49 (0.82 to 2.73) 0.192 |
consultant for “Fondazione Cesare Soro”. MB has served on scientific advisory boards for Biogen-Idec, Novartis and Genzyme and on steering committees for trials conducted by Novartis. He has received conference travel support from Biogen-Idec and Novartis; and his institution has received research support from Biogen-Idec, Merck-Serono and Novartis. PG is a consultant for Merck-Serono; he has received payments for lectures from the Canadian Multiple Sclerosis Society, Merck Serono and Teva-Neuroscience; and has received grants for travel from Novartis and Teva-Neuroscience. GI has had travel/accommodations/meeting expenses funded by Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi and Teva. RH received honoraria as a consultant on scientific advisory boards from Biogen Idec, Merck Serono, Sanofi-Genezyme and Teva; research funding from Biogen Idec and Merck Serono; and speaker honoraria from Sanofi-Genezyme. EP received honoraria and/or congress and travel/accommodation expense compensation from Sanofi Aventis, UCB, Lundbeck, Novartis, Bayer Schering, Biogen, Merck Serono, Genzyme, Teva and Associazione Marchigiana Sclerosi Multipla e altre malattie neurologiche. MT received speaking honoraria from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi and Teva, as well as research grants from Biogen Idec, Merck Serono and Novartis.

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