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Predictors of relapse and disability progression in MS patients who discontinue disease-modifying therapy

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ABSTRACT

Background: Discontinuation of disease-modifying therapies (DMTs) for MS is common. MSBase, a large global observational registry, affords a unique opportunity to investigate predictors of 'post-DMT' relapses and confirmed disability progression (CDP) in a diverse group of patients exposed to different DMTs.

Materials/methods: Main inclusion criteria: clinician-confirmed MS diagnosis (2010 McDonald criteria); age ≥ 18 at index DMT start; ≥12 months on index DMT prior to discontinuation; ≥24 months of follow-up post-discontinuation; did not restart DMT for ≥6 months. Predictors of time to first relapse and 3-month CDP were analyzed using Cox proportional hazards regression adjusted for age, gender, baseline EDSS, EDSS stability and relapse-free period for ≥1 year prior to discontinuation, calendar epoch, index DMT and reason for discontinuation.

Results: 4842 patients (74.2% female) from 20 MSBase Centers met our inclusion criteria. 3556 (73%) discontinued one of IFNβ preparations, 849 (18%) - glatiramer acetate, 308 (6%) - natalizumab and 129 (3%) – fingolimod; other DMTs were excluded because too few records were available. Overall post-discontinuation annualized relapse rate (95% CI) was 0.224 (0.219, 0.229) and CDP rate was 8.23 (7.72, 8.76) per 100 person-years. Risk of post-DMT relapse was higher in younger patients, female patients, those with moderate disability and a relapse within 1 year of discontinuation. Hazard of CDP increased with increasing disability at baseline

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and disease progression within 3 years prior to stopping DMT. Of all the DMTs, only natalizumab was associated with increased risk of both post-DMT relapse and CDP.
Conclusions: Knowledge of post-DMT relapse and disability progression rates and predictors of post-DMT disease activity allows for a more informed discussion of DMT discontinuation in those patients who are considering this option.

1. Introduction

It is not uncommon for MS patients to stop their disease-modifying therapy (DMT) due to intolerance, adverse events, lack of perceived benefit, planned pregnancy, personal or physician preference, or a combination of factors [1–3]. Knowledge of rates and predictors of 'post-DMT' relapses and disability progression would allow clinicians to better counsel their patients who are considering stopping therapy. A recent study of patients who stopped Interferon-β (IFN-β) has shown that a subset of patients who were over 45 years and did not have relapses for ≥4 years had a very low hazard of relapse [4]. It would be important to confirm these single-center results on a larger and more diverse, multi-center patient sample, and to extend the analysis to non-Interferon therapies. MSBase, a global observational registry that collects longitudinal data on nearly 60,000 MS patients from 32 countries, affords a unique opportunity to assess rates of post-DMT relapses and confirmed disability progression (CDP) and to identify predictors for relapses and CDP in a diverse group of patients who were exposed to a variety of DMTs.

2. Methods

The MSBase Registry is a global collaborative research group that collects data from MS patients at point-of-care using an internet-based, physician owned and operated system (http://www.msbase.org). Physicians record such clinical information as date of MS onset, diagnostic criteria used, Expanded Disability Status Score (EDSS) and relapse characteristics during the routine clinic visit and these data is then anonymized and uploaded to the MSBase server. Records are classified as complete and eligible for analyses if they meet a minimum required data set. Quality assurance is maintained with inbuilt data quality checking, which is applied to key data in the minimum data set. 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 center.

Inclusion criteria for our study were clinician-confirmed MS diagnosis (2010 McDonald criteria); age 18 years or older at index DMT start; ≥12 months on index DMT prior to discontinuation; patient followed for ≥24 months post-discontinuation; patient not restarted DMT for ≥6 months after discontinuing index DMT (thereby excluding 'therapy switchers'); not pregnant for ≥6 months prior and ≥ 24 months after DMT discontinuation. We further excluded from analyses data for any DMT for which < 100 patient records that met our inclusion criteria were available and off-label therapies, such as rituximab.

Categorical variables were summarized using frequency and percentage. Continuous variables were summarized using mean and standard deviation (SD), or median and interquartile range (IQR). Predictors of time to first relapse and 3-month CDP (defined as 1.5 EDSS steps for baseline EDSS 0; 0.5 EDSS steps for baseline EDSS 6–6.5; 1 EDSS step – for all other baseline EDSS) were analyzed using Cox proportional hazards regression. For the multivariate model, we adjusted for age, gender, EDSS at DMT discontinuation ('baseline'), EDSS stability for ≥1 year prior to baseline (yes/no), relapse-free for ≥1 year prior to baseline (yes/no), calendar epoch at baseline (≤2005; 2005–2010; ≥2011), index DMT, reason for discontinuation. Stoppers were censored at the point of restarting treatment, where applicable. Hazard proportionality was assessed via analysis of scaled Schoenfeld residuals. For all analyses $p < 0.05$ was considered significant. All analyses were conducted using Stata V.15 (StataCorp, College Station, Texas, USA).

3. Results

A total of 4842 patients (74.2% female) from 20 MSBase Centers met our inclusion criteria. Their age, was [median, (Interquartile range)], 35.9 years (29.3, 43.9); disease duration - 9.9 years (5.8, 15.6), EDSS - 3 (1.5, 5.5); and duration of post-DMT follow up - 5.6 years (3.6, 8.6). 3556 patients (73%) were on one IFNβ preparations at the time of discontinuation, 849 (18%) were on glatiramer acetate, 308 (6%) were on natalizumab and 129 (3%) on fingolimod. The number of patients for each of the index DMTs, duration of post-DMT follow-up, and respective unadjusted annualized relapse rates (ARR) and confirmed disability progression (CDP) rates are shown in Table 1a,1b. Overall post-discontinuation ARR (95% CI) was 0.224 (0.219, 0.229). ARR were the lowest for IFN-β 1b sc stoppers - 0.188 (0.180, 0.197) and the highest for natalizumab stoppers - 0.321 (0.291, 0.353). Overall CDP rates (95% CI) were 8.23 (7.72, 8.76) per 100 person-years. The rates were lowest for IFN-β 1a im - 6.40 (5.45, 7.51) and highest for natalizumab - 12.55 (10.04, 15.69). There were too few patients in MSBase who discontinued alemtuzumab, teriflunomide, dimethyl fumarate, ocrelizumab and cladribine and were then followed for ≥24 months post-discontinuation to be included in the statistical analyses.

Results of the Cox proportional hazards regression model that assessed hazards of post-DMT relapse and CDP are presented in Table 2. The demographic and disease-related variables at the time of discontinuation (baseline) are shown first. Risk of post-DMT relapse was slightly higher in younger patients: for every additional year older at baseline there was a 3% reduction in the rate of post-DMT relapse (adjusted Hazard Ratio, aHR = 0.97 95% CI (0.97, 0.98), $p < 0.001$). Female patients had marginally higher risk of relapse (1.10 (1.01, 1.20), $p = 0.042$). Patients with no pre-baseline relapses for > 1 years

Table 1a
Post-DMT relapses by index disease modifying therapy.

Index DMT group	N (%)	Post-DMT relapse events	Post-DMT follow-up years	Post-DMT ARR (95% CI)
All DMTs combined	4842 (100%)	7093	31691.41	0.224 (0.219, 0.229)
IFN-β 1a sc	1345 (27%)	1999	8649.63	0.231 (0.221, 0.242)
IFN-β 1b sc	1246 (26%)	1823	9681.26	0.188 (0.180, 0.197)
IFN-β 1a im	965 (20%)	1570	6536.54	0.240 (0.229, 0.252)
Glatiramer acetate	849 (18%)	1162	5076.22	0.229 (0.216, 0.243)
Natalizumab	308 (6%)	429	1336.1	0.321 (0.291, 0.353)
Fingolimod	129 (3%)	110	411.66	0.267 (0.220, 0.322)

Table 1b
Post-DMT confirmed disability progression by index disease modifying therapy.

Index DMT group	N (%)	N (%) contributing to CDP analysis	Post-DMT CDP events	Post-DMT follow-up years[a]	CDP per 100 person-years (95% CI)
All DMTs combined	4842 (100%)	2678	969	11779.87	8.23 (7.72, 8.76)
IFN-β 1a sc	1345 (27%)	822	299	3765.26	7.94 (7.09, 8.89)
IFN-β 1b sc	1246 (26%)	611	253	2953.10	8.57 (7.57, 9.69)
IFN-β 1a im	965 (20%)	481	149	2329.92	6.40 (5.45, 7.51)
Glatiramer acetate	849 (18%)	475	174	1872.85	9.29 (8.01, 10.78)
Natalizumab	308 (6%)	197	77	613.52	12.55 (10.04, 15.69)
Fingolimod	129 (3%)	92	17	245.22	6.93 (4.31, 11.15)

Legend: IFN-β – interferon-β; sc- subcutaneous; im – intramuscular; "Post-DMT" – follow up period after discontinuing disease-modifying therapy (DMT); ARR – annualized relapse rate; CI – confidence interval; CDP – confirmed disability progression.
[a] Censoring at time of CDP event, else end of follow-up period.

Table 2
Predictors of post-DMT relapse and confirmed disability progression: Results of Cox proportional hazards regression model.

Variable	Risk of relapse adjusted HR (95% CI) p-value	Risk of CDP adjusted HR (95% CI) p-value
Age at baseline (years)	0.97 (0.97, 0.98) < 0.001	1.00 (0.99, 1.01) 0.675
Female sex	1.10 (1.01, 1.20) 0.042	0.85 (0.74, 0.98) 0.021
Disease duration at baseline (years)	1.00 (1.00, 1.01) 0.508	0.99 (0.98, 1.00) 0.163
Baseline EDSS		
0–1.5	Reference	Reference
2–3.5	1.20 (1.06, 1.37) 0.004	1.79 (1.47, 2.17) < 0.001
4–5.5	1.54 (1.32, 1.79) < 0.001	2.20 (1.77, 2.75) < 0.001
6+	0.81 (0.68, 0.95) 0.012	2.62 (2.09, 3.28) < 0.001
No baseline EDSS	0.99 (0.91, 1.10) 0.936	N/A
Relapse free > 1 year pre-baseline		
Yes	0.50 (0.46, 0.55) < 0.001	0.88 (0.76, 1.01) 0.066
No	Reference	Reference
EDSS stability in 3 years pre-baseline		
Yes	0.99 (0.89, 1.10) 0.829	0.83 (0.71, 0.97) 0.019
No	Reference	Reference
N/A[a]	0.95 (0.85, 1.07) 0.391	0.85 (0.72, 0.99) 0.044
Discontinued DMT		
IFN-β 1a sc	1.05 (0.95, 1.17) 0.335	1.17 (0.96, 1.43) 0.125
IFN-β 1b sc	Reference	1.09 (0.88, 1.34) 0.435
IFN-β 1a im	1.09 (0.97, 1.22) 0.130	Reference
Glatiramer acetate	1.12 (0.99, 1.26) 0.073	1.30 (1.04, 1.62) 0.023
Natalizumab	1.57 (1.31, 1.87) < 0.001	1.74 (1.30, 2.32) < 0.001
Fingolimod	1.28 (0.97, 1.69) 0.085	0.95 (0.57, 1.60) 0.852
Reason for index DMT discontinuation[a]		
Disease progression[b]	Reference	Reference
Adverse event	1.69 (1.31, 2.18) < 0.001	0.85 (0.60, 1.19) 0.335
Convenience	1.56 (1.21, 2.00) 0.001	0.66 (0.46, 0.93) 0.019
Lack of improvement	1.60 (1.24, 2.07) < 0.001	0.89 (0.64, 1.24) 0.486
Lack of tolerance	1.51 (1.16, 1.95) 0.002	0.85 (0.60, 1.21) 0.369
Not reported	1.46 (1.17, 1.82) 0.001	0.85 (0.66, 1.11) 0.228
Other	1.35 (0.99, 1.84) 0.055	0.93 (0.57, 1.51) 0.771
Scheduled stop	1.59 (1.25, 2.03) < 0.001	0.55 (0.39, 0.78) 0.001

Legend: DMT – disease modifying therapy; EDSS – Extended Disability Severity Scale; HR - Hazard Ratio; IFN-β – interferon-β; sc- subcutaneous; im – intramuscular; ARR – annualized relapse rate; CI – confidence interval.
[a] Less than 3 years of pre-baseline follow-up.
[b] 48.8% did not report a reason for discontinuation.

had a 50% lower risk post-baseline compared to patients with a pre-baseline relapse (aHR = 0.50 (0.46, 0.55), $p < 0.001$). A similar magnitude of reduction in hazard ratio was seen when the relapse-free interval pre-baseline was increased to 2, 3 and 4 years (data not shown). The relation between post-DMT relapse risk and baseline disability conformed to an inverted-U shape. Compared to the non-disabled group (EDSS 0–1.5), the risk of post-DMT relapse was increased among the mildly disabled (EDSS 2–3.5) (aHR = 1.20 (1.06, 1.37), $p = 0.004$) and moderately disabled (EDSS 4–5.5) (aHR = 1.54 (1.32, 1.79) $p < 0.001$), but decreased among the most severely disabled (EDSS ≥6 group) patients (aHR = 0.81 (0.68, 0.95) 0.012). Hazard of CDP, on the other hand, increased with baseline disability: relative to the non-disabled patients (EDSS 0–1.5), risk of CDP increased steadily in mild (EDSS 2–3.5) (aHR = 1.79 (1.47, 2.17), p < 0.001), moderate (EDSS 5–5.5) (aHR = 2.20 (1.77, 2.75), p < 0.001), to most disabled patients (EDSS ≥6) (aHR = 2.62 (2.09, 3.28) < 0.001). Risk of CDP was lower (aHR = 0.83 (0.71, 0.97) 0.019) among those whose EDSS was stable within 3 years of stopping DMT compared to those who showed disease progression pre-baseline.

Adjusted hazard ratios of post-DMT relapse and CDP by index DMT are shown in Table 2. Relative to the reference DMTs with the lowest risk of post-discontinuation relapse and CDP, only natalizumab showed an increased risk of both post-DMT relapse (aHR = 1.57, 95%CI (1.31, 1.87), $p < 0.001$, as compared to INFβ 1b sc) and CDP (aHR = 1.74 (1.30, 2.32) p < 0.001) as compared to INFβ 1a im). Risk of CDP was modestly increased among patients who discontinued glatiramer acetate (aHR = 1.30 (1.04, 1.62), $p = 0.023$, as compared to INFβ 1a im).

Relative hazard of post-discontinuation relapse and CDP with respect to reason for discontinuation were limited to 2480 patients (51.1% of the cohort) for whom reason for discontinuation was recorded in MSBase. 'Disease progression' was associated with significantly lower risk of post-DMT relapse than any other category (with the exception of 'unspecified'), and a significantly higher risk of CDP than 'convenience' and 'scheduled stop' (Table 2).

4. Conclusions

TMSBase patients who discontinued different DMTs had overall post-discontinuation annualized relapse rate of 0.22 and CDP rate of 8.23 per 100 person-years. Patients who entered the progressive phase, required mobility aids (EDSS ≥ 6) or have been relapse-free for ≥1 year had lower chance of a relapse after stopping their therapy, while younger and moderately disabled patients were at the highest risk of relapse. Risk of disability progression, however, was highest risk in those who already entered the progressive phase or were severely impaired at baseline. Our observations on risk factors of post-DMT relapses and CDP rates are broadly consistent with the natural history studies that documented higher relapse rates in the younger patients [5, 6], lower relapse rates among the older and more disabled patients [7], and higher risk of disability progression in those who reached moderate

disability thresholds [8, 9]. The hazard ratios for predictors for post-DMT relapses were relatively modest, ranging from 0.5 for 'relapse-free for 1 year prior to stoppage' to 1.7 for 'stopped DMT due to adverse event'. Combining two predictors together did not materially improve the magnitude of hazard ratio (e.g. 'EDSS ≥ 6 and relapse-free for > 1 year subset' yielded aHR of 0.35 (95% CI, 0.27–0.47)). Thus, contrary to an earlier study on IFN-β stoppers [4], we were not able to identify a subset of patients with a very low risk of post-discontinuation relapse.

Rates of post-DMT disease activity were similar across DMTs with one important exception: former natalizumab users were at much higher risk of both post-DMT relapse and CDP as compared to any other DMT. This is consistent with the well-documented observation of disease reactivation and occasional disease rebound post-Natalizumab (reviewed in [10]). Our study shows that disease recrudescence post drug discontinuation is a phenomenon specific to natalizumab. It may be due to the unique mechanism of action of this drug, which causes egress of lymphocytes from bone marrow, increase in the number of activated lymphocytes in the periphery and alpha-integrin blockade. Upon natalizumab stoppage, integrin receptors are desaturated and circulating autoreactive lymphocytes are free to enter CNS and cause inflammation [11–13]. Alternative - perhaps, complementary - explanation for the higher risk of relapses in natalizumab stoppers is that these patients may have been selected for this highly-effective therapy due to their aggressive disease course pre-treatment. We sought to partly control for the potential bias by indication by introducing 'relapse-free period prior to discontinuation' variable into our regression model. Interestingly, fingolimod was not associated with an increase in hazards of relapse or CDP as compared to Interferons, even though there are reports of disease rebound post-fingolimod [14, 15]. This discrepancy could be due to the fact that fingolimod rebound is rare and may not be readily observed with the relatively small number of fingolimod stoppers in our study ($N = 129$).

Limitations of our work, in addition to the possible bias by indication mentioned above, include the other forms of selection bias. Lack of data completeness for 'reasons for drug discontinuation', which was only available for 51% of patients, is a potential source of selection bias. Moreover, patients who discontinue medication may be less likely to follow up in clinic if they do not have new symptoms of MS, which would inflate relapse rates among DMT stoppers. Patients who are unable to walk generally do not have an indication to be on a DMT, and even those who are receiving a DMT may not attend clinic as often as their ambulatory counterparts. These considerations could explain why the 'EDSS 6+' group mostly comprises of patients who use canes and walkers (EDSS 6 and 6.5) rather than wheelchair and bedbound patients. Our results, therefore, are not informative for patients at the higher extreme of age and disability spectrum.

Importantly, our study does not address the question of whether and when DMT discontinuation may be warranted. Rather it allows clinicians to better inform patients who are considering stopping their DMT what disease course might be expected after discontinuation. DMT stoppers had approximately 1 in 5 risk of relapse per year, which is lower than ARR in the placebo arms of recent clinical trials (msdiscovery.org/arr), but not negligible. The hazard for post-DMT relapse was further decreased, by approximately 50%, in some patient subgroups, such as those who have been relapse-free for ≥1 year or had 'disease progression' as reason for stopping. Hazards of relapse were approximately 50% higher in those with moderate disability compared to non-disabled or severely disabled patients. A similar observation was made in a French study of patients with progressive MS, in whom MRI activity prior to treatment withdrawal and EDSS < 6 were positively associated with disease activity after withdrawal [16]. Hazards of disability progresssion were highest in the most disabled patients and in former natalizumab users, who were are particularly high risk for both relapses and sustained disability increase. Discontinuation of natalizumab is known to present challenges even in the older patients without recent relapses [11].

Whether rate of relapses or progression would have been different had patients continued on their DMT cannot be determined in our study, which only considered DMT stoppers. In our prior work, MSBase patients with prolonged relapse-free period who stopped their DMT tended to have higher hazard for disease progression than propensity-score matched patients who continued on their DMT unless they have already entered the progressive phase [17]. Benefits of drug discontinuation - freedom from drug's side effects and costs - needs to be carefully weighed against potential long-term benefits of therapy - slowing of disease progression [18] and lower mortality [19]. Ultimately, the guidance on whether and when to stop DMT will have to await the results of randomized discontinuation trial, which is ongoing [20].

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Ilya Kister served on 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.

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Ludwig Kappos has served in the last 24 months as principal investigator for the following drug studies BOLD EXT., EXPAND (BAF312, Novartis), DECIDE, DECIDE EXT. (Daclizumab HYP, Biogen), ENDORSE (BG00012, Biogen), FINGORETT, FTY-UMBRELLA, INFORMS, INFORMS EXT LONGTERM. (Fingolimod, Novartis), MOMENTUM (Amiselimod, Mitsubishi) OCRELIZUMAB PHASE II EXT., OPERA, ORATORIO (Ocrelizumab, Roche), REFLEXION (IFN β-1a, Merck), STRATA EXT.(Natalizumab, Biogen Idec) and TERIFLUNOMIDE EXT. (Teriflunomide, Sanofi-Aventis). L. Kappos is a member in the Editorial Boards in the following journals: “Journal of Neurology”, “Multiple Sclerosis Journal”, “Neurology and Clinical Neuroscience “and” Multiple Sclerosis and Related Disorders”. Honoraria and other payments for all these activities have been exclusively used for funding of research of his department.

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