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Risk of early relapse following switch from injectables to oral agents for multiple sclerosis

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Steve Vucic did not declare any competing interests.

ABSTRACT

Background: Early relapse outcomes in long-term stable patients switching from IFN β /GA to oral therapy are unknown.

Objective: The objective of this study was to compare early relapse and progression in MS patients switching to oral therapy following a period of stable disease on interferon-beta or glatiramer acetate (IFN β /GA), relative to a propensity-matched comparator of patients remaining on IFN β /GA.

Methods: The MSBase cohort study is a global, longitudinal registry for Multiple Sclerosis. Time to first 6-month relapse in previously stable MS patients switching from platform injectables (“switchers”) to oral agents were compared with propensity matched patients remaining on IFN β /GA (“stayers”) using a Cox Marginal Model.

Results: Three-hundred and ninety-six switchers were successfully matched to 396 stayers on a 1:1 basis. There was no difference in the proportion of patients recording at least 1 relapse in the first 1-6 months by treatment arm (7.3% of switchers; 6.6% stayers, $p=0.675$). The mean Annualised Relapse Rate ($p=0.493$) and the rate of first 6-month relapse by treatment arm (HR 1.22, 95% CI 0.70, 2.11) were also comparable. There was no difference in the rate of disability progression by treatment arm (HR 1.43, 95% CI 0.63, 3.26).

Conclusion: This is the first study to compare early relapse switch probability in the period immediately following switch to oral treatment in a population previously stable on injectable therapy. There was no evidence of disease reactivation within the first 6 months of switching to oral therapy.

INTRODUCTION:

Switching disease-modifying treatment in multiple sclerosis is common, often triggered by breakthrough disease.¹ Where disease course is stabilised on platform injectables (IFN β /GA),

poor tolerability⁸⁻¹³ or the ease of administration offered by the increasing range of oral agents may further motivate patients and/or clinicians to consider a treatment switch. Recent concerns around disease reactivation in patients switching to fingolimod²⁻⁷ have highlighted the paucity of data on clinical outcomes shortly after switching to oral agents, particularly in previously stable patients seeking to switch for reasons other than breakthrough disease.

In patients with satisfactory disease control on injectables, unacceptable tolerability may form the primary trigger for considering treatment switch.¹⁴ Increasing availability of oral agents for MS has expanded treatment options. Oral agents including fingolimod, dimethyl fumarate (DMF) and teriflunomide have been reported to reduce MS relapse rates by between 32% to 55% relative to placebo in clinical trials.¹⁵⁻²⁰ A 12-month double-blind randomised trial observed a 48% decrease in relapse frequency on fingolimod relative to IFN β -1a-IM,¹⁹ whilst a phase 3 trial of teriflunomide observed no difference in annualised relapse rate (ARR) relative to a sub-cutaneous IFN β -1a comparator.²¹ A phase 3 comparison of DMF with glatiramer acetate observed a non-significant reduction in annualised relapse rate with DMF.²²

Head-to-head comparisons of clinical outcomes in patients switching to oral therapy relative to platform injectables are limited in volume. Modelling of switch data from the one-year TRANSFORMS extension trial estimated patients switching from IFN β -1a-IM to fingolimod on average doubled their time to first relapse.²³ Observational studies of fingolimod switching have further observed a significant reductions in ARR relative to other injectable agents, including an analysis by this study group which observed fingolimod switches associated with both a lower ARR and a lower rate of confirmed disability progression when compared against switching to IFN β /GA.^{23,24}

The current evidence base for clinical outcomes in a treatment switch context is largely limited to patients with active disease. Early relapse outcomes in stable patients switching from IFN β /GA to oral therapy are unknown. The objective of this study was to compare early ARR, time to first relapse and disability progression in MS patients switching to oral therapy following a period of stable disease on IFN β /GA, relative to a propensity-matched comparator of stable patients remaining on pre-baseline IFN β /GA. This method has been successfully employed previously to derive product comparisons of efficacy outcomes using MSBase registry data.²⁵⁻²⁶

Materials & Methods

MSBase Registry

All patients contributing to this study were sourced from the international MSBase Registry, a global, longitudinal, observational registry for Multiple Sclerosis. Established in 2004, the registry prospectively collects disease-related information from consenting patients attending MS treatment centers using an internet-based, physician-owned and operated system www.msbase.org²⁷. 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.

Inclusions

Relapsing Remitting MS (RRMS) patients aged between 18 and 75 years inclusive with a baseline EDSS between 0 and 5.5 who had been stable on IFN β /GA for a minimum of 12 months prior to baseline and then either switched to an oral agent or remained on IFN β /GA for a minimum of 6 months post baseline were included in this analysis. Stable disease was defined as an absence of clinical relapse events, no gadolinium –enhancing (Gd+) lesions or an increase in the number of T2 lesions on cerebral MRI and no change in EDSS score whilst on injectable DMD treatment within the 12 months pre-baseline. All cases satisfied the Poser criteria for definite MS or the McDonald criteria for MS.²⁸⁻³⁰

Outcomes & Definitions

The primary outcome was the occurrence of a relapse event within 1 to 6 months of baseline. Baseline for the switch group was the date of initiation of an oral agent. The baseline date for patients who remained on IFN β /GA (the “stayers”) was the date of the first observed EDSS visit from 1st January 2010 onwards in the presence of 12 months of stable disease as defined above. A relapse was defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for at least 24 hours, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous attack, also previously applied in an MSBase relapse phenotype analysis.³¹ Disability progression was analysed as a secondary variable. A confirmed disability progression event was defined as ≥ 3 -month confirmed increases of ≥ 0.5 points for patients with a baseline EDSS score > 5.5 , ≥ 1.0 point for those with a baseline EDSS score between 1.0 and 5.5, inclusive, and ≥ 1.5 points for those with a baseline EDSS score of 0. EDSS scores recorded within 30 days after a relapse onset were excluded from

analysis. A switch was defined as commencing an oral DMD within a maximum of three months of discontinuing the prior agent. The date filter for the stayers was identified and applied *a priori* to ensure both switch and stay groups were contemporaneous (the 2010 start date corresponding to that period in the registry where oral DMD initiations began to be recorded with sufficient frequency).

Statistical analyses

Categorical variables were summarised using frequency and percentage and compared using a chi-square test. Continuous variables were summarised using mean and standard deviation (SD) or median and inter-quartile range as appropriate, and compared using an analysis of variance or Kruskal-Wallis test as appropriate. A Bonferroni adjustment was applied to correct for multiple comparisons. Patients switching to oral therapy were propensity matched to a comparable patient remaining on IFN β /GA using the following baseline variables: age, sex, disease duration, EDSS, number of prior DMD commencements, proportion of disease duration on treatment and number of prior DMD starts as a proportion of baseline disease duration. The propensity score was derived using a logistic regression model where switching to oral DMD formed the dependent outcome variable and the various baseline factors were incorporated into the model as explanatory covariates. Patients from each treatment arm were 1:1 matched according to similarity of propensity score using a 5-to-1 digit matching algorithm.³² Given the larger number of IFN β /GA stayers available, many-to-one matching (2:1, 3:1 and 4:1) were also attempted. Matching success was assessed through the analysis of paired tests and standardized differences. A Wilcoxon signed-rank test and a McNemar Chi test were used to compare the post-matching balance of continuous and categorical baseline characteristics respectively between matched groups. Imbalance was defined as an absolute standardized difference equal to or greater than 0.20.³³

Analyses of time to first relapse on treatment and time to three-month confirmed disability progression were performed using a Cox Marginal Model, clustered for the matched pair. Hazard proportionality was assessed via analysis of scaled Schoenfeld residuals and for all models presented in this report, hazard proportionality was satisfied. Simultaneous censoring of the matched pair, censoring each member of the pair at the earliest censor point for each outcome analysed, was used to limit the influence of informative censoring secondary to systematic differences in follow-up duration by treatment arm on event ascertainment.

Rosenbaum sensitivity analyses across all outcomes were conducted to test the sensitivity of our propensity-matched models to unobserved heterogeneity secondary to baseline characteristics that were either not collected or incompletely observed.³⁴ All analyses were undertaken using Stata version 13 (StataCorp, College Station, Texas).

RESULTS

Patient characteristics

As of the 28th of January 2015, 401 “switch” patients and 3418 “stay” patients were eligible for propensity matching. Prior to matching, patients that switched to oral medications were older, had a longer disease duration, a greater number of prior DMD therapy commencements and a higher number of prior DMD initiations as a proportion of disease duration (Table 1). There was no difference in sex, baseline EDSS and the proportion of disease duration on treatment. There were no differences in the matched sample in any of these characteristics (Table 2). One-to-one matching was preferred for the primary analysis over any of the many-to-one matches secondary to the poorer quality of the secondary, tertiary and quaternary matches. Of the matched switchers, 282 (71.2%) switched to fingolimod, 64 (16.2%) to DMF and the remaining 50 (12.6%) to teriflunomide. Median (IQR) time to switching post-IFN β /GA cessation was 14 days (0, 39). Within the matched “stayers”, 158 (39.9%) remained on IFN β -1a-SC, 122 (30.8%) glatiramer acetate, 67 (16.9%) IFN β -1a-IM with the remaining 49 (12.4%) on IFN β -1b. Fingolimod switchers were younger at baseline relative to both DMF ($p(\text{rank-sum})=0.010$) and teriflunomide ($p(\text{rank-sum})=0.021$) had a higher baseline EDSS relative to both DMF ($p(\text{rank-sum})=0.002$) and teriflunomide ($p(\text{rank-sum})<0.001$). There was no difference in gender, disease duration and prior DMD exposure by oral switch product. Within the switchers, the reason for discontinuation of the pre-switch DMD was recorded for only 217 (54.8%) patients. Amongst these patients, the most frequently reported reasons for discontinuation were “lack of tolerance” ($n=68$ or 31.3% of the 217 switchers recording a discontinuation reason) and “convenience” ($n=64$, 29.5%).

Relapse

Fifty-five (6.9%) of the 792 matched patients recorded a relapse event in the 6 months following baseline. There was no difference in the proportion of patients recording at least 1 relapse in the first 1-6 months post-baseline by treatment arm (7.3% of switchers compared with 6.6% stayers, $p(\text{McNemar})=0.675$). In addition, there was no difference in the mean (SD) annualised relapse rate (ARR) within the first 6 months of baseline between the switch

group (0.2 [0.7]) and the stayers (0.2 [0.6], $p(\text{signed-rank})=0.4931$). There was no difference in the rate of first 6-month relapse by matched study arm (HR 1.22, 95% CI 0.70, 2.11) (Figure 1).

Disability progression

Within the first 6 months after switching to oral therapy there were 9 (2.3%) confirmed progression events compared with 4 (1.0%) in the stayers ($p(\text{McNemar})=0.269$). In addition, there were no differences in the rate of first disability progression events between switchers and stayers (HR 1.43, 95% CI 0.63, 3.26, reference=stayers).

Sub-group analysis

Amongst switchers, there was no difference in the rate of first 6-month relapse between the three oral agents (DMF adjusted HR: 1.38, 95% CI 0.56, 3.42; teriflunomide: aHR 0.58, 95% CI 0.13, 2.39; reference = fingolimod), when adjusted for baseline differences in age and EDSS. Amongst switchers the length of washout period was not associated with either early relapse (HR 0.83, 95% CI 0.62, 1.11; reference= less than 2 months) or significant disability progression (HR 1.33, 95% CI 0.68, 2.62; reference=less than 2 months).

Sensitivity analyses

Reapplying these models across full patient post-baseline on-treatment follow-up, there was no difference in time to any first relapse event between switchers and stayers (HR 0.87; 95% CI 0.63, 1.21, reference=stayers) (Figure 2). Similarly there was no difference in disability progression on oral therapy when compared with the stayer group (HR 1.48, 95% CI 0.79, 2.75, reference=stayers). Furthermore there was no difference in post-baseline on-treatment EDSS change between the switch group (mean (SD): 0.25 (1.21)) and stay group (mean (SD): 0.40 (1.06), $p(\text{signed-rank})=0.1799$). Mean (SD) post-baseline on-treatment follow-up was 2.1 (1.8) years. There was no difference in the rate of any first progression event between any of the three oral agents.

Unmeasured confounding

Rosenbaum sensitivity analyses of our propensity-matched relapse and progression models estimated that an unobserved confounder would need to produce a minimum 1.89 and 2.07 fold increase in the rate of relapse and confirmed disability progression respectively in order to reject the inference of a treatment effect in favour of selection effects. These represent

improbably large differences in the context of the observed point estimates and associated confidence intervals. This suggests that the effects of unmeasured confounding on the observed associations between treatment arm and both relapse and progression outcomes were not large enough to significantly change the inferences made.

DISCUSSION

Poor tolerability of IFN β /GA in patients demonstrating otherwise good control of disease on treatment is an increasingly common challenge for both patients and clinicians. Sub-optimal adherence secondary to administration issues or side effect profiles of platform injectables, increases the probability of breakthrough disease, which in turn risks undoing the good work of prior therapy. The broader range of oral therapies now available has considerably expanded the options for sequencing treatments in response to breakthrough disease and tolerability issues. This is the first study to examine the real world risk of early relapse in stabilised MS patients switching to oral therapy against a propensity matched comparator arm of patients with similar duration of stable disease who remain on IFN β /GA.

Treatment benefits observed in controlled trial settings can only be realised in clinical practice if patients are fully adherent with treatment regime. Administration convenience and patient preference for oral formulations, particularly in the setting of injection anxiety and previous experience with injection site reactions, may improve treatment adherence and thus maximise the efficacy available from oral agents. Such gains need to be balanced with potential risk of disease reactivation in the months shortly following treatment switch.²⁻⁷ The risk of early relapse following oral switch may be weighted higher by patients in our study population of long-term disease stable switchers relative to patients switching secondary to breakthrough disease. Our results suggest that early relapse in previously stable patients following a switch to oral agents was rare (only 7.3% of 396 switchers recorded a relapse within 1-6 months post switch). Further there was no difference in either the proportion of patients recording an early relapse event, the ARR or time to first relapse in switchers compared to stable patients who remained on baseline IFN β /GA therapy.

Disability progression, as measured by the EDSS, was also infrequent and no difference was observed between switchers and stayers within the first six months post-baseline. Whilst the present study did not establish significant differences in short-term disability progression, this

analysis was only exploratory since progression, unlike relapse rates, is observed and confirmed over several time points. It is unlikely that six months would be sufficiently long enough to characterise confirmed disability progression with appropriate power. This is consistent with the experience of clinical trials using disability progression as a study end-point.^{15,20}

On sensitivity analysis, stable patients switching to oral treatment demonstrated no difference in either rate of first relapse and first confirmed disability progression over *long-term* follow-up relative to the “stayers”. The present findings suggest that disease remains quiescent over both the immediate post-switching period (1-6 months) and longer term treatment horizon, at least in this population of previously stable patients. In any event, whilst no increase in event risk was observed in our study, a potential risk of increased disease activity needs to be considered when transitioning a stable RRMS patient from an injectable to oral treatment. In addition, the side-effect profile of oral agents including, but not limited to, bradycardia, gastrointestinal symptoms, flushing, hair-thinning,^{10,17,20,35} needs to be considered, particularly in a population of long-term stable patients considering regimen change. Rarer, severe complications may include the risk of progressive multifocal leukoencephalopathy, infectious or immunosuppressive complications, pregnancy associated sequelae and potential hepatotoxicity also need to be considered when risk-stratifying a previously stable patient for a potential treatment switch.^{19,20,36} Whatever the treatment decision, close monitoring of patients switching to oral agents is suggested given long-term safety profiles are less well-established relative to the platform injectables.

A limitation of this study stems from uncontrolled confounding of prognostic factors not included in the propensity match. Confounders that were either not collected or incompletely observed in the registry, such as cerebral and spinal cord MRI disease burden, were not formally adjusted. However, unobserved confounding in this case is unlikely to significantly influence the finding in the present study as indicated by the Rosenbaum sensitivity analysis. Another potential limitation of this study is that clinician-documented reasons for discontinuation were not available for all switches and thus were insufficiently powered to analyse. However of the discontinuation reason data that was available, lack of tolerance and convenience accounted for the majority of documented triggers for discontinuation in these previously stable patients. Whilst such data was available for only just over half the matched switchers (55%), it may be reasonable to infer that tolerance and convenience would remain

key drivers of treatment cessation across the full switcher sample. The relative magnitude of any tolerance or, in particular, convenience gains in switching to a specific oral DMD product needs to be balanced against the risk of adverse event and, depending on the regulatory setting, the expense of switching. A further limitation of this study is the lack of patient reported outcome data which may provide important insights into a patient's real-world experience following switch to oral therapy, particularly in light of the tolerance and convenience discontinuation triggers observed. Such an analysis would constitute an important future expansion of the current study.

The present study argues against the occurrence of rebound disease within the first 6 months of switching to oral therapy in patients that were stable on injectable or infusable treatments. Switching to an oral agent, in the setting of stable disease, needs careful consideration of the longer-term relapse risk (>6 months). Further studies assessing the factors underlying the increase in longer-term disease activity need to be undertaken in order to develop more appropriate management algorithms.

Author contributions:

T Spelman conceptualized and designed the study, conducted the statistical analysis, interpreted the analysis and drafted and revised the paper

L Mehkael interpreted the analysis and revised the paper

T Burke interpreted the analysis and revised the paper

H Butzkueven interpreted the analysis and revised the paper

S Hodgkinson interpreted the analysis and revised the paper

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Table 1 – Baseline characteristics of unmatched patients

Baseline Characteristic	Switch (n=401)	Stay (n=3418)	P-value
Age, years, median (IQR)	41.7 (35.1, 49.8)	40.1 (32.9, 48.1)	0.0016
Female sex, n (%)	301 (75.1)	2443 (71.5)	0.131
Disease duration, years, median (IQR)	9.1 (5.7, 15.2)	9.0 (4.7, 14.6)	0.0457
EDSS, median (IQR)	1.5 (1, 3)	1.5 (1, 2.5)	0.3286
Number of prior DMD starts – mean (SD)	1.7 (1.2)	0.5 (0.8)	<0.0001
Proportion disease duration on treatment – mean (SD)	0.6 (0.3)	0.6 (0.3)	0.0884
Number of prior DMD starts as a proportion of disease duration - mean (SD)	0.2 (0.2)	0.1 (0.1)	<0.0001

Abbreviations: EDSS = Expanded Disability Status Scale; IQR = interquartile range; SD = standard deviation; DMD = Disease-Modifying Drug

Table 2 – Baseline characteristics of propensity score-matched patients

Baseline Characteristic	Switch (n=396)	Stay (n=396)	P- value*
Age, years, median (IQR)	41.7 (35.0, 49.8)	42.9 (35.1, 51.5)	0.2121
Female sex, n (%)	298 (75.3)	296 (74.8)	0.8676
Disease duration, years, median (IQR)	10.7 (6.1, 16.7)	11.5 (6.3, 17.4)	0.1531
EDSS, median (IQR)	2.0 (1, 3)	2.0 (1, 2.5)	0.5290
Number of prior DMD starts – mean (SD)	1.7 (1.1)	1.7 (1.2)	0.2710
Proportion disease duration on treatment – mean (SD)	0.6 (0.3)	0.6 (0.3)	0.8991
Number of prior DMD starts as a proportion of disease duration - mean (SD)	0.2 (0.2)	0.2 (0.2)	0.1622

Abbreviations: EDSS = Expanded Disability Status Scale; IQR = interquartile range; SD = standard deviation; DMD = Disease-Modifying Drug

*All post-matching baseline characteristics had a standardized difference between -20% and +20%.

Figure legends

Figure 1 – Time to first relapse within 6 months post-baseline

Note: Vertical axis scaled to 0.50 through 1.00

Figure 2 – Sensitivity analysis: Time to *any* first post-baseline relapse

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