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Title

Association of initial disease-modifying therapy with conversion to secondary progressive multiple sclerosis among patients with relapsing-remitting multiple sclerosis.

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eTable S1: Data quality procedure

eTable S2: Patient disposition per centre

eTable S3: Characteristics of prematching, unmatched and matched patients at baseline

eTable S4: Propensity scores

eTable S5: Matching coefficients from propensity matching

eTable S6: EDSS scores after conversion to SPMS

eTable S7: Characteristics of patients presented for matching and those excluded due to data missingness

Keywords

disease modifying therapy, secondary progressive multiple sclerosis, conversion, propensity score

Key points

Question: Among patients with relapsing-remitting multiple sclerosis (RRMS), what is the association between disease-modifying therapies (DMTs) and the risk of conversion to secondary progressive multiple sclerosis (SPMS)?

Findings: In this cohort study involving 1,555 patients with RRMS, initial treatment with fingolimod, natalizumab or alemtuzumab was associated with a lower risk of conversion to SPMS compared with β -interferon or glatiramer acetate (hazard ratio 0.66).

Meaning: These findings, considered along with the risks associated with these therapies, may help inform decisions regarding DMT selection for patients with RRMS.

Abstract

Importance: Within two decades of onset, 80% of untreated patients with relapsing-remitting multiple sclerosis (RRMS) convert to a phase of irreversible disability accrual termed secondary progressive (SP) MS. The association between disease-modifying treatments (DMTs) on conversion to SPMS has rarely been studied and - to the best of our knowledge - never using a validated definition.

Objective: To determine the association between the use of DMTs, the type of initial DMT, and the timing of DMT escalation with the risk of conversion to SPMS using a validated definition of SPMS.

Design, Setting and Participants: Cohort study with prospective data collection from 68 neurology centers in 21 countries examining patients with RRMS commencing DMTs (or monitoring if untreated) between 1988-2012 with minimum 4 years' follow-up.

Exposure: The use, type and timing of the following DMTs: β -interferon or glatiramer acetate (β -IFN|GA), fingolimod, natalizumab or alemtuzumab.

Main outcomes and measures: Conversion to SPMS using a validated definition.

Results: Following propensity-score matching for baseline demographics, 1,555 patients were included (1,123 female, mean baseline age 35 (standard deviation 10) years, last visit date 14th February 2017. Compared to matched untreated patients, a lower hazard of conversion to SPMS was seen in patients initially treated with β -IFN|GA (hazard ratio (HR) 0.71 (95% CI 0.61–0.81), $p<0.001$, 5-year absolute risk (AR) 27% (58/213) vs 12% (49/407) respectively, median follow-up 7.6 (IQR 5.8–9.6) years), fingolimod (HR 0.37 (95% CI 0.22–0.62), $p<0.001$, 5-year AR 32% (56/174) vs 7% (6/85) respectively, follow-up 4.5 (IQR 4.3–5.1) years), natalizumab (HR 0.61 (95% CI 0.43–0.86), $p=0.005$, 5-year AR 38% (62/164) vs 19% (16/82) respectively, follow-up 4.9 (IQR 4.4–5.8) years) and alemtuzumab (HR 0.52 (95%CI 0.32–0.85), $p=0.009$, 5-year AR 25% (23/92) vs 10% (4/44) respectively, follow-up 7.4 (IQR 6.0–8.6) years). Initial treatment with fingolimod, alemtuzumab or natalizumab was associated with a lower risk of conversion than initial treatment with β -IFN|GA (HR 0.66 (95% CI 0.44–0.99), $p=0.046$, 5-year AR 7% (16/235) vs 12% (46/380) respectively, median

follow-up 5.8 (IQR 4.7-8.0) years). The probability of conversion was lower when β -IFN|GA was started within 5 years of disease onset versus later commencement (HR 0.77 (95%CI 0.61-0.98), $p=0.03$, 5-year AR 3% (4/120) vs 6% (2/38) respectively median follow-up 13.4 (IQR 11-18.1) years); and when patients on β -IFN|GA were escalated to fingolimod, alemtuzumab or natalizumab within 5 years of disease onset compared to later escalation (HR 0.76 (95% CI 0.66-0.88), $p<0.001$, 5-year AR 8% (25/307) vs 14% (46/331) respectively, median follow-up 5.3 (IQR 4.6-6.1) years).

Conclusions and Relevance: Among patients with RRMS, initial treatment with fingolimod, natalizumab or alemtuzumab was associated with a lower risk of conversion to SPMS compared to initial treatment with β -IFN|GA over a median 5.8 years of follow-up. These findings, considered along with these therapies' risks, may help inform decisions about DMT selection.

Introduction

Multiple sclerosis (MS) is amongst the most common causes of disability in young adults. Eighty five percent of patients present with the relapsing-remitting form (RRMS) for which several immunomodulatory disease-modifying therapies (DMTs) reduce relapse rates and disability accumulation.¹⁻⁵ Within two decades of onset, 80% of untreated patients with RRMS convert to a phase of sustained disability accrual termed secondary progressive multiple sclerosis (SPMS).⁶ This phase is responsible for much of the disease's negative physical, psychological and societal effects. Until recently no rigorous definition of SPMS existed, leading to varying criteria and contradictory results from one randomised trial extension⁷ and seven observational studies⁸⁻¹⁴ that predominantly examined the effects of β -interferon or glatiramer acetate (β -IFN|GA) on conversion to SPMS. Using a recently-published validated definition of SPMS,¹⁵ the rate of conversion to SPMS was examined between (i) different DMTs and an untreated cohort, (ii) fingolimod, alemtuzumab or natalizumab (F|A|N) versus β -IFN|GA, and (iii) treatment commencement or escalation within versus after 5 years of disease onset.

Methods

Ethical approval was granted by the Melbourne Health Human Research Ethics Committee and by each site's institutional review board. All enrolled patients provided written or verbal consent, as per local regulations.

Patients and inclusion criteria

This international observational cohort study utilised prospectively-collected clinical data from three sources (all accessed in February 2017). Untreated patients were selected from the neuroinflammatory service database at the University Hospital of Wales, a tertiary referral centre in South-East Wales. Clinical data was initially collected as part of a cross-sectional study¹⁶ then

through annual or semi-annual appointments. Treated patients were identified from MSBase, an observational cohort study collecting real-world data from patients with multiple sclerosis across 105 centers in 29 countries.¹⁷ Additional alemtuzumab-treated patients were identified from five European non-MSBase centers using alemtuzumab before it was licensed¹⁸ (Bristol, Cardiff, Swansea, Dublin and Dresden). Within MSBase, β -IFN|GA, fingolimod and natalizumab had sufficient patient numbers with more than 4-years on-treatment follow-up (while teriflunomide and dimethylfumarate did not, so they were not included). The 4-year minimum follow-up period represented the longest follow-up period without excluding the majority of patients in MSBase treated with natalizumab or fingolimod. Data were subject to rigorous data-quality procedures (eTable S1). For inclusion, patients needed to be classified as RRMS (clinically definite MS¹⁹) at baseline, required the complete MSBase minimum dataset (sex, date of birth, date of clinical onset and dates of relapses),²⁰ at least one Expanded Disability Status Scale²¹ (EDSS) score no more than 6 months before baseline and at least two EDSS scores after baseline (one to detect disability progression and another to confirm the increase later (see definition below)). Patients stopping their initial therapy within 6 months were excluded (as some drugs require 6 months to exert their effect²²). The untreated cohort received no DMTs, even briefly. DMT dose, frequency and timing followed published protocols^{18,23}: alemtuzumab (12–24 mg intravenous once per day for 5 days [cycle 1] or for 3 days [cycle 2 or more]); β -IFN (30-250 μ g subcutaneous or intramuscular injections administered between every other day to every other week); glatiramer acetate (20 mg subcutaneous injection once per day); fingolimod (0.5 mg oral once per day), and natalizumab (300 mg intravenously every 4 weeks). Given its administration schedule, quantifying the duration of alemtuzumab treatment effectiveness is challenging: first, the published period of reduced CD4 lymphocyte count (35 months/cycle²⁴) was used, and then a sensitivity analysis using the median period to re-treatment (7 years²⁵) was performed. If patients received multiple DMTs, the first was used as the DMT under study (except when comparing early versus late escalation from β -IFN|GA to F|A|N). Patients subsequently receiving different DMTs were excluded from analyses of single drugs versus untreated

patients but were included in all other analyses. Patients receiving therapies at any time during the study period that were unlicensed were excluded (mitoxantrone, cladribine, rituximab, ocrelizumab, siponimod or autologous stem-cell transplantation). Although ocrelizumab and cladribine have subsequently been licensed, there were insufficient numbers meeting the minimum 4 years' clinical follow-up criterion within MSBase to examine individually.

No licensed therapies have shown greater reduction in relapse rates than natalizumab or alemtuzumab.¹⁸ Patients receiving natalizumab or alemtuzumab who experienced relapses or disability-progression in this study were therefore already at the therapeutic ceiling of treatment. This was replicated for patients receiving β -IFN|GA (in all analyses) by restricting inclusion to patients treated and followed-up before fingolimod, alemtuzumab or natalizumab became available, preventing the exclusion of patients who might have been prescribed these more potent therapies as first-line or escalation therapy during follow-up, and thereby preventing selection bias towards milder disease among the β -IFN|GA group. (During this period, mitoxantrone was occasionally employed as escalation therapy for particularly aggressive disease: to ensure the β -IFN|GA cohorts were not biased towards milder disease, sensitivity analyses including these patients were performed). Consistent with previous work,¹⁸ patients participating in clinical trials were excluded as their trial treatment assignment was not documented within MSBase, and trial EDSS frequencies often differ to clinical practice. Patients with previous stem cell transplantation were also excluded.

Study design

To examine whether individual DMTs were associated with delayed or reduced conversion to SPMS, matching and analyses were repeated four times comparing untreated patients to those receiving initial treatment with (a) β -IFN|GA, (b) fingolimod, (c) natalizumab, or (d) alemtuzumab. In these analyses, the date of DMT commencement acted as the baseline date for treated patients. For untreated patients, the baseline date was the visit date when clinical and demographic parameters

(calculated at each visit and quantified using the propensity score) most closely matched the corresponding baseline values of individual treated patients.

Fingolimod,⁴ alemtuzumab⁵ and natalizumab²⁶ (F|A|N) confer greater reductions in relapse rate than β -IFN|GA. To examine whether they are associated with different effects on conversion to SPMS, patients receiving F|A|N as their initial DMT were matched and compared to patients initially treated with β -IFN|GA.

To examine the association between timing of DMT commencement and conversion to SPMS, patients initially treated with β -IFN|GA within 5 years of disease onset were matched and compared with those initially treated after 5 years. For patients treated within 5 years, the baseline was set at DMT commencement. For all patients treated after 5 years, the baseline was set at a visit within 5 years of symptom-onset, before therapy began, incorporating the period from baseline to treatment initiation into the follow-up. The date of this visit was identified by extracting the matching variables at each eligible visit within 5 years of symptom-onset, then using a matching process to identify when these variables most closely matched those of a patient treated within 5 years. By handling treatment exposure as a time-dependent variable, the analyses accounted for immortal time bias, including the untreated time from baseline to treatment initiation in the group treated after 5 years. This technique was repeated when comparing escalation from β -IFN|GA to F|A|N within or after 5 years of disease onset.

Outcome

The outcome in all analyses was conversion to SPMS based on an objective definition¹⁵ without functional scores: patients required an EDSS increase (if the EDSS score was 5.5 or less, an increase of 1 point was required; if the EDSS score was over 5.5 an increase of 0.5 points was required). This EDSS increase had to (i) occur in the absence of a relapse, (ii) be confirmed at subsequent appointments over at least 3 months; and (iii) the resultant EDSS score had to be 4 or more.¹⁵

Matching

Using the MatchIt package²⁷ (v2.4-22) the propensity of treatment was estimated using a multivariable logistic regression model using baseline age, sex, annualised-relapse rate in the year prior to baseline, EDSS score and disease duration. To minimise the difference in proportions of time on therapy during follow-up in the β -IFN|GA versus F|A|N analysis, patients were additionally matched on the proportion of time on therapy during the median follow-up period (first 5.8 years). Patients in the early versus late escalation from β -IFN|GA to F|A|N analysis were also matched on disease duration at the time of starting β -IFN|GA plus the individual therapy they were escalated to. To increase matching precision,^{18,28} patients were matched in a variable matching ratio (10:1 to 1:1) by nearest neighbour matching using the optimal caliper (0.1 standard deviations (SD) of the propensity score).²⁹⁻³¹ Where treatment initiation was not used as the baseline (the late group in the early versus late β -IFN|GA and escalation analyses; and the untreated group in all untreated analyses), any visit could serve as baseline (to optimise matching). A single patient could therefore be used multiple times in one analysis and across analyses. To account for this, replacement was permitted in these matching models. All subsequent models were weighted to account for the variable matching ratio (see below). Each patient's follow-up was censored to the shortest of the two follow-up times from each set, resulting in identical follow-up durations between groups. Sets where either patient subsequently had less than two EDSS scores following baseline were excluded.

Statistical analysis

All analyses were performed using the survival package (v3.3.1) in R. Setwise weighted conditional proportional hazards models (Cox) clustered for matched patient sets examined the proportions of patients free from conversion to SPMS. All models were adjusted for EDSS frequency plus any variables showing residual imbalance following matching (as denoted by a standardised difference (quantified by Cohen's d value) ≥ 0.2 ³² (which indicates less than 92% overlap between the groups)). The weights were calculated as the inverse of the number of times a patient was included in an

analysis to account for the variable matching ratio. The models comparing (i) β -IFN|GA with F|A|N, (ii) early versus late β -IFN|GA and (iii) early versus late escalation from β -IFN|GA to F|A|N were also adjusted for the proportion of time on therapy during the entire post-baseline setwise-censored follow-up. The Schoenfeld's global test³³ was used to detect violation of the proportional hazards assumption; when violated, Weibull accelerated failure time regression models were used. To estimate the conditional hazard ratio, robust estimation of variance based on the Huber sandwich estimator was used. The Efron approximation was used to resolve tied survival times. Graphs were censored at the latest point that each group contained at least 10 patients or less than 10% of the original group, whichever came first. The percentage of patients that had converted to SPMS are presented at 5 years and the last year before censor in the text. Two-sided significance testing was used. Results were considered significant at the $p < 0.05$ level. Because there was no adjustment for multiple comparisons, secondary analyses should be interpreted as exploratory.

Results

44,217 patients with multiple sclerosis (1,091 from the Welsh untreated cohort; 43,048 from MSBase and 78 alemtuzumab-treated patients from non-MSBase centers) were assessed for eligibility (Figure 1). To avoid informed censoring bias, the β -IFN|GA groups were limited to those treated and followed-up before F|A|N became available for escalation (baseline year 1996-1998 (Table 1)). Following exclusion of ineligible patients (Figure 1), the matching process then matched 1,555 patients from 68 centers in 21 countries (eTable S3): 230 from the Welsh untreated cohort; 1,272 from MSBase and 53 alemtuzumab-treated patients from non-MSBase centers (Table 1, eTables S3-4). Matching coefficients and post-SPMS EDSS scores are shown in eTables S5-6 respectively. The assumption of proportionality was not met in 6/9 analyses (requiring Weibull accelerated failure time regression models).

Compared with no treatment, treatment with each included therapy was associated with a significantly lower probability of converting to SPMS. For patients initially treated with β -IFN|GA (n=407), the hazard ratio (HR) was 0.71 (95% confidence interval (CI) 0.61–0.81), $p < 0.001$ in comparison to untreated patients (n=213); median censored follow-up 7.6 (IQR 5.8-9.6) years); at 5 years 12% vs 27% respectively had converted, while at 11 years 47% vs 57% had converted (Figure 2A). Fewer patients initially treated with fingolimod (n=85) converted compared to untreated patients (n=174) (HR 0.37 (95% CI 0.22–0.62), $p < 0.001$; median censored follow-up 4.5 (IQR 4.3-5.1) years): at 5 years 7% vs 32% respectively had converted, while at 6 years 7% vs 39% had converted (Figure 2B). Conversion to SPMS was also significantly lower for patients initially treated with natalizumab (n=82) compared to untreated patients (n=164) (HR 0.61 (95% CI 0.43–0.86), $p = 0.005$; median censored follow-up 4.9 (IQR 4.4-5.8) years): at 5 years 19% vs 38% respectively had converted, while at 6 years 34% vs 48% had converted (Figure 2C). The hazard ratio for converting to SPMS was significantly lower for patients initially treated with alemtuzumab (n=44) compared to untreated patients (n=92) (0.52 (95%CI 0.32–0.85), $p = 0.009$; median censored follow-up 7.4 (IQR

6.0-8.6) years): at 5 years 10% vs 25% respectively had converted, while at 8 years 21% vs 41% had converted (Table 1, Figure 2D).

The probability of converting to SPMS was significantly lower for patients initially receiving β -IFN|GA within 5 years of disease onset (n=120) compared to matched patients treated with β -IFN|GA later (n=38) (HR 0.77 (95%CI 0.61-0.98), p=0.03), median censored follow-up 13.4 (IQR 11-18.1) years.

Five years after baseline 3% vs 6%, respectively, had converted to SPMS, while at 17 years 29% vs 47% had converted (Figure 3A). Including patients escalated to mitoxantrone did not materially alter the results (HR 0.82 (95%CI 0.67-1.00), p=0.05). The probability of converting to SPMS was significantly lower when initial treatment with β -IFN|GA was commenced within 5 years of disease onset (n=164) compared to untreated patients (n=104) (HR 0.26 (95%CI 0.15-0.45), p<0.001) with the difference increasing proportionally throughout the 11 years of follow-up (corresponding to 14 years disease duration (Figure 3B)). In contrast, the significantly lower probability of conversion

following initial treatment with β -IFN|GA commencing 5-10 years after disease onset (n=95) compared to untreated patients (n=158, HR 0.67 (95%CI 0.51-0.87), p=0.003) waned after 5 years of treatment (disease duration 11.8 years) and disappeared at 7.8 years (disease duration 14.6 years,

Figure 3C)). The probability of converting to SPMS was significantly lower for patients escalated from β -IFN|GA to F|A|N within 5 years of disease onset (n=307) compared to matched patients escalated later (n=331, HR 0.76 (95%CI 0.66-0.88), p<0.001; median censored follow-up 5.3 (IQR 4.6-6.1)

years): at 5 years, 8% vs 14% respectively had converted while at 7 years, 14% vs 28% had converted (Figure 3D). This difference persisted when the alternative (7-year) definition of alemtuzumab treatment duration was employed in a sensitivity analysis (HR 0.78 (95%CI 0.67-0.91), p=0.001).

Patients initially receiving F|A|N (n=235) had a significantly lower risk of conversion to SPMS than matched patients initially receiving β -IFN|GA (n=380) (HR 0.66 (95% CI 0.44-0.99), p=0.046; median censored follow-up 5.8 (IQR 4.7-8.0) years). At 5 years, 7% vs 12% respectively had converted, while at 9 years, 16% vs 27% respectively had converted (Figure 4). This persisted in sensitivity analyses when the alternative (7-year) definition of alemtuzumab treatment duration was used (HR 0.60

(95%CI 0.39-0.90), $p=0.01$); and when patients in the β -IFN | GA group escalated to mitoxantrone were included (HR 0.88 (95%CI 0.84-0.91), $p<0.001$).

Discussion

In this observational cohort study that used prospectively-collected clinical data, initial treatment with fingolimod, alemtuzumab or natalizumab (F|A|N) was associated with a significantly lower risk of conversion to SPMS compared to initial treatment with β -IFN|GA. The risk of conversion was significantly lower for early compared to late treatment: either in the case of starting β -IFN|GA within 5 years of disease onset versus later commencement, or when escalating from β -IFN|GA to F|A|N within 5 years of disease onset versus later escalation.

These results suggest that initial treatment with β -IFN|GA is associated with reduced conversion to SPMS compared to untreated patients. There is no consensus in the literature. Intention-to-treat analysis of the study conducted by the IFN β Multiple Sclerosis Study Group found no difference in conversion rates between interferon and placebo 16 years later, though many placebo-treated patients subsequently received DMTs.⁷ Six of seven observational studies reported favourable associations between β -IFN|GA and SPMS conversion, both individually⁸⁻¹³ and in a meta-analysis.³⁴ The remaining observational study from British Columbia – the only one to circumvent immortal time bias³⁵ through treating interferon exposure as a time-dependent variable (ensuring time before interferon treatment contributed to the untreated follow-up time) – found no relationship between interferon exposure and SPMS conversion.¹⁴ These observational studies – all published before an objective SPMS definition became available¹⁵ – have highly heterogeneous methods including variable (or inaccessible) SPMS definitions, inconsistent exclusion of relapse-related disability-increases; and variable strategies for mitigating indication bias (arising from non-random treatment exposure), attrition bias (reflecting between-group differences in follow-up duration), detection bias (from differing EDSS frequency during follow-up) and immortal-time bias.⁸⁻¹⁴ In observational study designs, propensity score-based estimators better reflect true differences than nonexperimental estimators, such as multivariable regression or latent variable selection models, given that an overlap exists between the compared groups.³⁶ In this analysis, matching with a caliper was employed, which is more robust in scenarios with restricted sample size and strong treatment-

selection processes than unrestricted propensity score-based methods such as inverse probability of treatment weighting or optimal full matching.^{30,31} All models were adjusted for EDSS frequency to mitigate detection bias and setwise censoring of follow-up duration was used to mitigate attrition bias. To address the issue of immortal-time bias³⁵ disease-modifying therapy was treated as a time-dependent variable. The risk of SPMS conversion increases with disease duration,⁶ so it should be considered in evaluations of SPMS conversion rates in different treatment scenarios (Table 1, Figure 2). For instance, subgroups with longer disease duration at baseline (e.g. here natalizumab) are expected to be associated with a relatively greater SPMS conversion rate than those with shorter disease duration at baseline (e.g. here alemtuzumab or fingolimod).

Limitations

This study has several limitations. First, given its observational design, the study is unable to ascribe causality and cannot distinguish between prevention and delay of conversion to SPMS. The longest comparison however showed a favourable association of early (versus later) β -IFN|GA, enduring to the end of follow-up 17 years after baseline (median disease duration 20 years; Figure 3A). Second, the absence of EDSS functional score subcomponents precluded using the SPMS definition with the highest combination of sensitivity, specificity and accuracy; the definition used in this study, requiring total EDSS only, has previously been shown to be associated with a 1% loss of accuracy and 6% reduction in sensitivity.¹⁵ Third, the differing baseline demographics of each DMT cohort (Table 1) required differing matched untreated cohorts with differing follow-up durations; their relative therapeutic effects should therefore not be compared between analyses (Figures 2A-D). A particular problem with the fingolimod/untreated comparison was the inability to eliminate informed censoring bias because fingolimod-treated patients subsequently escalated to monoclonal antibody treatment (due to on-treatment disease activity) were excluded (Figure 2B). Such informed censoring does not affect the comparison between untreated patients and monoclonal antibodies (as patients cannot be escalated from these highly-effective therapies¹⁸) nor the untreated

comparisons with β -IFN|GA (where the inclusion criteria ensured more potent therapies were not generally available during the studied epoch). Fourth, the β -IFN|GA cohorts therefore came from an earlier period, leading to 10-11 years median difference in the baseline dates of the β -IFN|GA versus untreated analyses, and 13 years median difference in the β -IFN|GA versus F|A|N analysis. It is possible that unmeasured changes in care between time epochs - more specialist nurses, better symptomatic management, lower thresholds for escalating therapy for example - may have contributed to differences in SPMS conversion rates in these particular analyses. However, all other analyses (with contemporaneous groups (≤ 5 years difference, Table 1)) also support early and aggressive DMT use. The ability to match contemporaneous untreated patients to those commencing F|A|N (Table 1) took advantage of the United Kingdom's lower DMT uptake rates. The generalisability of the untreated group to other geographic regions cannot be guaranteed. Fifth, a large number of patients were excluded due to ineligibility (Figure 1). At least 65 patients were excluded through stopping their DMT within 6 months due to inefficacy (Figure 1). Though a modest number, their exclusion may have biased the remaining patients presented for matching towards a relatively milder disease. Those excluded due to missing data were slightly older with higher baseline EDSS scores (eTable S7). While the exclusion criteria have made the results more robust, the resultant unmatched cohorts are, by definition, unrepresentative of the whole unfiltered cohort. Despite the stringent matching criteria 63-97% of treated eligible patients were successfully matched, and beyond lower baseline relapse rates, the matched cohorts (Table 1) are similar to those in the original placebo-controlled phase III trials of these therapies.¹⁻³ Sixth, some factors were unavailable across all cohorts (for example smoking status; lesion number or brain volume on MRI; drug adherence; or the presence of oligoclonal bands in cerebrospinal fluid), precluding their inclusion in matching models. If these variables differed systematically between the compared groups, and are associated with the risk of SPMS conversion, then they might have acted as confounders. Through the use of an objective SPMS definition, any positive bias of outcomes by the clinician instigating the intervention or escalation should have been mitigated. Seventh, the

assessment of disability (and therefore SPMS conversion) relied on the EDSS. Although the most widely-used disability measure, it has high inter-rater variability at lower scores, limited sensitivity to cognitive impairment and – at scores over 3.5 – is largely determined by ambulation.³⁸ To mitigate inter-rater variability, this published definition of SPMS requires EDSS step 4 attainment and confirmation of EDSS increases on two occasions, at least 3 months apart. Eighth, the numbers of patients available in some analyses was quite small. Despite this, clinically and statistically significant differences between the groups were observed. Ninth, while relatively few patients contribute to the final periods of follow-up in Figures 2-4, the groups universally diverge long before this and the statistics are heavily weighted towards the left of each figure. Tenth, while death due to non-MS causes may represent a competing risk, we were unable to include this in the presented models due to incomplete reporting. Eleventh, this study did not assess the risks associated with DMTs, and so the association between initial F|A|N use and lower risk of SPMS conversion – which is consistent with these therapies' greater effect on relapse rates and disability metrics^{4,5,26} - must be considered in light of their greater risks, administration and monitoring schedules, and initial costs during the DMT selection process.

Conclusions

Among patients with RRMS, initial treatment with fingolimod, natalizumab or alemtuzumab was associated with a lower risk of conversion to SPMS compared to initial treatment with β -IFN|GA over a median 5.8 years of follow-up. These findings, considered along with these therapies' risks, may help inform decisions about DMT selection.

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WB conceptualised and designed the study, contributed data, performed statistical analysis, interpreted the results, drafted and edited the manuscript. DH, EH, GIAP, MG, PD, MT, AL, RB, PM, VVP, PS, DF, FG'M, JL-S, SF, VS, EP, FG, VJ, MW, CR, NS, AW, OP, TZ, MH, KH, JJ & CM recruited patients, contributed data, interpreted the results, and edited the manuscript. HB, AC & NR recruited patients, contributed data and oversaw the study design, results interpretation and manuscript drafting. TK designed the study, recruited patients, contributed data and oversaw the study design, statistical analysis, results interpretation and manuscript drafting.

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Legends for tables and figures

Table 1: Baseline and follow-up characteristics of matched patient groups. ^aDisease duration at the time of commencing β -interferon or glatiramer acetate (β -IFN | GA) in the late group was 6.8 (5.7-10.8) years [median (IQR)]. ^bDisease duration at the time of commencing fingolimod or alemtuzumab or natalizumab (F|A|N) in the late group was 7.3 (6.1—10.4) years [median (IQR)]. EDSS = Expanded Disability Status Scale, range 0 (no disability due to MS) to 10 (death due to MS). EDSS 2 indicates minimal disability in one (of eight) functional systems (but no impairment to walking). EDSS 3.5 indicates moderate disability in one functional system plus minimal disability in several others (but no impairment to walking). IQR = interquartile range. SD = standard deviation. Standardized difference quantified by Cohen's D.

Figure 1: Study design (DMT = disease modifying therapy; EDSS = Expanded Disability Status Scale); RCT = randomised controlled trial; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; *Where recorded, reasons for stopping were as follows: 341 due to intolerance, 65 due to inconvenience, 42 due to pregnancy (or planned pregnancy), 65 due to inefficacy (relapses, EDSS progression, MRI activity or patient perception of lack of improvement) and 15 due to non-compliance. **Ineligible treatments were defined as treatments not licensed for RRMS at the time of the study period (mitoxantrone, cladribine, rituximab, ocrelizumab, siponimod or autologous stem-cell transplantation).

Figure 2: Comparison of the cumulative hazard of conversion to secondary progressive multiple sclerosis (SPMS) in untreated patients versus matched patients treated with (A) β -interferon or glatiramer acetate (β -IFN | GA), median (interquartile range (IQR)) follow-up 7.6 (5.8 – 9.6) years; (B) fingolimod, (median (IQR) follow-up 4.5 (4.3 – 5.1) years; (C) natalizumab, median (IQR) follow-up 4.9 (4.4 – 5.8) years; (D) alemtuzumab, median (IQR) follow-up 7.4 (6 – 8.6) years. HR = hazard ratio. CI = confidence interval.

Figure 3: Comparison of the cumulative hazard of conversion to secondary progressive multiple sclerosis (SPMS) in (A) patients treated with β -interferon or glatiramer acetate (β -IFN|GA) within 5 years of disease onset vs matched patients treated with β -IFN|GA after 5 years of disease onset, median (interquartile range (IQR)) follow-up 13.4 (11 – 18.1) years; (B) patients treated with β -IFN|GA within 5 years of disease onset vs matched untreated patients, median (IQR) follow-up 7.5 (5.7 – 9.8) years; (C) patients treated with β -IFN|GA 5-10 years after disease onset vs matched untreated patients, median (IQR) follow-up 7.7 (5.8 – 9.7) years; (D) patients escalated from β -IFN|GA to fingolimod or alemtuzumab or natalizumab (F|A|N) within 5 years of disease onset vs patients escalated to the same therapy after more than 5 years, median (IQR) follow-up 5.3 (4.6 – 6.4) years. HR = hazard ratio. CI = confidence interval.

Figure 4: Comparison of cumulative hazard of conversion to secondary progressive multiple sclerosis (SPMS) in patients initially treated with fingolimod or alemtuzumab or natalizumab (F|A|N) vs matched patients initially treated with β -interferon or glatiramer acetate (β -IFN|GA), median (interquartile range) follow-up 5.8 (4.7 – 8) years. HR = hazard ratio. CI = confidence interval.

Table 1:

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	Initial β-IFN GA, n=407	Initial Untreated, n=213	Standardized Difference	Initial Fingolimod n=85	Untreated, n=174	Standardized Difference	Initial Natalizumab n=82	Untreated n=164	Standardized Difference	Initial Alemtuzumab n=44	Untreated n=92	Standardized Difference	Initial β-IFN GA within 5y, n=120	Initial β-IFN GA after 5y, n=38	Standardized Difference
Age, years Mean (SD)	35 (8)	35 (8)	0	39 (12)	39 (10)	0	39 (9)	38 (9)	0.03	35 (8)	35 (7)	0.08	30 (7)	31 (7)	0.14
Sex, Female, Number (%) Male, Number (%)	292 (72%) 115 (28%)	155 (73%) 58 (27%)	0.05	59 (69%) 26 (31%)	127 (73%) 47 (27%)	0.04	54 (66%) 28 (34%)	108 (66%) 56 (34%)	0.06	30 (68%) 14 (32%)	65 (71%) 27 (29%)	0.04	88 (73%) 32 (27%)	27 (70%) 11 (30%)	0.06
Disease duration, years Median (IQR)	5.7 (3.1 - 10.5)	5.1 (2 - 9.8)	0.05	4.9 (1.7 - 9.7)	5.1 (2.1 - 9)	0.03	6.2 (2 - 10.5)	5.2 (2.3 - 8.9)	0.15	3.2 (2 - 5.8)	3.8 (1.9 - 6.7)	0.17	3.2 (2.1 - 4.1)	3.5 (2.7 - 4.2) ^a	0.26
Relapses in year before baseline Mean (SD)	1.1 (1)	1.1 (0.9)	0	0.9 (0.9)	0.9 (1)	0.02	1.1 (1)	1.1 (1)	0.01	1.3 (1)	1.3 (1)	0.03	1.0 (1.1)	1.0 (0.9)	0
Disability, EDSS step Median (IQR)	2.5 (1.5 - 3.5)	2 (1 - 3.5)	0.1	2 (1 - 3.5)	2 (1.5 - 3.5)	0	2.5 (2 - 4.5)	3 (2 - 4.5)	0.28	3.5 (2 - 4.5)	3.5 (2 - 5.5)	0	2 (1.5 - 3)	2 (1 - 2.5)	0
Baseline year of inclusion Median (IQR)	1996 (1996-7)	2007 (2004-9)	N/A	2011 (2011-2)	2007 (2007-9)	N/A	2010 (2009-11)	2006 (2005-8)	N/A	2006 (2003-6)	2006 (2005-8)	N/A	1996 (1995-7)	1992 (1988-94)	N/A
Length of setwise-censored follow-up, years Median (IQR)	7.6 (5.8 - 9.6)	7.6 (5.8 - 9.6)	0	4.5 (4.3 - 5.1)	4.5 (4.3 - 5.1)	0	4.9 (4.4 - 5.8)	4.9 (4.4 - 5.8)	0	7.4 (6 - 8.6)	7.4 (6 - 8.6)	0	13.4 (11 - 18.1)	13.4 (11 - 18.1)	0
EDSS frequency during follow up, per year Median (IQR)	2 (1 - 3.2)	1 (0.7 - 1.5)	0.75	1.6 (1.1 - 2.6)	1 (0.7 - 1.5)	0.58	1.9 (1.3 - 2.9)	1.2 (0.7 - 1.8)	0.55	1.1 (0.9 - 1.5)	1.2 (0.9 - 1.9)	0.11	1.8 (1.1 - 2.6)	1.4 (0.9 - 2.1)	0.41
Proportion of time on therapy before censor or SPMS Median (IQR)	1 (0.9 - 1)	N/A	N/A	1 (1 - 1)	N/A	N/A	1 (1 - 1)	N/A	N/A	0.8 (0.6 - 1)	N/A	N/A	1 (0.8 - 1)	0.6 (0.4 - 0.7)	1.62

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	Initial β-IFN GA within 5y, n=164	Untreated, n=104	Standardized Difference	Initial β- IFN GA 5-10y, n=95	Untreated n=158	Standardized Difference	Escalation to F A N within 5y, n=307	Escalation to F A N after 5y, n=331	Standardized Difference	Initial F A N, n=235	Initial β- IFN GA, n=380	Standardized Difference
Age, years Mean (SD)	33 (8)	33 (7)	0.02	37 (7)	36 (8)	0.08	33 (9)	32 (8)	0.03	34 (11)	34 (9)	0.06
Sex, Female, Number (%) Male, Number (%)	113 (69%) 51 (31%)	76 (73%) 28 (27%)	0.07	66 (69%) 29 (31%)	111 (70%) 47 (30%)	0.02	218 (71%) 89 (29%)	233 (70%) 98 (30%)	0.09	162 (69%) 73 (31%)	267 (70%) 113 (30%)	0.01
Disease duration, years Median (IQR)	3 (2.1 - 4)	2.1 (1 - 3.5)	0.5	6.8 (5.9 - 8.3)	5.3 (2.1 - 10)	0.31	3 (2.1 - 4)	3.5 (2.5 - 4.3) ^b	0.41	6.5 (2.1 - 12)	5.1 (2.7 - 9.6)	0.2
Relapses in year before baseline Mean (SD)	1.3 (1)	1.2 (1)	0.06	1.1 (1)	0.9 (0.9)	0.18	1 (1.1)	1 (1)	0	1.2 (1.1)	1.3 (1.1)	0.1
Disability, EDSS step Median (IQR)	2 (1 - 3)	2 (1 - 3)	0	2.5 (1.5 - 3.5)	2.5 (1.5 - 3.5)	0	2 (1.5 - 3.5)	2 (1.1 - 3.0)	0	2 (1.5 - 3)	2 (1.5 - 3.5)	0.02
Baseline year of inclusion Median (IQR)	1996 (1995-7)	2006 (2005-8)	N/A	1996 (1995-7)	2006 (2004-8)	N/A	2010 (2009-11)	2005 (2003-7)	N/A	2009 (2008-11)	1996 (1996-7)	N/A
Length of setwise-censored follow-up, years Median (IQR)	7.5 (5.7 - 9.8)	7.5 (5.7 - 9.8)	0	7.7 (5.8 - 9.7)	7.7 (5.8 - 9.7)	0	5.3 (4.6 - 6.4)	5.3 (4.6 - 6.4)	0	5.8 (4.7 - 8)	5.8 (4.7 - 8)	0
EDSS frequency during follow up, per year Median (IQR)	2.4 (1.3 - 3.3)	1 (0.8 - 1.4)	1.37	1.7 (0.8 - 2.9)	1 (0.7 - 1.4)	0.61	2.3 (1.5 - 3.4)	2 (1.3 - 3.3)	0.17	1.8 (1.2 - 2.8)	2.2 (1.1 - 3.5)	0.3
Proportion of time on therapy before censor or SPMS Median (IQR)	1 (0.6 - 1)	N/A	N/A	1 (0.9 - 1)	N/A	N/A	1(0.9 - 1)	0.9 (0.7 - 1)	0.54	1 (1 - 1)	1 (0.9 - 1)	0