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Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis

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IMPORTANCE Within 2 decades of onset, 80% of untreated patients with relapsing-remitting multiple sclerosis (MS) convert to a phase of irreversible disability accrual termed secondary progressive MS. The association between disease-modifying treatments (DMTs), and this conversion has rarely been studied and never using a validated definition.

OBJECTIVE To determine the association between the use, the type of, and the timing of DMTs with the risk of conversion to secondary progressive MS diagnosed with a validated definition.

DESIGN, SETTING, AND PARTICIPANTS Cohort study with prospective data from 68 neurology centers in 21 countries examining patients with relapsing-remitting MS commencing DMTs (or clinical monitoring) between 1988-2012 with minimum 4 years' follow-up.

EXPOSURES The use, type, and timing of the following DMTs: interferon beta, glatiramer acetate, fingolimod, natalizumab, or alemtuzumab. After propensity-score matching, 1555 patients were included (last follow-up, February 14, 2017).

MAIN OUTCOME AND MEASURE Conversion to objectively defined secondary progressive MS.

RESULTS Of the 1555 patients, 1123 were female (mean baseline age, 35 years [SD, 10]). Patients initially treated with glatiramer acetate or interferon beta had a lower hazard of conversion to secondary progressive MS than matched untreated patients (HR, 0.71; 95% CI, 0.61-0.81; $P < .001$; 5-year absolute risk, 12% [49 of 407] vs 27% [58 of 213]; median follow-up, 7.6 years [IQR, 5.8-9.6]), as did fingolimod (HR, 0.37; 95% CI, 0.22-0.62; $P < .001$; 5-year absolute risk, 7% [6 of 85] vs 32% [56 of 174]; median follow-up, 4.5 years [IQR, 4.3-5.1]); natalizumab (HR, 0.61; 95% CI, 0.43-0.86; $P = .005$; 5-year absolute risk, 19% [16 of 82] vs 38% [62 of 164]; median follow-up, 4.9 years [IQR, 4.4-5.8]); and alemtuzumab (HR, 0.52; 95% CI, 0.32-0.85; $P = .009$; 5-year absolute risk, 10% [4 of 44] vs 25% [23 of 92]; median follow-up, 7.4 years [IQR, 6.0-8.6]). Initial treatment with fingolimod, alemtuzumab, or natalizumab was associated with a lower risk of conversion than initial treatment with glatiramer acetate or interferon beta (HR, 0.66; 95% CI, 0.44-0.99; $P = .046$); 5-year absolute risk, 7% [16 of 235] vs 12% [46 of 380]; median follow-up, 5.8 years [IQR, 4.7-8.0]). The probability of conversion was lower when glatiramer acetate or interferon beta was started within 5 years of disease onset vs later (HR, 0.77; 95% CI, 0.61-0.98; $P = .03$; 5-year absolute risk, 3% [4 of 120] vs 6% [2 of 38]; median follow-up, 13.4 years [IQR, 11-18.1]). When glatiramer acetate or interferon beta were escalated to fingolimod, alemtuzumab, or natalizumab within 5 years vs later, the HR was 0.76 (95% CI, 0.66-0.88; $P < .001$; 5-year absolute risk, 8% [25 of 307] vs 14% [46 of 331], median follow-up, 5.3 years [IQR], 4.6-6.1).

CONCLUSIONS AND RELEVANCE Among patients with relapsing-remitting MS, initial treatment with fingolimod, alemtuzumab, or natalizumab was associated with a lower risk of conversion to secondary progressive MS vs initial treatment with glatiramer acetate or interferon beta. These findings, considered along with these therapies' risks, may help inform decisions about DMT selection.

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Multiple sclerosis (MS) is among the most common causes of disability in young adults. Eighty-five percent of patients present with the relapsing-remitting form for which several immunomodulatory disease-modifying therapies (DMTs) reduce relapse rates and disability accumulation.[1-5] Within 2 decades of onset, 80% of untreated patients with relapsing-remitting MS convert to a phase of sustained disability accrual termed secondary progressive multiple sclerosis.[6] This phase is responsible for much of the disease's negative physical, psychological, and societal effects.

Until recently no rigorous definition of secondary progressive MS existed, leading to varying criteria and contradictory results from 1 randomized trial extension[7] and 7 observational studies[8-14] that predominantly examined the association of interferon beta or glatiramer acetate with conversion to secondary progressive MS.

Using a recently published validated definition of secondary progressive MS,[15] the rate of conversion to secondary progressive MS was examined between (1) different DMTs and an untreated cohort; (2) fingolimod, alemtuzumab, or natalizumab vs glatiramer acetate or interferon beta; and (3) treatment commencement or escalation within vs after 5 years of disease onset.

Key Points

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

Findings In this cohort study involving 1555 patients with relapsing-remitting MS, initial treatment with fingolimod, natalizumab, or alemtuzumab was associated with a lower risk of conversion to secondary progressive MS compared with interferon beta or glatiramer acetate (hazard ratio, 0.66).

Meaning These findings, considered along with the risks associated with these therapies, may help inform decisions regarding disease-modifying treatment selection for patients with relapsing-remitting MS.

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, in accordance with local regulations.

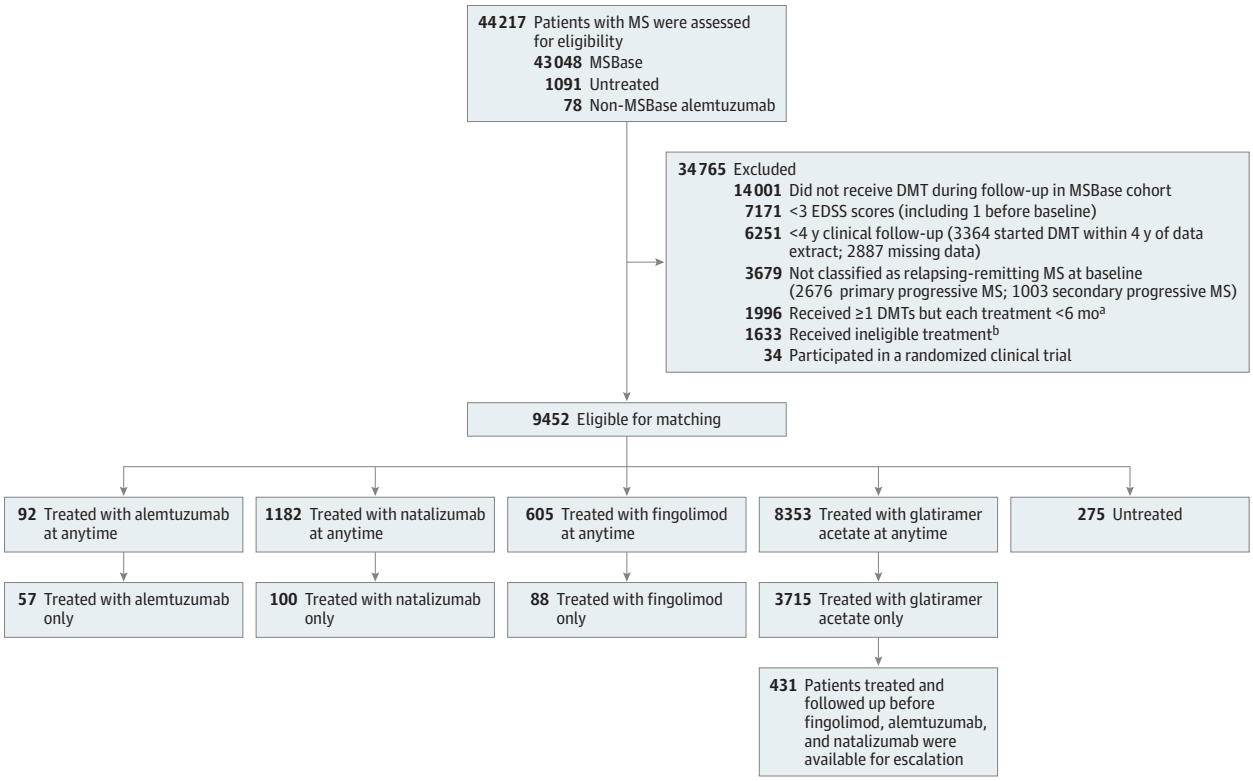
Patients and Inclusion Criteria

This international observational cohort study used prospectively collected clinical data from 3 sources (all accessed in February 2017). Untreated patients were selected from the neuroinflammatory service database at the University Hospital of Wales, a tertiary referral center in Southeast Wales. Clinical data were initially collected as part of a cross-sectional study[16] then through annual or semiannual appointments. Treated patients were identified from MSBase, an observational cohort study collecting real-world data from patients with MS across 105 centers in 29 countries (**Figure 1**).[17] Additional patients treated with alemtuzumab were identified from 5 European non-MSBase centers using alemtuzumab before it was licensed[18] (Bristol, Cardiff, Swansea, Dublin, and Dresden). Within MSBase, glatiramer acetate or interferon beta, fingolimod, and natalizumab had sufficient patient numbers with more than 4 years of receiving treatment follow-up (whereas teriflunomide and dimethyl-fumarate did not, so they were not included). The 4-year minimum follow-up period represented the longest follow-up without excluding the majority of patients in MSBase who were treated with natalizumab or fingolimod. Data were subject to rigorous data-quality procedures (eTable 1 in the Supplement).

For inclusion, patients needed to have been classified as having relapsing-remitting MS (clinically definite MS[19]) at baseline, had the complete MSBase minimum data set (sex, date of birth, date of clinical onset, and dates of relapses),[20] had at least 1 Expanded Disability Status Scale[21] (EDSS) score within 6 months before baseline, and had at least 2 EDSS scores after baseline (1 to detect disability progression and another to confirm the increase later, see definition below). Patients stopping their initial therapy within 6 months were excluded because some drugs require 6 months to take full effect.[22] The untreated cohort received no DMTs, even briefly. The 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]); interferon beta (30-250 µg 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 cell count (35 months/cycle[24]) was used, and then a sensitivity analysis using the median period to retreatment (7 years[25]) was performed. If patients received multiple DMTs, the first was used as the DMT under study (except when comparing early vs late escalation from glatiramer acetate or interferon beta to fingolimod, alemtuzumab, or natalizumab). Patients subsequently receiving different DMTs were excluded from analyses of single drugs vs 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 transplant). 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

Figure 1. MSBase Study Design of Patients With Multiple Sclerosis (MS)



[a] When recorded, reasons for stopping were included: 341 due to intolerance; 65, inconvenience; 42, pregnancy (or planned pregnancy); 65, inefficacy (relapses, EDSS progression, magnetic resonance imaging activity, or patient perception of lack of improvement); and 15, nonadherence.

[b] Ineligible treatments were defined as treatments not licensed for relapsing-remitting MS at the time of the study period (mitoxantrone, cladribine, rituximab, ocrelizumab, siponimod, or autologous stem-cell transplant).

DMT indicates disease-modifying therapy; EDSS, Expanded Disability Status Scale.

relapses or disability progression in this study were therefore already at the therapeutic ceiling of treatment. This was replicated for patients receiving glatiramer acetate or interferon beta (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 a first-line or escalation therapy during follow-up and thereby preventing selection bias toward milder disease among the glatiramer acetate or interferon beta group. (During this period, mitoxantrone was occasionally used as escalation therapy for particularly aggressive disease: to ensure the glatiramer acetate or interferon beta group was not biased toward milder disease, sensitivity analyses including these patients were performed). Consistent with previous work,[18] patients participating in clinical trials were excluded because their trial treatment assignation was not documented within MSBase, and trial EDSS frequencies often differ to clinical practice. Patients with previous stem cell transplants were also excluded.

Study Design

To examine whether individual DMTs were associated with delayed or reduced conversion to secondary progressive MS, matching and analyses were repeated 4 times comparing untreated patients with those receiving initial treatment with (1) glatiramer acetate or interferon beta, (2) fingolimod, (3) natalizumab, or (4) 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] alemtuzumab,[5] and natalizumab[26] confer greater reductions in relapse rate than glatiramer acetate or interferon beta. To examine whether they are associated with different effects on conversion to secondary progressive MS, patients receiving 1 of the 3 drugs as their initial DMT were matched and compared with patients initially treated with glatiramer acetate or interferon beta.

To examine the association between timing of DMT commencement and conversion to secondary progressive MS, patients initially treated with glatiramer acetate or interferon beta 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 glatiramer acetate or interferon beta to fingolimod, alemtuzumab, or natalizumab within vs after 5 years of disease onset.

Outcome

The outcome in all analyses was conversion to secondary progressive MS based on an objective definition[15] 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 more than 5.5, an increase of 0.5 points was required). This EDSS increase had to (1) occur in the absence of a relapse, (2) be confirmed at the next appointment (≤3 months later), and (3) the resultant EDSS score had to be 4 or more.[15]

Matching

Using the MatchIt package[27] (v2.4-22), the propensity of treatment was estimated using a multivariable logistic regression model using baseline age, sex, annualized relapse rate in the year prior to baseline, EDSS score, and disease duration.

To minimize the difference in proportions of time taking therapy during follow-up in the glatiramer acetate or interferon beta vs fingolimod, alemtuzumab, or natalizumab analysis, patients were additionally matched on the proportion of time taking therapy during the median follow-up period (first 5.8 years). Patients in the early vs late escalation from glatiramer acetate or interferon beta to fingolimod, alemtuzumab, or natalizumab analyses were also matched on disease duration at the time of starting glatiramer acetate or interferon beta plus the individual therapy to which they were escalated.

To increase matching precision,[18,28] patients were matched in a variable matching ratio (10:1 to 1:1) by nearest neighbor matching using the optimal caliper (0.1 standard deviations of the propensity score).[29-31] When treatment initiation was not used as the baseline (the late group in the early vs late glatiramer acetate or interferon beta and escalation analyses; and the untreated group in all untreated analyses), any visit could serve as baseline (to optimize matching). A single patient could therefore be used multiple times in 1 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 2 follow-up times from each set, resulting in identical follow-up durations between groups. Sets in which either patient subsequently had fewer than 2 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 secondary progressive MS. All models were adjusted for EDSS frequency plus any variables showing residual imbalance following matching (as denoted by a standardized difference, quantified by a Cohen d value, ≥0.2,[32] which indicates <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 (1) glatiramer acetate or interferon beta with fingolimod, alemtuzumab, or natalizumab; (2) early vs late glatiramer acetate or interferon beta; and (3) early vs late escalation from glatiramer acetate or interferon beta to fingolimod, alemtuzumab, or natalizumab were also adjusted for the proportion of time taking therapy during the entire postbaseline setwise-censored follow-up. The Schoenfeld global test[33] 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 (HR), 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 who had converted to secondary progressive MS 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 $P < .05$ level. Because there was no adjustment for multiple comparisons, secondary analyses should be interpreted as exploratory.

Results

A total of 44 217 patients with MS (1091 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 glatiramer acetate or interferon beta groups were limited to those treated and followed-up before fingolimod, alemtuzumab, or natalizumab became available for escalation (baseline years, 1996-1998; **Table 1** and **Table 2**). Following exclusion of ineligible patients (Figure 1), the matching process then matched 1555 patients from 68 centers in 21 countries (eTable 3 in the Supplement): 230 from the Welsh untreated cohort, 1272 from MSBase, and 53 alemtuzumab-treated patients from non-MSBase centers (Table 1, Table 2, and eTables 3-4 in the Supplement). Matching coefficients and EDSS scores after conversion to secondary progressive MS are shown in eTables 5 and 6 in the Supplement, respectively. The assumption of proportionality was not met in 6 of

Table 1. Baseline Characteristics of Matched Patient Groups

	Initial Treatment			Initial Treatment			Initial Treatment			Initial Treatment		
	Glatiramer Acetate or Interferon Beta (n = 407)	Untreated (n = 213)	Cohen d[a]	Fingolimod Treatment (n = 85)	Untreated (n = 174)	Cohen d[a]	Natalizumab Treatment (n = 82)	Untreated (n = 164)	Cohen d[a]	Alemtuzumab Treatment (n = 44)	Untreated (n = 92)	Cohen d[a]
Age, mean (SD), y	35 (8)	35 (8)	0	39 (12)	39 (10)	0	39 (9)	38 (9)	0.03	35 (8)	35 (7)	0.08
Sex, No. (%)												
Male	115 (28)	58 (27)		26 (31)	47 (27)		28 (34)	56 (34)		14 (32)	27 (29)	
Female	292 (72)	155 (73)	0.05	59 (69)	127 (73)	0.04	54 (66)	108 (66)	0.06	30 (68)	65 (71)	0.04
Disease duration, median (IQR), y	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
No. of 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
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
Baseline year of inclusion, median (IQR)	1996 (1996-1997)	2007 (2004-2009)		2011 (2011-2012)	2007 (2007-2009)		2010 (2009-2011)	2006 (2005-2008)		2006 (2003-2006)	2006 (2005-2008)	
Length of setwise-censored follow-up, median (IQR), y	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 (6.0-8.6)	7.4 (6.0-8.6)	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
Proportion of time receiving therapy before censor or secondary progressive MS, median (IQR)	1 (0.9-1)			1 (1-1)			1 (1-1)			0.8 (0.6-1)		

Abbreviations: EDSS, Expanded Disability Status Scale, range 0 (no disability due to MS) to 10 (death due to MS), 2 indicates minimal disability in 1 of 8 functional systems (but no impairment to walking); 3.5, moderate disability in 1 or 2 functional systems plus minimal disability in several others (but no impairment to walking); IQR, interquartile range; MS, multiple sclerosis.

[a] Standardized difference quantified by the Cohen d value.

Table 2. Baseline Characteristics of Matched Patient Groups

	Initial Glatiramer Acetate or Interferon Beta Treatment			Initial Treatment			Initial Treatment			Escalation to Fingolimod, Alemtuzumab, or Natalizumab			Initial Treatment		
	≤5 y (n = 120)	>5 y (n = 38)	Cohen *d*[a]	Glatiramer Acetate or Interferon Beta ≤5 y (n = 164)	Untreated (n = 104)	Cohen *d*[a]	Glatiramer Acetate or Interferon Beta at 5-10 y (n = 95)	Untreated (n = 158)	Cohen *d*[a]	≤5 y (n = 307)	>5 y (n = 331)	Cohen *d*[a]	Fingolimod, Alemtuzumab, or Natalizumab (n = 235)	Glatiramer Acetate or Interferon Beta (n = 380)	Cohen *d*[a]
Age, mean (SD), y	30 (7)	31 (7)	0.14	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, No. (%)															
Male	88 (73)	27 (70)		51 (31)	28 (27)		29 (31)	47 (30)		89 (29)	98 (30)		73 (31)	113 (30)	
Female			0.06	13 (69)	76 (73)	0.07	66 (69)	111 (70)	0.02	218 (71)	233 (70)	0.09	162 (69)	267 (70)	0.01
Disease duration, median (IQR), y	3.2 (2.1-4.1)	3.5 (2.7-4.2)[b]	0.26	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)[c]	0.41	6.5 (2.1-12)	5.1 (2.7-9.6)	0.2
No. of relapses in year before baseline, mean (SD)	1.0 (1.1)	1.0 (0.9)	0	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 (1.5-3)	2 (1-2.5)	0	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 (1995-1997)	1992 (1988-1994)		1996 (1995-1997)	2006 (2005-2008)		1996 (1995-1997)	2006 (2004-2008)		2010 (2009-2011)	2005 (2003-2007)		2009 (2008-2011)	1996 (1996-1997)	
Length of setwise-censored follow-up median (IQR), y	13.4 (11-18.1)	13.4 (11-18.1)	0	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 (4.7-8.0)	5.8 (4.7-8.0)	0
EDSS frequency during follow-up per year, median (IQR)	1.8 (1.1-2.6)	1.4 (0.9-2.1)	0.41	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 receiving therapy before censor or secondary progressive MS, median (IQR)	1 (0.8-1)	0.6 (0.4-0.7)	1.64	1 (0.6-1)			1 (0.9-1)			1 (0.9-1)	0.9 (0.7-1)	0.54	1 (1-1)	1 (0.9-1)	0

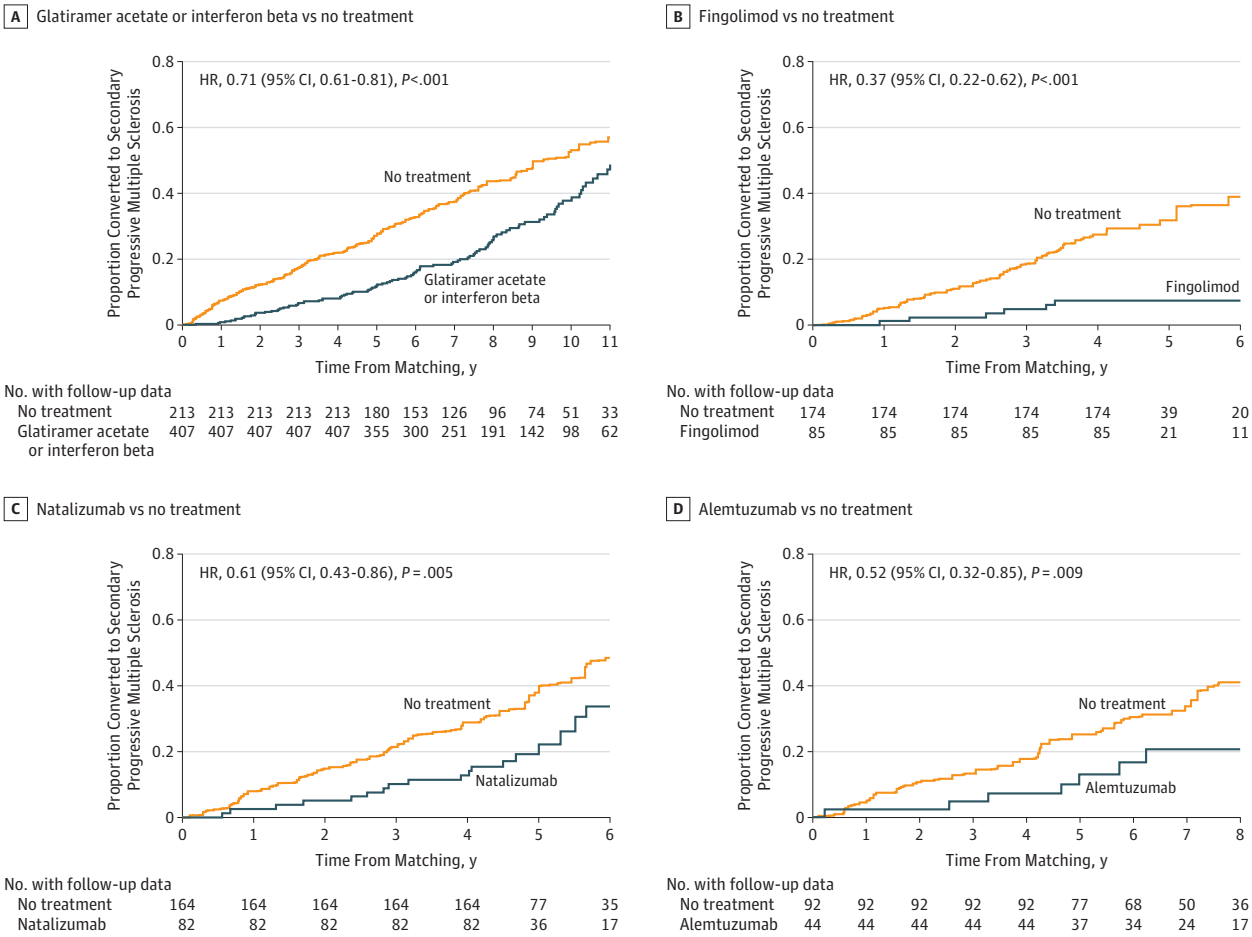
Abbreviations: EDSS, Expanded Disability Status Scale, range, 0 (no disability due to MS) to 10 (death due to MS), 2 indicates minimal disability in 1 of 8 functional systems (but no impairment to walking); 3.5, moderate disability in 1 functional system plus minimal disability in several others (but no impairment to walking); IQR, interquartile range; MS, multiple sclerosis.

[a] Standardized difference quantified by the Cohen *d* value.

[b] Median disease duration at the time of commencing interferon beta or glatiramer acetate in the late group was 6.8 years (IQR, 5.7-10.8).

[c] Median disease duration at the time of commencing fingolimod or alemtuzumab or natalizumab in the late group was 7.3 years (IQR, 6.1-10.4).

Figure 2. Comparison of the Cumulative Hazard of Conversion to Secondary Progressive Multiple Sclerosis in Untreated Patients vs Matched Treated Patients Compared by Initial Treatment



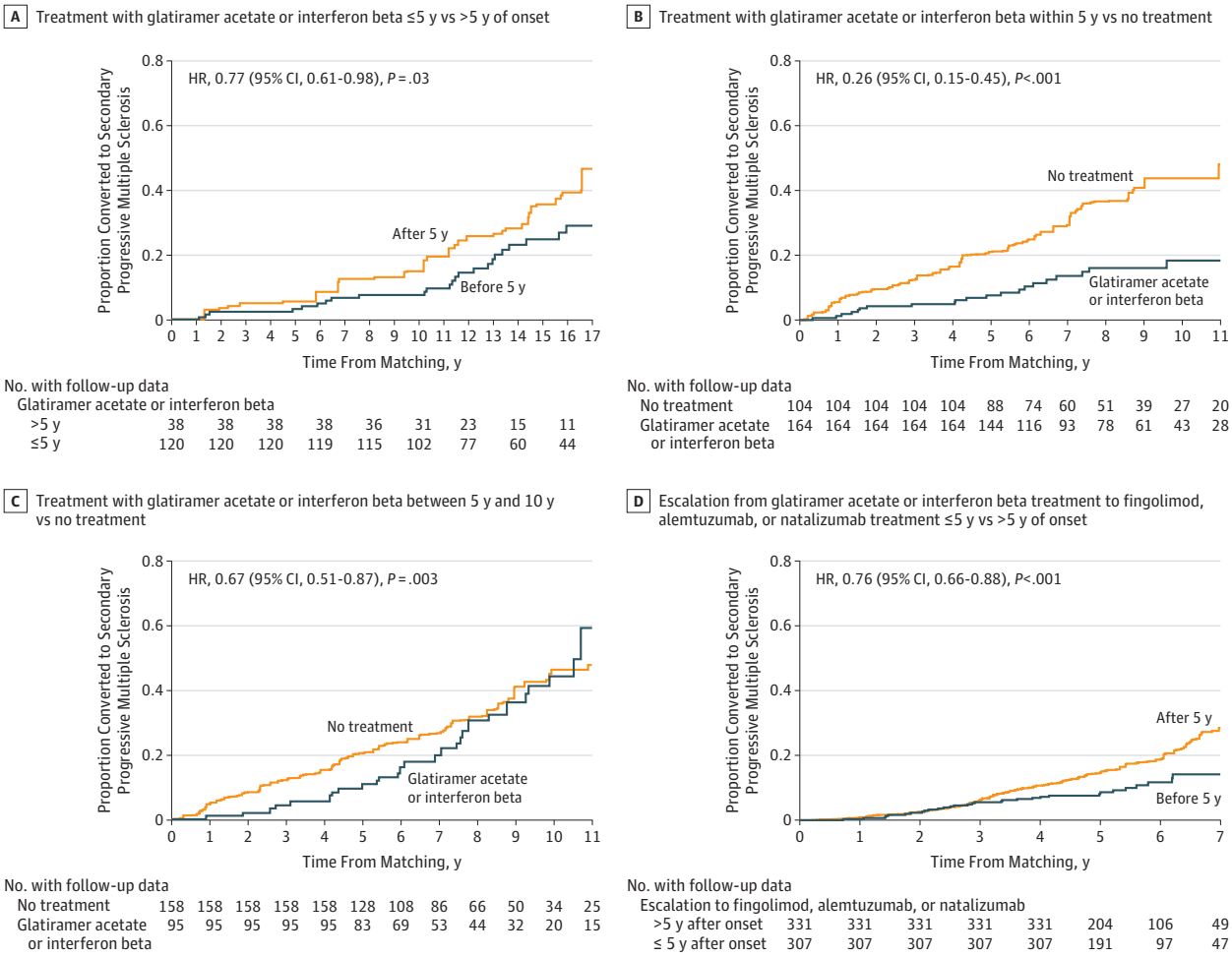
A, The median follow-up was 7.6 years (interquartile range [IQR], 5.8-9.6); B, 4.5 years (IQR, 4.3-5.1); C, 4.9 years (IQR, 4.4-5.8); and D, 7.4 years (IQR, 6-8.6) years. HR indicates hazard ratio.

9 analyses (requiring Weibull accelerated failure-time regression models). Patients excluded due to missing data were slightly older with higher baseline EDSS scores (eTable 7 in the Supplement)

Compared with no treatment, treatment with each included therapy was associated with a significantly lower probability of converting to secondary progressive MS. For patients initially treated with glatiramer acetate or interferon beta (n = 407), the HR was 0.71 (95% CI, 0.61-0.81; $P < .001$) compared with untreated patients (n = 213), median censored follow-up 7.6 years (interquartile range [IQR], 5.8-9.6 years), at 5 years, 12% vs 27%, respectively, had converted, and at 11 years, 47% vs 57% had converted (**Figure 2**A). Fewer patients initially treated with fingolimod (n = 85) converted compared with untreated patients (n = 174) (HR, 0.37; 95% CI, 0.22-0.62; $P < .001$; median censored follow-up, 4.5 years; IQR, 4.3-5.1 years), at 5 years, 7% vs 32%, respectively, had converted, and at 6 years, 7% vs 39% had converted (Figure 2B). Conversion to secondary progressive MS was also significantly lower for patients initially treated with natalizumab (n = 82) compared with untreated patients (n = 164) (HR, 0.61; 95% CI, 0.43-0.86; $P = .005$; median censored follow-up, 4.9 years; 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 secondary progressive MS was significantly lower for patients initially treated with alemtuzumab (n = 44) compared with untreated patients (n = 92) (HR, 0.52; 95% CI, 0.32-0.85; $P = .009$; median censored follow-up, 7.4 years; IQR, 6.0-8.6 years), at 5 years, 10% vs 25%, respectively, had converted, whereas at 8 years 21% vs 41% had converted (Table 1 and Figure 2D).

The probability of converting to secondary progressive MS was significantly lower for patients initially receiving glatiramer acetate or interferon beta within 5 years of disease onset (n = 120) compared with matched patients treated with glatiramer acetate or interferon beta later (n = 38) (HR, 0.77; 95% CI, 0.61-0.98; $P = .03$; median censored follow-up, 13.4 years; IQR, 11-18.1 years). Five years after baseline, 3% vs 6%, respectively, had converted to secondary progressive MS, and

Figure 3. Comparison of the Cumulative Hazard of Conversion to Secondary Progressive Multiple Sclerosis by Timing of Treatment

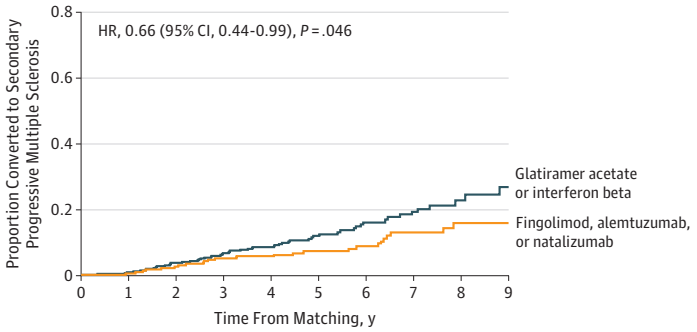


A, The median follow-up was 13.4 years (interquartile range [IQR], 11-18.1); B, 7.5 years (IQR, 5.7-9.8); C, 7.7 years (IQR, 5.8-9.7); and D, 5.3 years (IQR, 4.6-6.4).
HR indicates hazard ratio.

at 17 years 29% vs 47% had converted (**Figure 3**A). Including patients who had escalated to mitoxantrone did not materially alter the results (HR, 0.82; 95% CI, 0.67-1.00; P = .05). The probability of converting to secondary progressive MS was significantly lower when initial treatment with glatiramer acetate or interferon beta was commenced within 5 years of disease onset (n = 164) compared with untreated patients (n = 104) (HR, 0.26; 95% CI, 0.15-0.45; P < .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 glatiramer acetate or interferon beta commencing 5 to 10 years after disease onset (n = 95) compared with untreated patients (n = 158; HR, 0.67;95% CI, 0.51-0.87; P = .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 secondary progressive MS was significantly lower for patients escalated from glatiramer acetate or interferon beta to fingolimod, alemtuzumab, or natalizumab within 5 years of disease onset (n = 307) compared with matched patients escalated later (n = 331) with an HR of 0.76 (95% CI, 0.66-0.88; P < .001; median censored follow-up, 5.3 years; IQR, 4.6-6.1 years): at 5 years, 8% vs 14%, respectively, had converted and at 7 years, 14% vs 28% had converted (Figure 3D). This difference persisted when the alternative (7-year) definition of alemtuzumab treatment duration was used in a sensitivity analysis (HR, 0.78; 95% CI, 0.67-0.91; P = .001).

Patients initially receiving fingolimod, alemtuzumab, or natalizumab (n = 235) had a significantly lower risk of conversion to secondary progressive MS than matched patients initially receiving glatiramer acetate or interferon beta (n = 380) with an HR of 0.66 (95% CI, 0.44-0.99; P = .046; median censored follow-up, 5.8 years; IQR, 4.7-8.0 years). At 5 years, 7% vs 12%, respectively, had converted, and 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 = .01); and when

Figure 4. Comparison of Cumulative Hazard of Conversion to Secondary Progressive Multiple Sclerosis for Initial Treatment With Glatiramer Acetate or Interferon Beta vs Fingolimod, Alemtuzumab, or Natalizumab



No. with follow-up data										
Initial treatment										
Glatiramer acetate or interferon beta	380	380	380	380	380	252	182	142	93	44
Fingolimod, alemtuzumab, or natalizumab	235	235	235	235	235	148	103	80	54	30

The median follow-up was 5.8 years (interquartile range, 4.7-8). HR indicates hazard ratio.

patients in the glatiramer acetate or interferon beta group escalated to mitoxantrone were included (HR, 0.88; 95% CI, 0.84-0.91; $P < .001$).

Discussion

In this observational cohort study that used prospectively collected clinical data, initial treatment with fingolimod, alemtuzumab, or natalizumab was associated with a significantly lower risk of conversion to secondary progressive MS compared with initial treatment with glatiramer acetate or interferon beta. The risk of conversion was significantly lower for early treatment than for late treatment: either in the case of starting glatiramer acetate or interferon beta within 5 years of disease onset vs later commencement; or when escalating from glatiramer acetate or interferon beta to fingolimod, alemtuzumab, or natalizumab within 5 years of disease onset vs later escalation.

These results suggest that initial treatment with glatiramer acetate or interferon beta is associated with reduced conversion to secondary progressive MS compared with untreated patients. There is no consensus in the literature. An intention-to-treat analysis of the study conducted by the IFNβ Multiple Sclerosis Study Group found no difference in conversion rates between interferon and placebo 16 years later, but many patients treated with placebo subsequently received DMTs.[7] Six of 7 observational studies reported favorable associations between glatiramer acetate or interferon beta and secondary progressive MS conversion, both individually[8-13] and in a meta-analysis.[34] The remaining observational study from British Columbia—the only study to circumvent immortal time bias[35] 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 secondary progressive MS conversion.[14] These observational studies—all published before an objective secondary progressive MS definition became available[15]—have highly heterogeneous methods including variable (or inaccessible) secondary progressive MS definitions, inconsistent exclusion of relapse-related disability increases; and variable strategies for mitigating indication bias (arising from nonrandom 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 used, 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 bias,[35] DMT was treated as a time-dependent variable. The risk of secondary progressive MS conversion increases with disease duration,[6] so time from MS onset should be considered in evaluations of secondary progressive MS conversion rates in different treatment scenarios (Table 1, Table 2,and Figure 2). This may have reduced the strength of the association of natalizumab with reduction in conversion to secondary progressive MS because it was used by many patients with longer disease duration at baseline than other agents.

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 secondary progressive MS. The longest comparison however showed a favorable association of early (vs later) glatiramer acetate or interferon beta, enduring to the end of

follow-up 17 years after baseline (median disease duration 20 years; Figure 3, A). Second, the absence of EDSS functional score subcomponents precluded using the secondary progressive MS 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 (Figure 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 disease activity while being treated) were excluded (Figure 2B). Such informed censoring does not affect the comparison between untreated patients and monoclonal antibodies (because patients cannot be escalated from these highly-effective therapies[18]) nor the untreated comparisons with glatiramer acetate or interferon beta (for which the inclusion criteria ensured more potent therapies were not generally available during the studied epoch). Fourth, the glatiramer acetate or interferon beta cohorts therefore came from an earlier period, leading to 10 to 11 years median difference in the baseline dates of the glatiramer acetate or interferon beta vs untreated analyses, and 13 years' median difference in the analysis comparing glatiramer acetate or interferon beta with fingolimod, alemtuzumab, or natalizumab. 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 secondary progressive MS conversion rates in these particular analyses. However, all other analyses (with contemporaneous groups; ≤5 years difference, Table 1 and Table 2) also support early and aggressive DMT use. The ability to match contemporaneous untreated patients to those commencing fingolimod, alemtuzumab, or natalizumab (Table 1) took advantage of the United Kingdom's lower DMT uptake rates. The generalizability 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). Although a modest number, their exclusion may have biased the remaining patients presented for matching toward a relatively milder disease. Those excluded due to missing data were slightly older with higher baseline EDSS scores (eTable 7 in the Supplement). Although 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% to 97% of treated eligible patients were successfully matched. Beyond lower baseline relapse rates, the matched cohorts (Table 1) are similar to those in the original placebo-controlled phase 3 trials investigating 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 secondary progressive MS conversion, then they might have acted as confounders. Through the use of an objective secondary progressive MS 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 secondary progressive MS conversion) relied on the EDSS score. Although the most widely used disability measure, it has high interrater variability at lower scores, limited sensitivity to cognitive impairment, and, at scores higher than 3.5, is largely determined by ambulation.[37,38] To mitigate interrater variability, this published definition of secondary progressive MS requires EDSS step 4 attainment and confirmation of EDSS increases on 2 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 Figure 2, Figure 3, and Figure 4, the groups diverge before this and the statistics are heavily weighted toward 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 fingolimod, alemtuzumab, or natalizumab use and lower risk of secondary progressive MS 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 relapsing-remitting MS, initial treatment with fingolimod, alemtuzumab, or natalizumab was associated with a lower risk of conversion to secondary progressive MS compared with initial treatment with glatiramer acetate or interferon beta. These findings, considered along with these therapies' risks, may help inform decisions about DMT selection.

ARTICLE INFORMATION

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