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Association Between Use of Interferon Beta and Progression of Disability in Patients With Relapsing-Remitting Multiple Sclerosis

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Context Interferon beta is widely prescribed to treat multiple sclerosis (MS); however, its relationship with disability progression has yet to be established.

Objective To investigate the association between interferon beta exposure and disability progression in patients with relapsing-remitting MS.

Design, Setting, and Patients Retrospective cohort study based on prospectively collected data (1985-2008) from British Columbia, Canada. Patients with relapsing-remitting MS treated with interferon beta (n=868) were compared with untreated contemporary (n=829) and historical (n=959) cohorts.

Main Outcome Measures The main outcome measure was time from interferon beta treatment eligibility (baseline) to a confirmed and sustained score of 6 (requiring a cane to walk 100 m; confirmed at >150 days with no measurable improvement) on the Expanded Disability Status Scale (EDSS) (range, 0-10, with higher scores indicating higher disability). A multivariable Cox regression model with interferon beta treatment included as a time-varying covariate was used to assess the hazard of disease progression associated with interferon beta treatment. Analyses also included propensity score adjustment to address confounding by indication.

Results The median active follow-up times (first to last EDSS measurement) were as follows: for the interferon beta–treated cohort, 5.1 years (interquartile range [IQR], 3.0-7.0 years); for the contemporary control cohort, 4.0 years (IQR, 2.1-6.4 years); and for the historical control cohort, 10.8 years (IQR, 6.3-14.7 years). The observed outcome rates for reaching a sustained EDSS score of 6 were 10.8%, 5.3%, and 23.1% in the 3 cohorts, respectively. After adjustment for potential baseline confounders (sex, age, disease duration, and EDSS score), exposure to interferon beta was not associated with a statistically significant difference in the hazard of reaching an EDSS score of 6 when either the contemporary control cohort (hazard ratio, 1.30; 95% CI, 0.92-1.83; $P=.14$) or the historical control cohort (hazard ratio, 0.77; 95% CI, 0.58-1.02; $P=.07$) were considered. Further adjustment for comorbidities and socioeconomic status, where possible, did not change interpretations, and propensity score adjustment did not substantially change the results.

Conclusion Among patients with relapsing-remitting MS, administration of interferon beta was not associated with a reduction in progression of disability.

JAMA. 2012;308(3):247-256 www.jama.com

MULTIPLE SCLEROSIS (MS) IS a chronic disease that often affects people in the prime of their lives. A key feature of MS is clinical progression of the disease over time manifested by the accumulation of disability. Interferon beta drugs are the most widely prescribed disease-modifying drugs (DMDs) approved by the US Food and Drug Administration for the treatment of relapsing-onset MS, the most common MS disease course. Although a substantial reduction in brain lesion development, as evidenced by magnetic resonance imaging (MRI),[1] and a one-third relative reduction in relapse frequency were demonstrated in the pivotal clinical trials of interferon beta for relapsing-remitting MS,[2] there is a lack of well-controlled longitudinal studies investigating the effect of interferon beta on disability progression.

Typically, drug efficacy (as established through randomized clinical trials conducted under optimal conditions) is greater than drug effectiveness (as measured in "real-world" settings).[3] Patients participating in clinical trials tend to be highly selected in

For editorial comment see p 290.

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terms of comorbidities, motivation, cognition, and ability to adhere to medication schedules. Moreover, follow-up protocols are highly structured, supportive, and specialized, and the duration of therapy in clinical trials is typically shorter than under usual care conditions. For all these reasons, the relationship between interferon beta exposure and disease progression is difficult to delineate based on clinical trials.

Several postmarketing studies have suggested the effectiveness of interferon beta, as measured by relapses, disability, or MRI.[4-10] Although much has been learned from these studies, the validity of the findings has been brought to question[11-14] because of major methodological issues including immortal time bias,[13,15] selection bias,[10,12,16] small sample sizes,[6,8,9] and insufficient follow-up.[4,6,7]

We set out to investigate the association between interferon beta exposure and disability progression in relapsing-remitting MS using a database of MS cases in the province of British Columbia, Canada.

METHODS

To address the methodological limitations of earlier studies, we selected 2 distinct control cohorts, used a comparable baseline for the treated and untreated cohorts, adjusted for potential confounders, increased treatment exposure accuracy, and addressed immortal time bias by treating exposure as a time-dependent variable.

Design and Setting

This was a retrospective record-linkage cohort study based on prospectively collected data. Multiple sclerosis–related clinical data were obtained from the British Columbia Multiple Sclerosis (BCMS) database. Established in 1980, the BCMS database is estimated to capture 80% of the British Columbia MS population[17,18] and links the 4 MS clinics in British Columbia during the study period (1985-2004). The database has been used extensively to examine the natural history of MS.[19-24] These studies purposely selected patients predominantly in the era prior to interferon beta treatment, with minimal DMD exposure, and were not designed to examine the effect of drug treatment.

For the current study, linked data were obtained from province-wide health administrative databases including PharmaNet (British Columbia's prescription drug database) to obtain data on exposure to interferon beta; Medical Service Plan Payment Information (data on medical services provided by practitioners) and the Discharge Abstract (hospital separations) database to capture preexisting comorbid conditions; and Census Geodata to provide information on socioeconomic status (SES). The linkage was performed through Population Data BC, a pan-provincial population health data resource. Patients were identified through the BCMS database and linked via their personal health number, a unique lifelong identifier.

This study was approved by the University of British Columbia's Clinical Research Ethics Board, which includes patient informed consent.

Study Population

All patients with definite relapsing-onset MS (Poser or McDonald criteria) who registered with a BCMS clinic between April 1985 and December 2004 and reached eligibility for interferon beta treatment during the same period were included. We used a broad criterion for interferon beta treatment eligibility, adapted from the British Columbia government's reimbursement scheme, defined as having a definite relapsing-onset course, age 18 years or older, and a score of 6.5 or lower on the Expanded Disability Status Scale (EDSS). The EDSS ranges from 0 to 10; higher scores indicate higher disability. An EDSS score of 6.5 indicates "constant bilateral assistance required to walk about 20 m without resting."[25] Because of the prohibitively high cost of the DMDs and the government scheme, patients were unable to obtain a DMD outside of a BCMS clinic. The date of the first clinic visit at which a patient reached eligibility for interferon beta treatment was used as the study entry (baseline) for each participant. Patients with fewer than 2 prospective EDSS measurements from baseline to study end were excluded. Patients exposed to a non–interferon beta DMD, a cytotoxic immunosuppressant for MS, or an MS clinical trial were excluded (if exposure occurred prior to baseline) or data were censored (if exposure occurred after baseline). EDSS scores were recorded at clinic visits by the MS neurologist, who was not blinded to patient treatment status. Patient follow-up was to the most recent EDSS score recorded prior to December 31, 2008 (the study end date).

Our a priori sample size calculation[26] (to assess study feasibility) was based on a Cox proportional hazards regression model assuming a 40% reduction in the hazard of reaching an EDSS score of 6 in patients treated with interferon beta[10] compared with untreated patients. It was estimated that a total of 161 patients were required to reach an EDSS score of 6 during follow-up to achieve a power of 80% at a 2-sided significance level of .05. Assuming that 10% of patients would reach an EDSS score of 6 during follow-up, 805 patients were required in each group.

Defining Treated and Untreated Comparison Cohorts

The treated cohort comprised patients exposed to interferon beta who first became eligible between July 1995 and December 2004 (July 1995 represents the first interferon beta licensing date in Canada). Two separate untreated comparison cohorts were selected. The contemporary cohort comprised patients first eligible in the same period (July 1995–December 2004) who remained unexposed to interferon beta, while the historical cohort included those first eligible prior to the approval of interferon beta (April 1985–June 1995) who remained unexposed to interferon beta during the study period. The historical cohort represents

patients eligible for interferon beta treatment in an era when there was no access to licensed DMDs for MS; this helps minimize indication bias. The contemporary untreated cohort represents an equivalent time-period group, limiting the influence of potential period changes that are difficult to measure, such as patient care or management, and allowing additional factors to be considered, including SES and comorbidities (only available for the treated and contemporary control patients).

Defining Treatment Exposure

Drug exposure information was obtained through the BCMS and PharmaNet databases. During the study period, 4 preparations of interferon beta became available: in 1995, interferon beta-1b (Betaseron, 250 µg subcutaneously on alternate days) and in 1998, interferon beta-1a (Avonex, 30 µg intramuscularly once weekly; and Rebif, 22 µg and 44 µg subcutaneously 3 times per week).[27] All interferon beta preparations were considered 1 therapeutic class; switches between products were not considered interruptions. The majority (93%) of exposed patients had only a short break (<3 months) or no break between consecutive interferon beta prescriptions. We therefore did not consider the intervening stoppages between consecutive prescriptions of interferon beta as changes in treatment status.

Outcome

The main outcome measure was time from baseline to a confirmed and sustained EDSS score of 6, considered irreversible disability when all subsequent EDSS scores were 6 or higher, with at least 1 measurement more than 150 days later. An EDSS score of 6 indicates "intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 m with or without resting."[25] If the outcome was not reached, patients were censored at the last recorded EDSS measurement or at the preceding EDSS measurement if the last score was 6 or higher to avoid overestimation of the time to an EDSS score of 6. The secondary outcome was time from baseline to a confirmed and sustained EDSS score of 4 ("fully ambulatory without aid, up and about 12 hours a day despite relatively severe disability; able to walk without aid 500 m").[25] The assessors (ie, the MS neurologists) were not blinded to patient treatment status.

Comorbidity and SES

The Charlson comorbidity index was calculated using the Deyo validated adaptation[28] based on hospital admissions or physician visits in the 2 years prior to baseline. Socioeconomic status was estimated through Statistics Canada's generated neighborhood income data, aggregated as quintiles.[29] Comorbidity and SES data were available for the contemporary cohorts only.

Statistical Analyses

Basic demographic and clinical characteristics of the interferon beta–treated and the untreated cohorts were compared using the Pearson χ^2 test for categorical variables, the *t* test for continuous variables, and the Mann-Whitney Wilcoxon test for discrete quantitative variables.

Cox proportional hazards regression models, with interferon beta treatment as a time-dependent covariate, were used to assess the hazard of disease progression (time to EDSS scores of 6 and 4), expressed as hazard ratios (HRs) with 95% confidence intervals. This allowed the time from baseline to initiation of an interferon beta drug and the time from stopping interferon beta to the end of follow-up to contribute to the untreated follow-up time. The model was adjusted for the following baseline covariates: sex, age, disease duration, and EDSS score. Further adjustment for SES and Charlson comorbidity index was performed for the contemporary cohorts. The proportional hazards assumption for baseline covariates was examined using log-log plots. Additional analyses, including a propensity score–adjusted model, detailed in the eAppendix (available at http://www.jama.com), were conducted to explore further the association between treatment and disability progression and to examine potential biases.

Statistical analyses were performed using SPSS version 16.0 (SPSS Inc). All statistical tests were 2-sided and $P < .05$ was considered statistically significant.

RESULTS

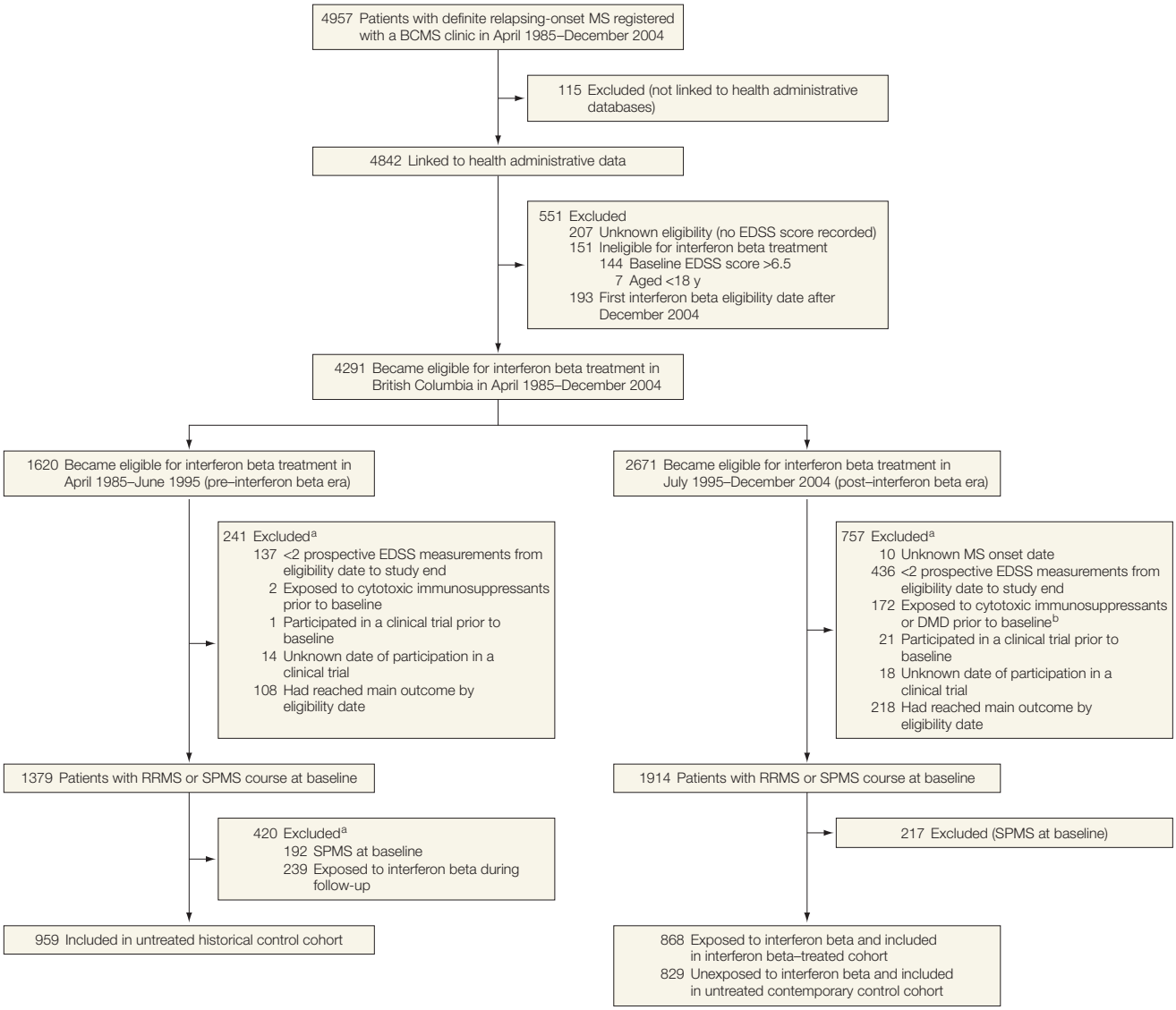
A total of 2656 patients were included in the main analyses; 868 formed the interferon beta cohort, 829 the contemporary control cohort, and 959 the historical control cohort (FIGURE 1 outlines the study selection). The demographics were comparable between excluded and included patients (73% of excluded patients were female with a mean age at MS onset of 31.9 [SD, 10.1] years vs 76% female with a mean age at MS onset of 31.9 [SD, 9.3] years for included patients).

The TABLE shows the baseline characteristics of the 3 cohorts. Some differences between the treated and control cohorts were observed but were generally considered clinically minor in most instances. Nonetheless, final results were derived from multivariable models adjusted for these baseline characteristics. Disease duration and EDSS scores differed among the 3 cohorts, although differences were small; the median EDSS score was 2.0 in all 3 cohorts; the mean was 2.1 in the treated cohort and 2.0 in both untreated comparison cohorts. The baseline disease duration was shorter in the treated cohort compared with the untreated cohorts (median, 3.0 [interquartile range {IQR}, 1.2-8.2] years in the treated cohort vs 5.6 [IQR, 1.8-12.3] years in the contemporary untreated cohort and 5.1 [IQR, 1.5-11.8] years in the historical untreated cohort. The median annualized relapse rate was 0.5 (IQR, 0-1.2) in the treated cohort, 0.5 (IQR, 0-1.0) in the contemporary control cohort, and 0.5 (IQR, 0-1.4) in the historical control cohort. Compared with the treated cohort, the contemporary controls were similar by sex, MS onset age, and Charl-

son comorbidity index but were older, with a lower annualized relapse rate and a tendency toward a lower SES. The historical controls were similar by sex, age, and annualized relapse rates but were younger at MS onset. EDSS assessment rates were similar for the treated, contemporary control, and historical control cohorts (0.99, 0.91, and 1.10 times per year, respectively).

The treated cohort contributed 2557 patient-years of interferon beta–exposed time and 1347 patient-years of unexposed time (1028 patient-years before and 319 patient-years after interferon beta treatment). The contemporary and historical control cohorts contributed 2915 and 7574 patient-years of unexposed time, respectively. Follow-up time (first to last EDSS measurement) differed between groups, being considerably longer for the historical untreated cohort (median, 10.8 [IQR, 6.3-14.7] years), who by definition entered the study much earlier than the contemporary cohorts. The median follow-up times for the contemporary cohorts were 5.1 (IQR, 3.0-7.0) years for the treated cohort and 4.0 (IQR, 2.1-6.4) years for the untreated

Figure 1. Selection of Interferon Beta–Treated and Untreated Cohorts From the BCMS Database for the Main Analysis



BCMS indicates British Columbia Multiple Sclerosis; DMD, disease-modifying drug; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.
[a]The sum of the individual reasons exceeds the total number of patients because some patients met more than 1 condition.
[b]Eight exposed to a cytotoxic immunosupressant, 62 to glatiramer acetate, and 112 to interferon beta.

Table. Baseline Demographic and Clinical Characteristics[a]

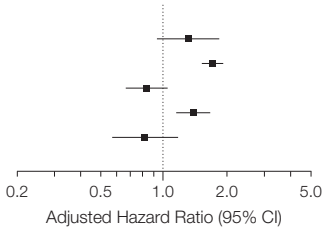
Characteristics	Interferon Beta–Treated Patients (n = 868)	Contemporary Untreated Patients (n = 829)[b]	*P* Value, Treated vs Contemporary Untreated Patients	Historical Untreated Patients (n = 959)[c]	*P* Value, Treated vs Historical Untreated Patients
Sex, No. (%)					
Male	208 (24.0)	192 (23.2)	.70[d]	238 (24.8)	.67[d]
Female	660 (76.0)	637 (76.8)		721 (75.2)	
Age at MS onset, y					
Mean (SD)	32.3 (9.3)	33.0 (9.4)	.17[e]	30.7 (9.0)	<.001[e]
No. (%)					
<20	64 (7.4)	59 (7.1)	.37[d]	105 (10.9)	.01[d]
20 to <30	328 (37.8)	281 (33.9)		379 (39.5)	
30 to <40	297 (34.2)	298 (35.9)		326 (34.0)	
40 to <50	147 (16.9)	149 (18.0)		124 (12.9)	
≥50	32 (3.7)	42 (5.1)		25 (2.6)	
Disease duration, y					
Mean (SD)	5.8 (6.6)	8.3 (8.5)	<.001[e]	7.7 (7.9)	<.001[e]
Median (IQR)	3.0 (1.2-8.2)	5.6 (1.8-12.3)		5.1 (1.5-11.8)	
Age at baseline, y					
Mean (SD)	38.1 (9.2)	41.3 (10.0)	<.001[e]	38.4 (9.5)	.56[e]
No. (%)					
<20	12 (1.4)	6 (0.7)	<.001[d]	10 (1.0)	.71[d]
20 to <30	171 (19.7)	102 (12.3)		173 (18.0)	
30 to <40	319 (36.8)	281 (33.9)		378 (39.4)	
40 to <50	273 (31.5)	269 (32.4)		292 (30.4)	
≥50	93 (10.7)	171 (20.6)		106 (11.1)	
EDSS score					
Mean (SD)	2.1 (1.2)	2.0 (1.2)		2.0 (1.3)	
Median (range)	2.0 (0-6.5)	2.0 (0-6.5)	.02[f]	2.0 (0-6.5)	.002[f]
Annualized relapse rate in the 2 y prior to baseline[g]					
Mean (SD)	0.9 (1.1)	0.6 (1.0)	<.001[e]	0.9 (1.1)	.29[e]
Median (IQR)	0.5 (0-1.2)	0.5 (0-1.0)		0.5 (0-1.4)	
Active follow-up time, first to last EDSS measurement, mean (SD), y	5.2 (2.8)	4.5 (2.9)	<.001[e]	10.5 (5.5)	<.001[e]
Charlson comorbidity index[h]					
Median (range)	0 (0-3)	0 (0-3)		NA	
Score, No. (%)					
0 (No comorbidity)	854 (98.4)	807 (97.3)	.14[d]	NA	
≥1 (≥1 Comorbid condition)	14 (1.6)	22 (2.7)			
Neighborhood income quintile, No. (%)[i]					
1 (Lowest)	141 (16.9)	154 (19.4)	.04[f]	NA	
2	147 (17.6)	165 (20.8)			
3	179 (21.4)	155 (19.5)			
4	178 (21.3)	158 (19.9)			
5 (Highest)	190 (22.8)	162 (20.4)			

Abbreviations: EDSS, Expanded Disability Status Scale; IQR, interquartile range; NA, data not available/incomplete.
[a] Baseline was considered the first date a patient became eligible for interferon beta treatment.
[b] Untreated patients who first became eligible for treatment in the post–interferon beta era (July 1995–December 2004).
[c] Untreated patients who first became eligible for treatment in the pre–interferon beta era (April 1985–June 1995).
[d] By Pearson χ^2 test.
[e] By *t* test.
[f] By Mann-Whitney Wilcoxon test.
[g] If this period included multiple sclerosis onset, this first-onset attack was not included as a relapse.
[h] Deyo adaptation of the Charlson comorbidity index,[28] based on hospital admissions or physician visits in the 2 years prior to baseline and derived from *International Classification of Diseases, Ninth Revision, Clinical Modification* codes, excluding hemiplegia, paraplegia, and dementia to avoid misclassifying complications of multiple sclerosis as comorbidity. All relevant comorbidities are aggregated into a single variable theoretically ranging from 0 to 33; higher scores indicate more comorbidity.
[i] Used as a proxy for socioeconomic status.[29] Data were missing for 33 patients in the interferon beta–treated cohort and 35 patients in the contemporary control cohort.

Figure 2. Multivariable Time-Dependent Cox Regression Analysis of Potential Factors Associated With Time to Confirmed and Sustained EDSS Score of 6 for Interferon Beta–Treated Patients (n=868) vs a Contemporary Untreated Cohort (n=829), With Interferon Beta Treatment as a Time-Varying Covariate

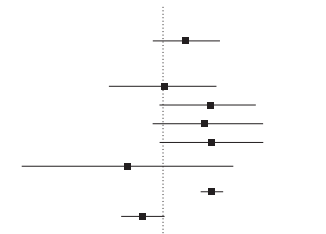
A

Factors	Adjusted Hazard Ratio (95% CI)
Interferon beta–exposed time[a] (vs unexposed time[b])	1.30 (0.92-1.83)
EDSS score at baseline (per 1 point)[c]	1.70 (1.52-1.91)
Disease duration at baseline (per 10 y)	0.82 (0.65-1.03)
Age at baseline (per 10 y)	1.37 (1.14-1.66)
Female[d] (vs male[e])	0.81 (0.56-1.16)



B

Factors	Adjusted Hazard Ratio (95% CI)
Interferon beta–exposed time[f] (vs unexposed time[g])	1.28 (0.90-1.84)
Neighborhood income level (vs quintile 5 [highest income])[h]	
Quintile 4[i]	1.02 (0.55-1.87)
Quintile 3[j]	1.67 (0.96-2.91)
Quintile 2[k]	1.57 (0.89-2.77)
Quintile 1 (lowest income)[l]	1.70 (0.96-3.01)
Charlson comorbidity index ≥1[m] (vs 0[n])	0.68 (0.21-2.16)
EDSS score at baseline (per 1 point)[c]	1.71 (1.51-1.93)
Disease duration at baseline (per 10 y)	0.80 (0.63-1.01)
Age at baseline (per 10 y)	1.49 (1.23-1.81)
Female[o] (vs male[p])	0.76 (0.52-1.11)



EDSS indicates Expanded Disability Status Scale. Panel A shows findings when patient characteristics are considered potential confounders. Covariates included in the model were sex, age at baseline, disease duration at baseline, EDSS score at baseline, and interferon beta exposure as a time-varying covariate. Fifty-four patients who were censored before the earliest event did not contribute to the analysis. Panel B shows findings when additional covariates (socioeconomic status [SES] and the Charlson comorbidity index) were also considered. A further 68 patients were excluded due to missing SES. Fifty-two patients who were censored before the earliest event did not contribute to the analysis.

[a]2556.9 person-years (65 patients reached the outcome).

[b]4262.6 person-years (73 patients reached the outcome, 29 during the unexposed time in the interferon beta–treated cohort and 44 in the contemporary control cohort).

[c]EDSS at baseline ranged from 0 to 6.5.

[d]1297 patients (95 reached the outcome, 67 in the interferon beta–treated cohort and 28 in the contemporary control cohort).

[e]400 patients (43 reached the outcome, 27 in the interferon beta–treated cohort and 16 in the contemporary control cohort).

[f]2486.8 person-years (60 patients reached the outcome).

[g]4104.0 person-years (67 patients reached the outcome, 24 during the unexposed time in the interferon beta–treated cohort and 43 in the contemporary control cohort).

[h]352 patients (22 reached the outcome, 16 in the interferon beta–treated cohort and 6 in the contemporary control cohort).

[i]336 patients (20 reached the outcome, 13 in the interferon beta–treated cohort and 7 in the contemporary control cohort).

[j]334 patients (30 reached the outcome, 19 in the interferon beta–treated cohort and 11 in the contemporary control cohort.

[k]312 patients (27 reached the outcome, 18 in the interferon beta–treated cohort and 9 in the contemporary control cohort).

[l]295 patients (28 reached the outcome, 18 in the interferon beta–treated cohort and 10 in the contemporary control cohort).

[m]36 patients (3 reached the outcome, 1 in the interferon beta–treated, and 2 in the contemporary control cohort).

[n]1593 patients (124 reached the outcome, 83 in the interferon beta–treated cohort and 41 in the contemporary control cohort).

[o]378 patients (87 reached the outcome, 60 in the interferon beta–treated cohort and 27 in the contemporary control cohort).

[p]1251 patients (40 reached the outcome, 24 in the interferon beta–treated and 16 in the contemporary control cohort).

cohort. Information regarding the proportion of patients reaching the outcome within 10 years after baseline, interferon beta prescription patterns, and right-censoring are described in the "Additional Results" section of the eAppendix.

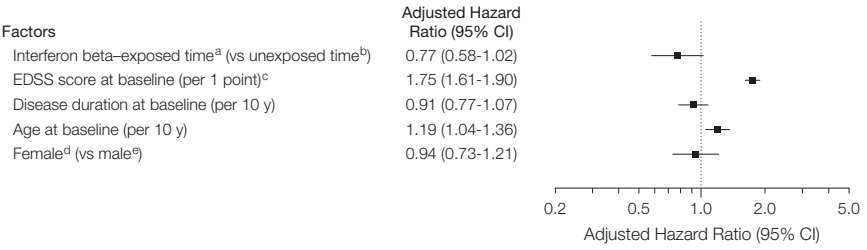
The adjusted Cox regression analysis, with interferon beta exposure as a time-dependent covariate, found no strong evidence of an association of interferon beta exposure with the hazard of reaching an EDSS score of 6 when either the contemporary (FIGURE 2A) or historical (FIGURE 3) control cohorts were considered; in each case the 95% confidence intervals included 1. However, the direction of the estimated HRs of reaching the outcome differed depending on which control cohort was included, with an HR of 1.30 (95% CI, 0.92-1.83; $P=.14$) when the contemporary controls were considered and an HR of 0.77 (95% CI, 0.58-1.02; $P=.07$) using the historical controls. The number of individuals reaching the outcome were 94 (10.8%), 44 (5.3%), and 222 (23.1%) in the treated, contemporary untreated, and historical untreated cohorts, respectively. In both analyses, a higher baseline EDSS score and an older age at baseline were associated with a higher hazard of reaching an EDSS score of 6, while female sex and a shorter disease duration were associated with a lower but not statistically significant hazard of reaching the outcome (Figure 2A and Figure 3).

When comorbidity and SES were added to the contemporary model, findings were similar (Figure 2B). Low or middle SES (quintiles 1-3), when compared with high SES (quintiles 4-5), was associated with a higher hazard of reaching the outcome, although this was not statistically significant. Comorbidity was not significantly associated with time to an EDSS score of 6. Adding the annualized relapse rate to the model (based on the 2 years before baseline) did not change the direction of findings (HR, 1.37; 95% CI, 0.97-1.94; $P=.08$ using contemporary controls and HR, 0.77; 95% CI,

0.58-1.02; $P=.07$ using historical controls).

Findings were also similar for the secondary outcome (EDSS score of 4) and in the additional analyses (eFigure 1, eFigure 2, eFigure 3, eFigure 4, eFigure 5, eFigure 6, and eFigure 7), including propensity score adjustment (eAppendix). The number of individuals reaching the secondary outcome was 156 (18.6%) in the treated cohort, 68 (8.6%) in the contemporary control cohort, and 268 (29.5%) in the historical control cohort. With propensity score adjustment, comparison with the contemporary control cohort for progression to an EDSS score of 6 resulted in an HR of 1.34 (95% CI, 0.93-1.92; $P=.12$); comparison with the historical control cohort resulted in an HR of 0.84 (95% CI, 0.63-1.11; $P=.23$).

Figure 3. Multivariable Time-Dependent Cox Regression Analysis of Potential Factors Associated With Time to Reach Confirmed and Sustained EDSS Score of 6 for Interferon Beta–Treated Patients (n=868) vs a Historical Untreated Cohort (n=959), With Interferon Beta Treatment as a Time-Varying Covariate



EDSS indicates Expanded Disability Status Scale. Covariates included in the model were sex, age at baseline, disease duration at baseline, EDSS score at baseline, and interferon beta exposure as a time-varying covariate. Twenty patients who were censored before the earliest event did not contribute to the analysis.
[a]2556.9 person-years (65 patients reached the outcome).
[b]8921.3 person-years (251 patients reached the outcome, 29 during the unexposed time in the interferon beta–treated cohort and 222 in the historical control cohort).
[c]EDSS at baseline ranged from 0 to 6.5.
[d]1381 patients (231 reached the outcome, 67 in the interferon beta–treated cohort and 164 in the historical control cohort).
[e]446 patients (85 reached the outcome, 27 in the interferon beta–treated cohort and 58 in the historical control cohort).

COMMENT

Among patients with relapsing-remitting MS, administration of interferon beta was not associated with a reduction in progression of disability, despite using a clinically relevant, important, and irreversible disability milestone as the main outcome. The lack of evidence for a strong association between interferon beta treatment and disability progression persisted whether a contemporary or a historical (pre– vs post–interferon beta era) untreated comparison cohort was considered, a secondary outcome (EDSS score of 4) was examined, or additional analyses were performed, including a propensity score–adjusted model (eAppendix). The difference in the direction of the hazard of progression between the contemporary and historical approaches, which is informative for future studies, is of interest.

Previous postmarketing studies have suggested a positive association between interferon beta and MS disability outcomes.[4-10,30] However, conducting adequately controlled longitudinal observational studies is challenging, and many such studies have faced methodological issues. One of the larger studies to date, from 2 Italian centers,[10] was susceptible to immortal time bias[13,15] because of differing baselines for the treated and untreated cohorts. The use of a propensity score method in that study[10] could not address immortal time bias. An independent reanalysis found no apparent beneficial association with interferon beta treatment once this bias was considered.[13] Another methodological issue included the use of a control group comprising individuals too ill to start interferon beta treatment (owing to significant comorbidities).[10] Both of these issues could bias the study to show a treatment effect when one might not exist.[12,13] Another relatively large Canadian study used patients as their own controls.[5] This approach minimized some potential biases but may not have sufficiently acknowledged the variable and unpredictable individual progression profiles of MS patients.[5] A sizable UK-based observational study was unable to demonstrate a beneficial association with the use of DMDs in relapsing-remitting MS after 2 years of treatment, finally concluding that further follow-up was needed.[31]

Our study endeavored to address these shortcomings. First, we considered interferon beta treatment as a time-dependent variable, thereby addressing immortal time bias[13,15] and accounting for the changing treatment status of patients over time. Second, in the face of no single ideal comparison group, we adopted a dual approach, using both pre– and post–interferon beta era untreated cohorts. Third, we were able to access a large cohort of MS patients with a substantial follow-up and similar rates of disability assessment (thereby minimizing surveillance bias).[32] Fourth, the unique health system in Canada allowed linkage between clinical and province-wide health administrative databases, creating a comprehensive and rich data source.

Our findings are also relevant for the design of future related observational studies; we found that patients eligible for interferon beta treatment in the interferon beta era but who chose not to start treatment had a non–statistically significant more favorable overall outcome compared with those who started treatment in the same era. This may be explained by "indication bias," whereby patients whose clinical status is not improving or is getting worse are prescribed drug therapy.[33] This potential bias was also apparent in a reanalysis of the Italian study,[10,13] which used a contemporary (post–interferon beta era) comparison cohort, but was

not evident in our pre–interferon beta era comparison, for which the historical control group did not have the same access to DMD treatment. This provides a possible explanation for the differences in the direction of the HRs in our contemporary and historical approaches and encourages the use of more than 1 control group in observational studies whenever possible.[34] Our estimated HR was greater than 1 in the contemporary approach, which may reflect residual confounding by indication, despite the adjustments made.

The decision to start (or not start) treatment is complex, and likely not all factors are captured by observational studies—this can particularly affect any "contemporary" analysis based on a post–interferon beta era untreated comparison cohort. In a health care system with free access to DMDs, possible reasons for not starting a DMD might include stable disease, needle phobia, unwillingness to receive or adhere to a noncurative treatment, planned pregnancy, and personal or religious concerns about using interferon beta, a human albumin–containing product. In our study, the contemporary untreated cohort had a lower annualized relapse rate and longer disease duration but similar disability level (EDSS score) at baseline compared with the treated cohort. Although these factors were adjusted for, they could indicate a more favorable outcome; a low or moderate initial relapse frequency (1-3 relapses during the first 5 years after onset of symptoms) has been associated with a subsequent nonprogressive MS course.[35]

Our data suggest that the historical control group might be the more appropriate choice; however, it has its own limitations, including the possibility that factors other than drug treatment may have changed over time, such as patient care and management and rates of disease progression. However, strong evidence to suggest a change in disease progression over time was not found in relapsing-onset MS patients in British Columbia.[36] Nonetheless, in the event that further studies become available, future meta-analyses of similar observational data may be of value.

Our findings, however, are consistent with the longer-term clinical trial–related studies. A 16-year follow-up of MS patients originally randomized to receive placebo or interferon beta treatment in a 2-year clinical trial was unable to show benefit in the treatment group in terms of progression to an EDSS score of 6 or secondary progressive MS.[37] There were few deaths in the study, although an unexpected excess occurred in the original placebo group; findings were considered hypothesis generating by the authors, who cautioned that no survival benefit could be confirmed.[37] In addition, no effect of interferon beta treatment on disability progression could be found in patients with clinically isolated syndrome (considered at high risk of developing MS).[38] Some have tried to evaluate the impact of delayed vs early or higher vs lower cumulative exposure to interferon beta treatment through open-label extension studies, reporting better outcomes with early or higher cumulative exposure.[39,40] However, dropouts and lack of blinding have confounded findings.[41]

We also found that the lower SES quintiles (vs the highest quintile) were associated with a higher hazard of disability progression, although these findings were not statistically significant. Socioeconomic status is a complex concept, reflecting more than just income, and a low SES is a strong determinant of poor overall health.[42] We were unable to find another study examining the association between SES and MS disability progression. Given that there are relatively few predictors of MS disease progression, further investigation of potentially modifiable factors such as psychosocial, behavioral, or environmental pathways that may attenuate SES is warranted.

Our study also has some limitations. We considered interferon beta drugs as a single therapeutic class, although given the complexity of the differing approval dates and product switching, a robust comparison between products would be extremely challenging. We were not able to consider neutralizing antibodies—high titers have been associated (somewhat controversially) with reduced interferon beta effectiveness.[43] Our study was not designed to examine adverse events associated with interferon beta treatment. Although we considered a broad range of confounders, unmeasured confounding is possible, as with any observational study. We could consider only patients attending a BCMS clinic. This primarily affects recruitment into the untreated cohorts (because of virtual complete capture of patients taking interferon beta for their MS during the study period). It is possible that very mild or very severe disease would prevent attendance at clinic, although systematic occurrence of one of these scenarios appears unlikely.

In addition, we considered 1 main and 1 secondary outcome; both were based on reaching irreversible disability milestones. Although these are clinically relevant and important outcomes, and our conservative definitions served to minimize assessment variation and random fluctuations that have impeded the measurement of disease progression in clinical trials,[44,45] it remains possible that interferon beta treatment might positively affect other outcomes not considered here. The EDSS has recognized limitations[46]; however, it is the most widely used and internationally recognized disability assessment tool in MS, its use being ubiquitous in MS clinical trials and observational studies. Limitations relevant to the study EDSS end points include reliance on ability to walk and an inability to capture well the myriad MS symptoms (cognition; fatigue; bowel, bladder, or sexual function; visual acuity; or health-related quality of life). Also, despite the propensity score adjustment, residual confounding by indication could still be present, as suggested by the estimated HR of greater than 1 in the contemporary approach. Finally, we cannot rule out the possibility that despite our sample size, our study may have been underpowered to detect an association between inter-

feron beta treatment and disease progression.

In conclusion, we did not find evidence that administration of interferon beta was associated with a reduction in disability progression in patients with relapsing-remitting MS. The ultimate goal of treatment for MS is to prevent or delay long-term disability. Our findings bring into question the routine use of interferon beta drugs to achieve this goal in MS. It is, however, possible that a subgroup of patients benefit from interferon beta treatment and that this association would not be discernable in our comprehensive "real-world" study. Further work is needed to identify these potential patients; perhaps through pharmacogenomic or biomarker studies, paving the way for a tailored, personalized medicine approach. Our findings also encourage the investigation of novel therapeutics for MS.

Author Contributions: Dr Tremlett had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Shirani, Zhao, Kingwell, van der Kop, Petkau, Tremlett.
Acquisition of data: Shirani, Kingwell, van der Kop, Oger, Tremlett.
Analysis and interpretation of data: Shirani, Zhao, Karim, Evans, Kingwell, Oger, Gustafson, Petkau, Tremlett.
Drafting of the manuscript: Shirani, Tremlett.
Critical revision of the manuscript for important intellectual content: Shirani, Zhao, Karim, Evans, Kingwell, van der Kop, Oger, Gustafson, Petkau, Tremlett.
Statistical analysis: Shirani, Zhao, Karim, Gustafson, Petkau.
Obtained funding: Zhao, van der Kop, Gustafson, Petkau, Tremlett.
Administrative, technical, or material support: Shirani, Evans, Kingwell, Oger, Tremlett.
Study supervision: Tremlett.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Shirani reports receiving travel grants to present at and attend conferences from the endMS Research and Training Network and the European Committee for Treatment and Research in Multiple Sclerosis. Mr Karim reports having had travel and accommodation costs covered to present at a conference from the endMS Research and Training Network. Dr Evans reports receiving travel grants to present at and attend conferences from the endMS Research and Training Network and the European Committee for Treatment and Research in Multiple Sclerosis. Dr Kingwell reports having had travel and accommodation costs covered to present at and attend conferences from the endMS Research and Training Network, the International Society for Pharmacoepidemiology, and Bayer Schering Pharma. Dr Oger reports receiving speaker honoraria, consulting fees, travel grants, research grants, and/or educational grants from Aventis, Bayer, Biogen-Idec, BioMS, Corixa, Genentech, Novartis, Serono, Shering, Talecris, and Teva-Neurosciences. He receives fees for services from Bayer, Novartis, and Biogen Idec to serve on advisory committees. Dr Petkau reports having received research funds from Bayer Pharma and consulting fees and/or fees for service on data safety monitoring boards from Bayer Canada, Bayer Pharma, Bayhill Therapeutics, BTG International, Merck-Serono, and Novartis. Dr Tremlett reports having received speaker honoraria and/or travel expenses to speak at conferences from the Consortium of MS Centres, US National MS Society, Swiss Multiple Sclerosis Society, University of British Columbia Multiple Sclerosis Research Program, Bayer Pharmaceuticals (invited speaker, honoraria declined), and Teva Pharmaceuticals (invited speaker). Unless otherwise stated, all speaker honoraria are either donated to an MS charity or to an unrestricted grant for use by her research group. No other disclosures were reported.
Funding/Support: This study was supported by grant MOP-93646 from the Canadian Institutes of Health Research (CIHR; principal investigator: Dr Tremlett) and grant RG 4202-A-2 from the National Multiple Sclerosis Society (NMSS; principal investigator: Dr Tremlett). Dr Shirani is funded through a postdoctoral fellowship from the Multiple Sclerosis Society of Canada and grants from the CIHR (MOP-93646) and the NMSS (RG 4202-A-2). Dr Zhao receives research funding from the CIHR, the Multiple Sclerosis Society of Canada, and the NMSS. Dr Evans is funded through grants from the CIHR (MOP-93646), the NMSS (RG 4202-A-2), and the Michael Smith Foundation for Health Research. Dr Kingwell is supported by postdoctoral fellowships from the Multiple Sclerosis Society of Canada and the Michael Smith Foundation for Health Research. Dr Oger receives support from the Christopher Foundation and the University of British Columbia (UBC). He receives fees for service from the Medical Services Commission of British Columbia. Dr Gustafson is supported by the Natural Sciences and Engineering Research Council of Canada. Dr Petkau holds research grants from the CIHR, the Multiple Sclerosis Society of Canada, the NMSS, and the Natural Sciences and Engineering Research Council of Canada. Dr Tremlett is funded by the Multiple Sclerosis Society of Canada (Don Paty Career Development Award), is a Michael Smith Foundation for Health Research Scholar, and is the Canada Research Chair for Neuroepidemiology and Multiple Sclerosis. She has also received research support from the NMSS, CIHR, and UK Multiple Sclerosis Trust. The BCMS database has been funded from various sources (including the above) and also by an unrestricted grant from Donald Paty, MD, FRCPC, University of British Columbia, and the MS/MRI Research Group.
Role of the Sponsor: The funding institutions had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Online-Only Material: The Author Video Interview, eAppendix, and eFigures 1 through 7 are available at http://www.jama.com.
Additional Contributions: We gratefully acknowledge the BCMS clinic neurologists who contributed to the study through patient examination and data collection (current members listed in alphabetical order): D. Adams, MD, FRCPC (Kelowna MS clinic); D. Craig, MD, FRCPC (Kelowna MS clinic); L. Daly, MD, FRCPC (Prince George MS clinic); V. Devonshire, MD, FRCPC (UBC MS clinic); S. Hashimoto, MD, FRCPC (UBC and Victoria MS clinics); J. Hooge, MD, FRCPC (UBC and Prince George MS clinics); O. Hrebicek, MD, FRCPC (Victoria MS clinic); L. Kastrukoff, MD, FRCPC (UBC and Prince George MS clinics); S. Meckling, MD, FRCPC (Kelowna MS clinic); D. Parton, MD, FRCPC (Victoria MS clinic); A.-L. Sayao, MD, FRCPC (UBC MS clinic); and A. Traboulsee, MD, FRCPC (UBC MS clinic). We also thank P. Rieckmann, MD (Sozialstiftung Bamberg Hospital, Bamberg, Germany) for helpful revisions of the original Canadian Institutes of Health Research grant. None have received compensation for their role in the study. We also thank the UBC MS clinic nurses and staff and the UBC's Clinical Trials Group. We are grateful to Tom Duggan, BA, University of British Columbia, for significant help with data manipulation and conversion and the Pharmacoepidemiology in MS Research Group for research support. We are thankful to Population Data BC and the British Columbia Ministry of Health for support with linkage to British Columbia administrative health care and health services data (hospital separations and medical service plan payment information), as well as PharmaNet for drug information. We also thank Feng Zhu, MSc, University of British Columbia, for help with code development. Finally, we are indebted to all MS patients who participated in this study. Messrs Duggan and Zhu were compensated through study research grants.

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