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A non-parametric propensity score for estimating the effect of interferon-beta or glatiramer acetate on long-term outcomes of multiple sclerosis

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ABSTRACT

Background: The few observational studies that investigated the long-term effects of interferon-beta and glatiramer acetate were usually focused on progression to irreversible disability and other outcomes such as number of relapses and transition to secondary-progressive multiple sclerosis (SPMS) have been rarely studied. The objective of this paper is to estimate the effect of interferon-beta/glatiramer acetate on progression to irreversible disability, transition from relapsing-remitting multiple sclerosis (RRMS) to SPMS and the rate of relapses over 10 years.

Methods: Analyses included 2498 patients with confirmed diagnosis of RRMS followed in Montréal from 1977 to 2016. Marginal structural models with propensity score for treatment and censoring were used to account for potential confounding and attrition. Specifically, we used pooled logistic regression for progression to irreversible disability and transition to SPMS, and Poisson models for the rate of relapses.

Results: 77% of subjects were female and the median age at RRMS diagnosis was 35 years. The hazard of progression to irreversible disability was lower among treated patients than untreated patients (HR=0.73, 95% CI [0.57–0.94]). We did not find evidence of an association between interferon-beta/glatiramer acetate and the rate of transition to SPMS either over the 3-month intervals or for the duration of treatment. Patients treated for >5 years had a lower rate of relapses compared to those untreated (HR=0.70, 95% CI [0.57–0.86]).

Conclusion: Treatment with interferon-beta/glatiramer acetate suggests a beneficial effect on progression to irreversible disability and rate of relapses, but not on transition to SPMS.

1. Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system (Pugliatti et al., 2006). The disease severity varies greatly between patients and is characterized by sequences of relapses and progression of disability (Kamm et al., 2014). Canada has one of the highest prevalence of MS worldwide with approximately 93,500 persons diagnosed with MS (Gilmour et al., 2018).

Clinical trials suggest that immunomodulatory drugs reduce the progression of MS (Kappos et al., 2015; Tsivgoulis et al., 2015; Davis et al., 2017). While clinical trials are the gold-standard to evaluate the efficacy of drugs, they generally have a short duration of follow-up (Tsivgoulis et al., 2015) and include young patients with low levels of disability (Tsivgoulis et al., 2015). High quality observational studies can better assess the long-term effect of immunomodulatory drugs on MS in real-life situations as they do not exclude people based on MS severity and have longer follow-up (Montalban, 2011; Grootendorst et al., 2010).

The few observational studies (Veugelers et al., 2009; Izquierdo et al., 2015; Trojano et al., 2007; Karim et al., 2014; Brown et al., 2007; Goodin et al., 2011; Drulovic et al., 2013; Shirani et al., 2012) that investigated the long-term effects of interferon-beta and glatiramer acetate on irreversible disability measured by the Expanded Disability

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Status Scale (EDSS) led to conflicting results. Most of the studies (Veugelers et al., 2009; Izquierdo et al., 2015; Drulovic et al., 2013) showing a beneficial effect of treatment on MS failed to account for potential time-dependent confounding in the association of interferon-beta/glatiramer acetate and irreversible disability. Karim et al. addressed this bias and found no association between interferon-beta and progression to irreversible disability (Karim et al., 2014).

Investigations of other clinically important outcomes such as number of relapses and transition to SPMS have also lead to contradictory results (Goodin et al., 2011; Drulovic et al., 2013; Bergamaschi et al., 2016; Tedeholm et al., 2013; Zhang et al., 2015; Brown et al., 2019). This may be explained by the lack of standardized definition of transition to SPMS, but also to insufficient consideration for confounding (Lorscheider et al., 2016). Recently, Brown et al. estimated the effect of immunomodulatory drugs on the risk of conversion to secondary progressive MS (Brown et al., 2019). They found that patients treated with interferon-beta/glatiramer acetate had a lower hazard of conversion to SPMS than matched untreated patients (Brown et al., 2019).

Finally, most studies ignore the cumulative treatment effect of interferon-beta or glatiramer acetate on the outcomes of MS, even if it is recommended to model cumulative effects to capture long-term treatment effect (Abrahamowicz et al., 2012; Pazzagli et al., 2018). Only Karim et al. estimated the effect of the cumulative exposure of interferon-beta and progression to irreversible disability and they found no significant association with MS outcomes (Karim et al., 2014).

As MS is a heterogeneous disease, the investigation of multiple outcomes is necessary to capture different dimensions of disease progression (Lavery et al., 2014). The objective of this study is to estimate the effect of current and 10-year cumulative use of interferon-beta/glatiramer acetate on: i) progression to irreversible disability, ii) transition from RRMS to SPMS, and iii) number of relapses. Interferon-beta and glatiramer acetate were studied as a single exposure because they have a similar efficacy (Wingerchuk and Carter, 2014).

2. Methods

2.1. Study design

Data were drawn from a prospective cohort of 3905 patients with MS followed at the Centre Hospitalier de l'Université de Montréal (CHUM) Multiple Sclerosis Clinic from 1977 to 2016. Information on progression of MS, history of treatments and reproductive history were collected at each visit. Patients with confirmed diagnosis of RRMS and no prior transition to SPMS were included in the analysis. In Canada, the first immunomodulatory drug was licensed on July 1st, 1995; therefore, patients who had their diagnosis before 1995 were only included in the analysis from July 1st, 1995, as they could not be exposed before that date. Moreover, MS patients taking other immunomodulatory drugs were excluded.

This study was approved by the Ethics Research Committee of the CHUM Research Centre.

2.2. Analytic samples

Patients were followed from the date of first diagnosis until April 30, 2016. First diagnosis refers to the clinically isolated syndrome. Because visits were not pre-scheduled on a regular basis, follow-up was divided into 3-month intervals and pooled across subjects (D'Agostino et al., 1990). Three outcomes (progression to irreversible disability, transition to SPMS and number of relapses) were studied. Visits to the MS clinics were used to define the outcome. If no visit occurred in a given three-month interval, we assumed that the disease severity (EDSS) was at the same level than it was in the previous interval and that no event (relapses or transition to SPMS) occurred in the given interval. For progression to irreversible disability and the number of relapses, subjects were followed until their last visit, while for transition to SPMS, they were followed either until SPMS transition or end of follow-up, whichever came first.

2.3. Description of variables

2.3.1. Study outcomes

Progression to irreversible disability was defined as the first documented EDSS ≥ 6 and <10, which corresponds to the threshold used in the literature to identify progression to irreversible disability (Veugelers et al., 2009; Trojano et al., 2007; Karim et al., 2014; Goodin et al., 2011). As a sensitivity analysis, we also considered the early disability accumulation using an EDSS ≥ 4 and <10 (Trojano et al., 2007; Confavreux et al., 2003; Debouverie et al., 2008; Leray et al., 2010) (Supplemental material, Table S1). Transition to SPMS was defined using the date of diagnosis of SPMS. The MS clinic defines the diagnosis of SPMS as having one-unit increase in EDSS over at least 6 months, among patients with EDSS ≥ 4 who did not experience a relapse. At each visit, patients reported their symptoms, which were classified as relapse or not by their neurologist. At the first visit, the neurologist also recorded the history of patients' previous relapses.

2.3.2. Exposures

The main exposure variable was an indicator of use of interferon-beta/glatiramer acetate in the 3-month interval versus not having used any medication during the 3-month interval. Prescription start dates and durations were used to measure exposure of interferon-beta/glatiramer acetate under the assumption of perfect adherence to treatment. A patient who stopped using the treatment for a period was considered untreated during this interval. The cumulative effect of interferon-beta/glatiramer acetate was defined as the total number of years treated (excluding interruptions) and was categorized as follows: 0 year, ≤ 2 years, between >2 and 5 years, and > 5 years.

2.3.3. Potential confounders and predictors of the association between interferon-beta/glatiramer acetate and the clinical outcomes

We hypothesized that the association between the use of interferon-beta/glatiramer acetate and each of the three outcomes could be confounded by pregnancy in the past 3 months, number of relapses in the past 3 months, EDSS in the past 3 months, age and time since RRMS onset, as shown in the directed acyclic graphs (Fig. 1). Using the date of pregnancy, we created an indicator taking the value of 1 if the patient was pregnant in the past 3 months and 0 otherwise. The variables age and time since RRMS onset were created using the date of RRMS diagnosis and were both considered as continuous variables. We also considered the results of the cerebral spinal fluid (CSF) test and sex as predictors. A variable indicating the results of the CSF test was coded as follows: no test, normal test, abnormal test. An abnormal CSF test refers to positive oligoclonal bands.

2.4. Missing values

The EDSS score was not systematically measured at each visit, leading to missing values in EDSS in the past 3 months, EDSS at RRMS onset and the outcome progression of irreversible disability. Multivariate Imputation by Chained Equations procedure (Azur et al., 2011; Buuren and Groothuis-Oudshoorn, 2011) was used to impute only EDSS in the past 3 months and EDSS at RRMS onset.

2.5. Statistical analyses

We estimated the effect of interferon-beta/glatiramer acetate on each of the clinical outcomes using marginal structural models. Three models were used for each of use and cumulative use of interferon-beta/glatiramer acetate: a pooled logistic regression model for both the progression to irreversible disability and transition to SPMS and a pooled

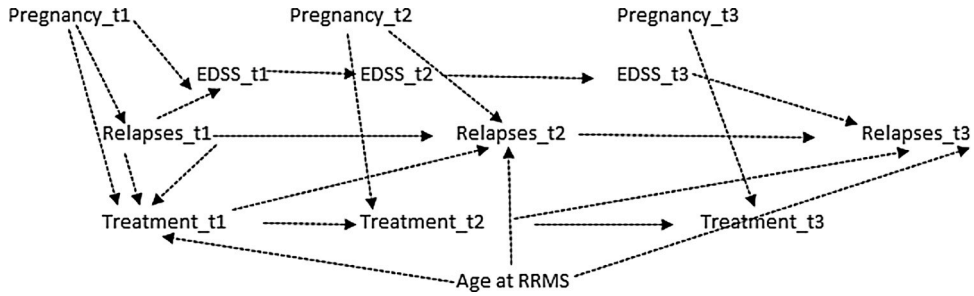

Fig. 1. Directed acyclic graphical showing the relationships between the use of interferon-beta/glatiramer acetate, number of relapses and time-dependent confounders, with 3 time points: t1, t2, t3.

Poisson regression model for the number of relapses. Hazard ratios were estimated from the pooled logistic regression model and rate ratio from the Poisson regression. Pooled logistic regression approximates the Cox model when the time intervals are short and the event rate in each intervals are low, as in the current analysis (D'Agostino et al., 1990). Intra-individual correlations were taken into account using generalized estimating equations.

2.5.1. Estimation of probability of treatment and censoring

Inverse probability of treatment models (Rosenbaum and Rubin, 1983) recreates a pseudo-population with balanced covariates between patients treated with interferon-beta/glatiramer acetate and those untreated.

The treatment propensity score was estimated using entropy balancing, a non-parametric approach which combines the possibility of incorporating a large number of moment conditions in the calculation of the weights, with the possibility of directly implementing the exact balance (Hainmueller, 2012). The dependent variable was the use of interferon-beta or glatiramer acetate in the past 3 months. The model included potential confounders of the association between interferon-beta/glatiramer acetate and the clinical outcomes measured at baseline and in the past 3 months as well as predictors of the clinical outcomes. More specifically, CSF and sex were considered as predictors of progression to irreversible disability. For transition to SPMS, we considered CSF, sex and progression to irreversible disability. CSF, sex and transition to SPMS were considered as predictors of the number of relapses.

To control for attrition in our cohort, we estimated a propensity of censoring score using the entropy balancing. The dependent variable was the probability of not being censored by the end of each 3-month interval and included the same independent variables as for the treatment propensity score.

To improve the precision of the models, we stabilized the weights (Robins et al., 1999). Finally, we created a global weight by multiplying the stabilized treatment weights and the stabilized censoring weights. We also evaluated the balance of the stabilized weights by comparing the distribution of covariates between the treatment groups using absolute means differences and the overall shape of the two distributions using Kolmogorov-Smirnov (KS) distance (Greifer, 2020). Mean differences of less than 0.10 suggest a good level of balance between treatment groups (Stuart et al., 2013) and KS distance of less than 0.05 suggests a good overlapping between the two distributions (Greifer, 2020).

As sensitivity analysis, we estimated the effect over 5 years of follow-up in order to make comparisons with short-term follow-up studies.

Analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and R 3.5.0 (R Core Team, Vienna, Austria; 2014).

3. Results

A total of 3008 patients had a confirmed diagnosis of RRMS. We further excluded 21 patients because they had only one visit, 272 patients because they had their diagnosis of RRMS before July 1st, 1995 and they did not have data available after the introduction of immunomodulatory drugs; and 217 patients because they used other immunomodulatory drugs. Therefore, 2498 patients were retained for the analysis (Figure S1). Patients retained in the analysis were similar to those not retained in terms of age and EDSS score at first visit (Table S2).

About three quarters of patients were female and the median age at MS diagnosis was 35 years (Interquartile range (IQR) =28–42). The median duration of follow-up was 13 years (IQR=7–20). The proportion with an EDSS score ≥6 was 5% both at first visit and at 5 years, and 8% at 10 years. The correlation in EDSS scores within patients was high (intraclass correlation coefficient=85.4%)). The proportion of patients who have transitioned to SPMS was 16%. Approximately 30% of patients with RRMS were prescribed interferon-beta as their first MS medication, with a median duration of use of 3 years, whereas 15% used glatiramer acetate as their first medication with a median duration of 4 years (Table 1).

Table 1
Characteristics of patients included in the analysis, Montreal, Canada, 1977–2016.

Characteristics	Patients with RRMS (n = 2498)	
Female,%	77.2	
Age at MS diagnosis, median (IQR[a]), years	35.2 (28.2, 42.4)	
Duration of follow-up, median (IQR[a]), years	12.9 (6.7,19.7)	
At baseline		
	EDSS score ≥ 4,%	9.6
	EDSS score ≥ 6,%	5.1
At 5 years of follow-up		
	EDSS score ≥ 4,%	7.8
	EDSS score ≥ 6,%	5.1
At 10 years of follow-up		
	EDSS score ≥ 4,%	12.4
	EDSS score ≥ 6,%	8.4
Variation in the EDSS scores within patients (ICC[b]),%	85.4	
Transition to SPMS,%	16.3	
Interferon-beta		
	First use,%	31.3
	Duration, years, median (IQR[a])	2.91 (1.1, 7.3)
Glatiramer acetate		
	First use,%	15.0
	Duration, years, median (IQR[a])	3.7 (1.2, 8.0)
Never being treated,%	42.1	

[a] Interquartile range.

[b] Intraclass correlation coefficient.

3.1. Inverse probability of treatment and censoring weighting

Because the distribution of weights was highly similar across imputation sets, we showed the results of the modeling of treatment and censoring weights for the first set of imputed data. The means of all stabilized weights at each interval were close to 1 (Figure S2), suggesting a correct specification of the models (Hernan and Robins, 2006). Once stabilized, treatment weights were balanced between patients treated with interferon-beta/glatiramer acetate and those untreated, with a mean difference lower than 0.10 for all variables and a KS distance lower than 0.05 (Figure S3) for the majority of the variables.

3.2. Causal effects of interferon-beta/glatiramer acetate on the clinical outcomes of MS

3.2.1. Progression to irreversible disability

We observed a reduction of 27% in the rate of progression to irreversible disability among people treated with interferon-beta/glatiramer acetate in the past 3 months compared to untreated patients (HR=0.73, confidence interval, 95% CI [0.57–0.94]) (Table 2). We did not find evidence of an association between progression to irreversible disability and the cumulative effect of treatment. Indeed, the estimates were close to the null and the confidence intervals were relatively precise.

3.3. Transition to SPMS

We did not find evidence of an association between interferon-beta/glatiramer acetate and the rate of transition to SPMS either over the 3-month intervals or for the duration of treatment. However, we observed a non-statistically significant increase in the rate of transition to SPMS among patient treated for more than 5 years compared to untreated patients (HR=1.21, 95% CI= [0.73–1.99]).

3.4. Rate of relapses

We observed a non-statistically significant reduction of 18% in the rate of relapses among patients treated with interferon-beta/glatiramer acetate between 2 and 5 years compared to untreated patients (Rate Ratio (RR)=0.82, 95% CI [0.56–1.21]). The reduction was statistically significant when we considered patients treated for > 5 years compared to untreated patients (RR=0.70, 95% CI= [0.57–0.86]).

When we estimated the effects over 5 years of follow-up (Table S4), we did not find evidence of an association between interferon-beta/glatiramer acetate and progression to irreversible disability, either over the 3-month intervals or for the duration of treatment. We observed a non-statistically significant reduction of 38% in the hazard of transition to SPMS among patients treated with interferon-beta/glatiramer acetate for ≤2 years compared to untreated (HR=0.62, 95% CI [0.36–1.07]). Similar results for the rate of relapses over 10 years was observed over 5 years of follow-up.

4. Discussion

In this study, we estimated the effect of interferon-beta/glatiramer acetate as well as their cumulative effect on three clinical outcomes of MS over 10 years of follow-up.

We found a reduction in the hazard of progression to irreversible disability among patients treated with interferon-beta/glatiramer acetate, although the association between the cumulative effect of interferon-beta/glatiramer acetate and progression to irreversible disability was not statistically significant. Karim et al. estimated the effect of interferon-beta as well as the cumulative effect on irreversible disability, and found no association between the use of interferon-beta (nor the cumulative effect) and time to progression to irreversible disability (Karim et al., 2014). Several reasons may explain the differences between their results and ours for the main exposure. The exposure and outcome variables were not defined in the same way. For the exposure variable, we considered people treated with interferon-beta and glatiramer acetate versus untreated patients, whereas Karim et al. considered only people treated with interferon-beta versus untreated patients (Karim et al., 2014) The outcome in Karim et al.'s study was time to reach progression to irreversible disability, while in our study it was progression to irreversible disability.

Our results for transition to SPMS were in the same direction as those of Brown et al. only for patients treated at ≤ 2 years, who found a significant decrease among people treated with interferon-beta or glatiramer acetate compared to those untreated (Brown et al., 2019). The small number of people who transitioned in some time intervals may have hampered our ability to detect significant results.

Even though the rate of relapses is one of the primary endpoints in clinical trials (Kappos et al., 2015; Lavery et al., 2014), it is seldom considered in observational studies. In this study, we did not find an association between the use of interferon-beta/glatiramer acetate in the past 3 months and the rate of relapses. Nevertheless, the results suggest that the cumulative treatment effect is related to a lower rate of relapses, and the effect was more noticeable when the patients had a duration of treatment > 5 years.

Our results underscore the importance of studying multiple outcomes in order to achieve a better understanding of the effect of immunomodulatory drugs on different aspects of MS progression. Disability progression may be difficult to detect in early stage of MS (Lavery et al., 2014); therefore, the number of relapses, which is a clinical measure of disease activity, can provide relevant information

Table 2
Estimates of association between interferon-beta/glatiramer acetate and the clinical outcomes of MS (main analysis), imputed data, Montreal, Canada, 1977–2016.

	Hazard Ratio [95% Confidence Interval][a]		Rate Ratio [95% Confidence Interval][b]	
	Progression to irreversible disability (EDSS ≥ 6 and EDSS < 10)	Transition to SPMS	Rate of relapses	
Use of interferon-beta/glatiramer within 3 months				
Untreated	REF	REF	REF	
Treated	**0.73 [0.57–0.94]**	1.00 [0.73–1.37]	0.97 [0.87–1.09]	
Cumulative duration of treatment				
0 year	REF	REF	REF	
≤2 years	1.00 [0.74–1.35]	0.84 [0.55–1.29]	0.96 [0.84–1.09]	
>2 to 5 years	0.95 [0.70–1.28]	0.98 [0.66–1.48]	0.82 [0.56–1.21]	
> 5 years	0.81 [0.54–1.21]	1.21 [0.73–1.99]	**0.70 [0.57–0.86]**	

EDSS, Expanded disability status scale.

[a] Estimated from pooled logistic regression model with propensity scores for treatment and censoring.

[b] Estimated from pooled Poisson regression model with propensity scores for treatment and censoring.

regarding disease severity. Moreover, the use of different outcomes related to MS course and progression allows for a more holistic evaluation of the effectiveness of the treatment.

To make a causal interpretation, assumptions such as conditional exchangeability, positivity, consistency, and accurate specification of the model should be respected. The associations of interest between interferon-beta/glatiramer acetate and the outcomes of MS were estimated on a dataset for which the distribution of potential confounders was balanced between the exposed and unexposed, reducing the likelihood of confounding. Although we controlled for many potential confounders such as number of relapses in the past 3 months, EDSS in the past 3 months, we did not have information on variables related to magnetic resonance imaging and neutralizing antibodies which can lead to residual confounding. Practical positivity can be violated due to small sample sizes in some intervals (Hernan and Robins, 2020). For this analysis, we considered people treated with interferon-beta/glatiramer acetate in the past 3 months versus those without medication in the past 3 months and, from our perspective, the exposure is well-defined. Finally, we assume that the weights were correctly specified (Cole and Hernan, 2008).

Additional limitations should be acknowledged. Since the variables have been collected in the context of clinical monitoring, they can be subject to a lack of accuracy. Relapses were assessed by clinicians based on information reported by patients. Due to the high heterogeneity in patient population, potential misclassification bias can be introduced in the study. Despite the long follow-up, the number of progressions to irreversible disability or transitions to SPMS were low, although in line with previous reports (Barzegar et al., 2020; Gross and Watson, 2017). A low number of events may lead to imprecise results. In addition, the fact that there is a long time between the onset of MS and progression to irreversible disability may affect our ability to detect differences in disability outcomes. Finally, there were some missing values for the variables related to EDSS. We used multiple imputations for the confounders; however, we did not impute progression to irreversible disability. We compared the distribution of imputed variables to those excluding the missing values and they were almost the same (Figure S4).

In conclusion, the effect of the use of interferon-beta/glatiramer acetate differed depending on the outcome used. To our knowledge, this is the first study to examine the effect of two immunomodulatory drugs on disease activity and MS progression. These results highlight the importance of considering multiple outcomes relevant to MS when assessing the long-term effect of immunomodulatory drugs and provide real-life evidence on the effect of these treatments.

CRediT authorship contribution statement

Miceline Mésidor: Conceptualization, Methodology, Formal analysis, Software, Visualization, Writing - original draft, Writing - review & editing. **Marie-Pierre Sylvestre:** Conceptualization, Methodology, Supervision, Validation, Writing - review & editing. **Marie-Claude Rousseau:** Conceptualization, Methodology, Supervision, Validation, Writing - review & editing. **Elaine Roger:** Conceptualization, Writing - review & editing. **Pierre Duquette:** Conceptualization, Investigation, Project administration, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103050.

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