Multiple Sclerosis and Related Disorders 8 (2016) 78–85

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Adherence and persistence to drug therapies for multiple sclerosis: A population-based study

Charity Evans [a,*], Ruth Ann Marrie [b], Feng Zhu [c], Stella Leung [d], Xinya Lu [e], Dessalegn Y. Melesse [d], Elaine Kingwell [c], Yinshan Zhao [c], Helen Tremlett [c]

[a] College of Pharmacy & Nutrition, University of Saskatchewan, 104 Clinic Place, Saskatoon, SK S7N 5E5, Canada
[b] Departments of Internal Medicine and Community Health Sciences, University of Manitoba, Health Sciences Centre, GF 543-820 Sherbrook Street, Winnipeg, MB, Canada R3A 1R9
[c] Department of Medicine (Neurology), University of British Columbia, UBC Hospital, 2211 Wesbrook Mall, Vancouver, BC, Canada V6T 2B5
[d] Department of Community Health Sciences, University of Manitoba, Health Sciences Centre, GF 543-820 Sherbrook Street, Winnipeg, MB, Canada R3A 1R9
[e] Saskatchewan Health Quality Council, 241-111 Research Drive, Saskatoon, SK, Canada S7N 3R2

ARTICLE INFO

Article history:
Received 4 December 2015
Received in revised form
1 February 2016
Accepted 4 May 2016

Keywords:
Multiple sclerosis
Disease-modifying therapies
Medication adherence
Medication persistence

ABSTRACT

Objective: We aimed to estimate the prevalence and predictors of optimal adherence and persistence to the disease-modifying therapies (DMT) for multiple sclerosis (MS) in 3 Canadian provinces.
Methods: We used population-based administrative databases in British Columbia (BC), Saskatchewan, and Manitoba. All individuals receiving DMT (interferon-B-1b, interferon-B-1a, and glatiramer acetate) between 1-January-1996 and 31-December-2011 (BC), 31-March-2014 (Saskatchewan), or 31-March-2012 (Manitoba) were included. One-year adherence was estimated using the proportion of days covered (PDC). Persistence was defined as time to DMT discontinuation. Regression models were used to assess predictors of adherence and persistence; results were pooled using random effects meta-analysis.
Results: 4830 individuals were included. When results were combined, an estimated 76.4% (95% CI: 69.1–82.4%) of subjects exhibited optimal adherence (PDC $\geq$80%). Median time to discontinuation of the initial DMT was 1.9 years (95% CI: 1.6–2.1) in Manitoba, 2.8 years (95% CI: 2.5–3.0) in BC, and 4.0 years (95% CI: 3.5–4.6) in Saskatchewan. Age, sex and socioeconomic status were not associated with adherence or persistence. Individuals who had $\geq$4 physician visits during the year prior to the first DMT dispensation were more likely to exhibit optimal adherence compared to those with fewer (0–3) physician visits.
Conclusions: We observed adherence that is higher than what has been reported for other chronic diseases, and other non-population-based MS cohorts. Closer examination as to why adherence appears to be relatively better in MS and how adherence influences disease outcomes could contribute to our understanding of MS, and prove useful in the management of other chronic diseases.

1. Introduction

The therapeutic options for managing multiple sclerosis (MS) have grown considerably over the past 20 years, with several disease-modifying therapies (DMT) now available. While efficacy rates vary between agents, the DMTs all reduce disease activity to some extent (Filippini et al., 2003; PRISMS, 1998; Jacobs et al., 1996; The IFNB Multiple Sclerosis Study Group, 1993). However, even the most efficacious DMT will have limited effectiveness if adherence to the prescribed treatment is poor.

Adherence to drug therapies for many chronic conditions is estimated at only 50% (World Health Organization, 2003; Osterberg and Blaschke, 2005), and non-adherence has been associated with increased morbidity, mortality, and health care costs (World Health Organization, 2003; Osterberg and Blaschke, 2005; Simpson et al., 2006). While slightly higher adherence rates have been reported in MS, most studies have evaluated small, non-population-based cohorts, with varying definitions for adherence, and relied on self-reported outcomes over short observation periods, which limits the applicability of the results (Menzin et al., 2013). Findings regarding the factors associated with levels of adherence, including age, sex, socioeconomic status, and comorbidity have been inconsistent, therefore it is unknown whether these factors

* Corresponding author.
E-mail addresses: charity.evans@usask.ca (C. Evans), rmarrie@hsc.mb.ca (R.A. Marrie), f.zhu@stat.ubc.ca (F. Zhu), stellaleung1@gmail.com (S. Leung), xlu@hqc.sk.ca (X. Lu), desyiz@gmail.com (D.Y. Melesse), elainejk@mail.ubc.ca (E. Kingwell), yinshan@msmri.medicine.ubc.ca (Y. Zhao), helen.tremlett@ubc.ca (H. Tremlett).

http://dx.doi.org/10.1016/j.msard.2016.05.006

play a role in adherence to the DMTs for MS. Better knowledge of factors influencing adherence is important for clinicians and patients.

We aimed to estimate the level of adherence to first-line DMTs, and to identify factors associated with optimal adherence using population-based data from three Canadian provinces.

2. Materials and methods

2.1. Data sources

We used population-based health administrative data from British Columbia (BC), Saskatchewan (SK), and Manitoba (MB). Each province maintains its own health services databases and population registry that are linkable using anonymized unique identifiers. Although maintained separately, these databases all contain information on hospital separations (Canadian Institute for Health Information creator, 2012), physician services (British Columbia Ministry of Health creator, 2012), prescription drug dispensations (BC Ministry of Health creator, 2012), vital status, and residency (British Columbia Ministry of Health creator, 2012). Almost the entire population in each province (BC, 4.6 million; SK, 1.1 million; MB, 1.3 million) is captured, with the exception of member of the armed forces, Royal Canadian Mounted Police, and federal penitentiary inmates. Prescription costs for registered First Nations patients ($<10\%$ of the population) are paid for by another government agency, and were only captured by the prescription databases for part of the study period. These databases have been successfully accessed to investigate medication adherence and persistence in other chronic diseases (Ediger et al., 2009; Evans et al., 2012; Dormuth et al., 2009). Ethics approval was granted by the governing Research Ethics Boards in each province, and approval for administrative data access was provided by the relevant provincial data steward.

2.2. Study cohort

The study period varied between provinces due to data availability. It began on January 1, 1996 in all provinces and ended either December 31, 2011 (British Columbia), March 31, 2014 (Saskatchewan) or March 31, 2012 (Manitoba). All subjects who received a prescription dispensation for a first-line DMT (beta-interferon-1b, beta-interferon-1a, glatiramer acetate) during their respective study period were eligible for inclusion. Natalizumab is second-line therapy in Canada, and due to small numbers was not included in the analyses. Oral therapies were also not included as the study preceded their approval in Canada.

Individual subjects were followed from their index date (first dispensation of a DMT) until their exit date of death, loss of beneficiary status, or the end of the study period, whichever came first. Because women are advised to discontinue DMT three months before conception, women with a delivery diagnosis code (International Classification of Disease [ICD]-9/10 codes 630-679 and O00-O99) were censored one year before their delivery date or at their exit date if it fell within this one year period. All subjects had to have at least one year of follow-up before and after their index date. No other formal exclusion criteria were applied. However, as only those subjects with relapsing-onset MS are eligible to receive coverage for a DMT in these provinces, subjects with a primary progressive disease course would, by definition, be excluded. The first DMT was approved for use in Canada in mid-1995, but did not receive provincial formulary coverage for another 1–2 years (depending on the province). This means that virtually all included subjects were incident users (i.e. had not received a DMT prior to their index date). This, combined with similar prescribing criteria across the three provinces (Appendix e-A), allows for baseline comparability of the subjects.

2.3. Study outcomes

The primary outcome was the proportion of patients achieving optimal adherence at one year. Adherence was estimated using the proportion of days covered (PDC), one of the most commonly used measures employed with administrative data (Ho et al., 2009). It provides a more conservative measure of adherence, and has been recommended when measuring adherence to a class of medications (Horne et al., 2013). The PDC was calculated by dividing the number of days of DMT supplied by the number of days of observation (Ho et al., 2009; Martin et al., 2009). A PDC $\geq 80\%$ was considered optimal. The 80% threshold is widely used in adherence research, and has been associated with fewer hospitalizations and decreased mortality (Osterberg and Blaschke, 2005; Simpson et al., 2006; Karve et al., 2009). To be comparable with other studies, we estimated the proportion of subjects with optimal adherence over their entire study period (i.e. index to exit date) as a sensitivity analysis. We also examined patterns of DMT persistence, including the median time to discontinuation of the initial and any DMT, and the proportion of subjects who discontinued their DMT within the first 6, and 12 months of therapy. A discontinuation of any DMT was defined as a >90-day interruption in treatment. A discontinuation of the initial DMT was defined as more than 90 days of treatment interruption or a switch to another first- or second-line (natalizumab, fingolimod) DMT.

2.4. Statistical analysis

We described the demographic and clinical characteristics of subjects at the index date using frequencies, means, and standard deviations. We used multivariable logistic regression to examine the association between optimal adherence and the following covariates: age (continuous variable), sex, initial DMT dispensed, index year (1996–1998, 1999–2000, 2001–2002, 2003–2005, 2006–2008, 2009-study end), and socioeconomic status in quintiles. Socioeconomic status was estimated by linking the first 3 postal code digits to Canadian census data to determine median household income for the residential area. We also included the number of physician visits, hospitalizations and non-MS medication classes (using the Anatomical Therapeutic Chemical classification at the fourth level) in the one year before the index date as a proxy measure of health care utilization, comorbidity, and "pill burden". Covariates were selected based on statistical significance, clinical relevance or both. The time to DMT discontinuation was estimated using Kaplan-Meier survival analysis; Cox regression was used to identify any associations between the above covariates and DMT discontinuation. Multivariable logistic regression was also used to examine the association between the covariates and DMT discontinuation within 6, and 12 months of DMT initiation.

Analyses were conducted separately in each province and combined using random effects meta-analysis. Random effects models were chosen, because tests for heterogeneity (I^2 test) suggested moderate (25–50%) to high ($>75\%$) levels of heterogeneity between the outcome data from the 3 provinces (Higgins et al., 2003). Statistical analyses were performed using SAS (Enterprise Guide 4.3), and R (Version 3.1.0).

3. Results

A total of 4830 subjects were included in the analyses (BC, $n=2323$; SK, $n=1297$; MB, $n=1210$). At the index date, the mean age was 40.4 years (SD 10.0), and 75.8% were female. Most subjects