Impact of Adherence with Disease-Modifying Therapies on All-Cause Mortality Rates Among Veterans with Multiple Sclerosis

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Background: Adherence to disease-modifying therapies (DMTs) is essential for reducing multiple sclerosis (MS)-related relapses and disability. However, no known data exist regarding rates of adherence to DMTs and their impact on mortality. The present study aimed to determine the effect of adherence to DMTs on all-cause mortality in patients with MS in a real-world setting.

Material/Methods: We reviewed electronic records of 279 patients with MS and followed them longitudinally in our MS clinic between January 1, 2000 and December 31, 2019. The inclusion criteria were complete electronic records along with documentation of initial and final functional outcome measures, including mortality. The exclusion criteria were incomplete electronic records and lack of documentation of initial and final functional outcome measures.

Results: Of 279 patients with MS, 148 (53.0%) were non-adherent to any DMT medication(s). Of the 131 (47.0%) MS patients who were adherent, 13 (4.7%) had poor adherence and 118 (42.3%) had good adherence. More patients in the good-adherence group survived (94.9%) compared to the non-adherence group (66.9%, P < 0.001). The odds of being alive were 12 times higher among those who adhered to their DMT compared to those who did not.

Conclusions: This study indicates that veterans who adhere to their DMTs are 12 times more likely to be alive than those who are non-adherent, even after adjusting for variables known to affect S-related mortality such as age at entry, MS type, MS duration, body mass index, and diabetes.

Keywords: Multiple Sclerosis • Veterans • Medication Adherence • Mortality

Abbreviations: 2-MWT – 2-minute walk test; ANOVA – analysis of variance; BMI – body mass index; DM – diabetes mellitus; DMTs – disease-modifying therapies; EDSS – Expanded Disability Severity Scale; MMSE – Mini-Mental State Examination; MPR – medication possession ratio; MS – multiple sclerosis; MRC – Medical Research Council; MRI – magnetic resonance imaging; PP – primary-progressive; RR – relapsing-remitting; SP – secondary progressive; TFIM – total functional independence measure

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Background

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that mainly affects young adults, with the highest incidence at ages 20-40 years, and it follows a variable course. Its etiology is multifactorial, with both genetic susceptibility and environmental exposure contributing to its pathogenesis [1]. MS remains an incurable disease, hence treatments designed to modify disease progression or alleviate symptoms using disease-modifying therapies (DMTs) are essential. Maintaining adherence to DMTs to help derive the maximum possible clinical benefit and reduce substantial disability is challenging [2].

Adherence describes the extent to which a patient acts in accordance with the timing, dosing, and frequency of medication prescribed by a physician who has prescribed a DMT. This study uses the term “adherence” rather than “compliance” because adherence better reflects the action required of the patient and avoids judgmental connotations associated with the term “noncompliance” [3]. Patients have found it challenging to maintain long-term adherence to therapies for chronic medical conditions [4]. Published estimates of adherence among patients with relapsing-remitting MS from clinical trials vary between 41% and 88% depending on the study’s definition of adherence [5-8]. Adherence rates reported in clinical trials for different injectable DMTs vary from 79% to 85% for once-weekly interferon beta-1a (IM IFNb-1a) to 49-78% for other injectable DMTs [4]. Poor adherence has been associated with worsening morbidity, increased health care cost, and increased mortality [9].

MS carries a high morbidity and shortens lifespan by 6-10 years despite advances in MS-specific treatment and in treatments for its co-morbidities [10,11]. Amezgua et al studied patients with MS in the United States from 1999 to 2015 and found that mortality increased with age in both sexes and in both non-Hispanic Whites and Blacks, peaking at 55-64 years for Blacks and 65-74 years for Whites, with White females being the most affected [12].

Our previous study of 226 veterans with MS reported a mortality of 14% at the end of the 15-year period. Patients with MS died prematurely, with a standardized mortality ratio (SMR) of 1.35 relative to the general (Oklahoma) population [13]. The main causes of death documented were MS disease (57% of cases), infection (43%), and cancer and respiratory failure (18% each). Similarly, in their study of patients with MS in British Columbia, Canada, Kingwell et al [14] found a high SMR of 2.71, with MS being the underlying cause in 50.4% cases, followed by infection (genitourinary, respiratory, and septicemia), respiratory diseases, and suicide. Thorman et al [15], in their study of patients with MS in Denmark between 1980 and 2005, found that MS-related mortality was higher in MS patients with stroke, Parkinson’s disease, cardiovascular disease, lung cancer, cancer, and diabetic co-morbidities.

Previous studies of adherence in patients with MS have covered relatively brief time periods [16], have been retrospective [17,18], or have focused on patients in clinical trials [19] whose experience differs from patients in many real-world clinical practices. Since our previous study in military veterans with MS followed in the MS clinic at the Oklahoma City Veterans Affairs Medical Center (VAMC) showed effective management of co-morbidities to reduce all-cause mortality over time [13], the aim of the present study was to compare the effect of adherence vs non-adherence to DMTs on all-cause mortality in veterans with MS. The results of the present study will help guide neurologists taking care of patients with MS to actively encourage adherence to DMTs to reduce MS-related mortality.

Material and Methods

Participants

This study was approved by our local Institution Review Board, and they determined that the study was exempt from patient informed consent. In this observational study we reviewed the electronic records of 279 veterans who were diagnosed with MS (using the McDonald criteria) [20] and followed longitudinally in our MS clinic between January 1, 2000 and December 31, 2019. The MS clinic has a structured approach in which all patients with MS on initial and yearly clinical evaluation undergo neuroimaging and blood tests for complete blood count for lymphocyte count, blood chemistry for renal and liver functions, vitamin D level [25-Hydroxy], and JVC antibody titers.

Eligibility Criteria

The inclusion criteria were complete electronic records of veterans with MS who were regularly followed-up in our MS clinic with documentation of both initial and final functional outcome measures including mortality. Exclusion criteria were incomplete electronic records and lack of documentation of initial and final functional outcome measures plus mortality.

Study Design: Single-Center

Data collected included demographic and clinical measures (age, gender, race, height, weight), MS status, age at MS onset, clinical MS subtype (relapsing-remitting [RR], secondary-progressive [SP], and primary-progressive [PP]) MS [21], duration of the disease, initial documented cognition (Mini-Mental Status Examination [MMSE]), presence of co-morbidities (hypertension, hyperlipidemia, diabetes mellitus, hypothyroidism,
current smoking habit, alcohol use), and presence of MS-related complications (fatigue, depression). These comorbidities are the most common causes of disability and death in the general US population [22]. MS-related severity and disability was measured using the Expanded Disability Severity (EDSS) [23] and Total Function Independence Measures (TFIM) scales [24]. This study conforms to all STROBE guidelines and reports the required information accordingly (see Supplementary Checklist).

**Intervention(s) or Treatment**

We classified adherence to DMT use as (1) non-adherence, (2) poor adherence, and (3) good adherence. Investigators made the classification after verbally inquiring about each individual’s DMT use during face-to-face interactions and subjectively examining injection sites as indicated during follow-up visits. Information gathered from interviews and injection site examination was cross-checked with data on prescription refills in electronic medical records from our facility’s pharmacy, which is the sole dispenser of DMT medications for our veterans with MS. Switching between different DMTs (oral, injections, and infusions) was allowed.

We judged veterans to be non-adherent if they initially took but then stopped taking the prescribed DMTs or if they refused to take the prescribed DMTs to begin with due to adverse effects, because they perceived lack of effect on disease progression, or because they believed their disease was stable or improving. Veterans were categorized as demonstrating poor adherence if they took their prescribed DMT infrequently either because they were forgetful (cognitive impairment) or depressed. We considered veterans to show good adherence if they took their DMT regularly as prescribed.

We validated their categorization of adherence by calculating the medication possession ratio (MPR) using pharmacy refill data. The MPR was calculated as the sum of the day’s supply obtained between the first and last pharmacy refill divided by the total number of days over a 1-year period. This clinical definition was supported by an MPR cut score of <0.8 equals non-adherence, 0.8-0.9 equals poor adherence, and greater than 0.9-1.0 equals good adherence [25].

**Assessment of Mortality**

Deaths were ascertained for all patients with MS who were followed-up in our clinic at any time over the 20-year study period. Causes, dates, and locations of death (home, long-term care facility, or hospital) were obtained from information provided to our clinic coordinator or social worker by the patient’s care provider or next of kin, and from death certificates filed with the Oklahoma State Department of Health.

**Statistical Analysis**

1. The 2 groups defined by the outcome of interest – mortality – were described using means and standard deviations (SD) for continuous variables and using counts and percentages for categorical variables. Continuous variables were compared between the 2 groups using the analysis of variance (ANOVA) F-test or Kruskal-Wallis test, depending on data normality of distribution. Categorical variables were compared using the chi-squared test or Fisher’s exact test.

2. Trends in mortality among the 3 groups defined by adherence were assessed using the Cochran-Armitage test.

3. Survivorship among the 3 adherence groups was compared using Kaplan-Meier analysis and in a Cox proportional hazards regression model that adjusted for other covariates, including age at entry, MS type and duration, body mass index (BMI), and diabetes mellitus (DM). The proportional hazard assumption of the Cox model was examined by testing the added interaction term between predictors and time. Non-significant testing indicated no violation of this assumption.

Statistical significance was defined as a P value <0.05 using two-tailed analysis. No multiple comparison adjustment was conducted because of the very small number of multiple comparisons. Statistical analyses were performed using the R packages (v3.5.3 Vienna, Austria).

**Results**

Of the 279 patients with MS, 148 (53.0%) were non-adherent to any DMT medications, 131 (47.0%) were adherent, 13 (4.7%) had poor adherence, and 118 (42.3%) had good adherence. Of the 279 patients with MS who were followed over the 20-year study period, 223 were alive (79.9%) and 56 were dead (20.1%). Those who had died and those who remained alive differed at the time of initial presentation in terms of age of entry in years, duration of MS in years, MS type, MS-related impairment, DMT use, EDSS and TFIM scores, hypertension, DM, and BMI (Table 1).

Table 2 compares the primary outcome – mortality – among the 3 groups defined by adherence to DMTs. Of the 148 non-adherent patients, 99 (66.9%) were alive and 49 (33.1%) were dead compared to 112 of the 118 (94.9%) adherent patients who were alive and 6 (5.1%) who were dead (P<0.001). Of the 13 patients who demonstrated poor adherence 12 (92.3%) were alive and 1 (7.7%) died. The Cochran-Armitage test indicated a trend of decreasing mortality among the groups defined by adherence (non-, poor-, or good; P=1.23e-8). Thus, more patients in the good-adherence group survived (94.9%) than in the non-adherent group (66.9%, P<0.001). The unadjusted odds of being alive for an adherent patient (either poor or good adherence) was 12 times that of a non-adherent patient. Kaplan-Meier
**Table 1.** Demographics based on multiple sclerosis survival (dichotomized).

|                         | Alive (n=223) | Dead (n=56) | p-value      |
|-------------------------|---------------|-------------|--------------|
| **Age @ entry (years)** | Mean (SD)     |             | <0.001       |
| Mean (SD)               | 49.3 (12.2)   | 61.9 (10.0) |              |
| **Duration of MS (years)** | Mean (SD)     |             | <0.001       |
| Mean (SD)               | 21.4 (12.3)   | 34.6 (13.3) |              |
| <10                     | 17 (15.4%)    | 1 (1.9%)    | <0.001       |
| ≥10 and ≤19             | 73 (33.0%)    | 5 (9.2%)    |              |
| ≥20                     | 114 (51.6%)   | 48 (88.9%)  |              |
| **Time in study (years)** | Mean (SD)     |             | <0.001       |
| Mean (SD)               | 8.15 (3.57)   | 12.2 (3.36) |              |
| **MS type**             |               |             |              |
| Relapsing remitting     | 107 (48.9%)   | 8 (15.1%)   | <0.001       |
| Progressive (primary and secondary) | 78 (35.6%) | 42 (79.2%) |              |
| Other (CIS RIS)         | 30 (13.7%)    | 1 (1.9%)    |              |
| Unclassified category   | 4 (1.8%)      | 2 (3.8%)    |              |
| **Initial MMSE Mean (SD)** |             |             | 0.104        |
| Mean (SD)               | 27.5 (3.13)   | 25.6 (8.04) |              |
| **EDSS Mean (SD)**      | 3.57 (2.81)   | 6.73 (2.18) | <0.001       |
| 0-3                     | 120 (55.8%)   | 3 (7.1%)    | <0.001       |
| 3.5-6                   | 49 (22.8%)    | 8 (16.3%)   |              |
| ≥6                      | 46 (21.4%)    | 31 (73.8%)  |              |
| **Initial TFIM Mean (SD)** |             |             | <0.001       |
| Mean (SD)               | 110 (21.1)    | 81.4 (29.6) |              |
| **Hypertension (yes)**  | 102 (48.6%)   | 38 (70.4%)  | 0.006        |
| **Diabetes mellitus (yes)** | 30 (14.2%) | 19 (35.2%) |              |
| **Body mass index Mean (SD)** | 28.4 (5.27) | 25.7 (7.49) | 0.018        |
| **Depression (yes)**    | 142 (64.8%)   | 33 (60.0%)  | 0.532        |
| **Fatigue (yes)**       | 142 (66.4%)   | 35 (81.4%)  | 0.07         |
| **DMT**                 |               |             |              |
| Infusion                | 17 (7.6%)     | 1 (1.8%)    | <0.001       |
| Injectables             | 41 (18.4%)    | 5 (8.9%)    |              |
| Never/none/other        | 99 (44.4%)    | 50 (89.3%)  |              |
| Oral                    | 66 (29.6%)    | 0 (0%)      |              |

DMT – disease modifying therapies; MS – multiple sclerosis; MMSE – Mini-Mental State Examination; TFIM – Total Functional Independence Measure; EDSS – Expanded Disability Scale Score.

**Table 2.** Comparison of mortality in groups defined by adherence to disease-modifying therapies.

| Survival   | Overall (n=279) | Non-adherent (n=148) | Poor-adherence (n=13) | Good-adherence (n=118) | P-value |
|------------|-----------------|-----------------------|-----------------------|------------------------|---------|
| Alive      | 223 (79.9%)     | 99 (66.9%)            | 12 (92.3%)            | 112 (94.9%)            | 0.066   |
| Dead       | 56 (20.1%)      | 49 (33.1%)            | 1 (7.7%)              | 6 (5.1%)               | 0.001   |

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analysis estimated that the overall median survival time for all patients was 39 years (95% CI [33,50]) (Figure 1). The overall 10- and 20-year survival rates were 97.5% and 86.4%, respectively. The median survival time was 35 years (95% CI [30,41]) for non-adherent patients and 52 years (95% CI [38, NA]) for patients with good adherence. There was only 1 death in the poor-adherence group, with a survival time of 62 years.

A Cox proportional hazards model was fit for the groups with good adherence and non-adherence. The 13 patients with poor adherence were excluded from the analysis. The model included covariates known to affect MS-related survival, which included age at entry, MS type and duration, BMI, and DM. After adjustment, the risk of death in the non-adherence group was 7.5 times (95% CI [2.71, 20.5], P<0.001) higher than in the good-adherence group, and there was no violation of the proportional hazard assumption, with global test and per-predictor test P values greater than 0.05.

When we performed a subset analysis of primary outcome measure between the groups only for patients with RRMS, there were 44 non-adherent patients; 37 (84.1%) were alive and 7 (15.9%) were dead compared to 60 of the 61 (98.4%) adherent patients who were alive and 1 (1.6%) who died. All 10 patients who demonstrated poor adherence survived. The Cochran-Armitage test indicated a significant association between the trend of non-/poor/good adherence and mortality (P=0.005) (Table 3).

**Table 3.** Comparison of mortality in groups defined by adherence to disease-modifying therapies only for patients with relapsing-remitting multiple sclerosis.

| Survival | Overall (n=115) | Non-adherent (n=44) | Poor-adherence (n=10) | Good-adherence (n=61) | P-value Non vs poor | Non vs good | Good vs poor |
|----------|---------------|---------------------|-----------------------|----------------------|-------------------|------------|------------|
| Alive    | 107 (79.9%)   | 37 (84.1%)          | 10 (100%)             | 60 (98.4%)           | 0.326             | 0.01       | 1          |
| Dead     | 8 (20.1%)     | 7 (15.9%)           | 0 (0%)                | 1 (1.6%)             |                   |            |            |

**Discussion**

The main findings of this study in veterans with MS who were regularly followed (longitudinally) over our clinic’s 20-year history were as follows: (1) 53.0% of veterans with MS were non-adherent to their DMT medications; (2) mortality among the veterans was 20.1%; (3) veterans who were adherent to their DMT medications were 12 times more likely to be alive than veterans who were non-adherent to their DMT medications; (4) veterans with MS were more likely to be alive if they began attending the clinic when younger (<30 years), were men, whose duration of MS was less than 10 years, whose diagnosis was RRMS, who were not cognitively impaired, whose MS was less severe (initial EDSS score 0-3), and who initially had less functional disability (higher TFIM score).

The reasons why 53.0% of veterans were non-adherent to DMT medication included: perceived lack of beneficial effect on the disease; adverse effects of medication, especially injection site reactions and depression; and complaints of having to take the DMT over a prolonged period. Of the veterans who took their DMT as prescribed, 9.9% (13/131) had poor adherence due to forgetfulness or depression. Other investigators have found similar rates of non-adherence (30-50%) among adults with chronic illnesses such as diabetes or hypertension [26]. Over the last 15 years, although several studies have been conducted to improve rates of medication adherence, the rate of medication non-adherence has not appreciably changed [26].

Although there is no information in the literature regarding adherence to DMTs and mortality in a clinical setting, Goodin et al [27] in their cohort of 372 patients who participated in the pivotal randomized clinical trial (RCT) of interferon beta (IFNβ)-1b on
all-cause mortality over a 21-year period showed patients as-
signed to IFNβ-1b 250 μg had a 46% reduction in all-cause mor-
tality compared with placebo (P=0.0173). Similarly, Kingwell et al, in their multi-center population-based observational study in British Columbia, Canada (1980-2004) and Rennes, France (1976-2013) found a 32% reduction in mortality in MS patients on interferon beta (IFNβ)-1b treatment compared to controls [28]. Our study showed a 28% decrease in mortality in MS patients adherent to their prescribed DMTs. Our study differs from the above-mentioned studies in that: (1) it was not randomized or population-based, and (2) these studies looked solely at the ef-
cacy of (IFNβ)-1b use and no other prescribed DMTs.

Despite these limitations, this study has certain strengths. All the patients in the electronic database of the MS registry were included. Thus, the data were standardized and complete, and reflected regular follow-up at 4, 8, and 12 months. The data collected over a 20-year period included hospital pharmacy pre-
scription and dispensing data, which permitted validation of adherence to DMTs. These factors limit the potential for selec-
tion and recall biases [29] and reflect real-world clinical practice.

Based on the study results, we hope to add a clinical pharma-
cist to our MS team to co-manage (including education, in-
creased frequency of disease monitoring via telephone or in-
person follow-up visits, and refill reminders) in addition to our present ongoing effort of patient and family (caregiver) edu-
cation (eg, recurrent and personalized telephone counseling sessions) and medication regimen management (to reduce the frequency of taking the medication on a daily to weekly basis) and further help improve the adherence rate.

Conclusions

This study indicates that veterans who adhere to their DMTs are 12 times more likely to be alive than non-adherent groups, even after adjusting for age at entry, MS type, MS duration, BMI, and DM, which are variables known to affect MS-related mortality.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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