Rates of Early Treatment for US Veterans With Multiple Sclerosis

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Yan Xie, PhD¹, Joanne LaFleur, PharmD, MSPH^{2,3},
Aaron Kamaau, MD, MPH, MS⁴, Kristin Knippenberg, MFA^{2,3},
Scott L. DuVall, PhD^{2,3,5}, Jodie Haselkorn, MD^{6,7}, and Richard E. Nelson, PhD^{2,5}

Abstract

Background: Early treatment of patients with multiple sclerosis (MS) may prevent neurological damage and reduce the risk of disability. However, little is known about the timing of treatment initiation following diagnosis and long-term outcomes in the general population of the Department of Veterans Affairs (VA) benefits-eligible patients. **Objective:** Our objective was to characterize treatment for MS patients in the VA at various time points following diagnosis date. **Methods:** In our historical database cohort study of US veterans, we calculated the proportion of MS patients from 1999 through 2010 with at least one prescription for a medication used to treat the condition at 6, 12, 24, 36, 48, 60, and 72 months following the index date. We also stratified the treatments given into 3 categories based on their role within the course of the disease: disease modifying, relapse, and symptom. Finally, we performed our calculations separately by MS subtype: relapsing-remitting, secondary-progressive, primary-progressive, and progressive-relapsing. **Results:** A total of 6803 patients were included in the analysis. Only 27.4% of MS patients received a prescription for MS medication within the first 6 months after diagnosis. The most common treatments were interferon β -1a, glatiramer, amantadine, and prednisone, with disease-modifying agents being more than twice as frequently prescribed as medications for relapse or symptoms. Patients with relapsing-remitting MS were the most likely to be treated, followed by progressive-relapsing MS. **Conclusions:** Our results suggest that treatment rates are low in VA MS patients in the 6 years following their first diagnosis of MS.

Keywords

multiple sclerosis, treatment, veterans, epidemiology, immunosuppressants, databases, corticosteroids, interferons

Introduction

Multiple sclerosis (MS), characterized by autoimmune-mediated demyelination of the central nervous system, is estimated to affect nearly 400 000 individuals in the United States.¹ There is no known cure for MS, but treatment with a number of different classes of drugs, such as β -interferons, glucocorticoids, immunostimulants, and immunosuppressants, may slow the disease and help patients maintain a more normal quality of life.² Current treatment guidelines for MS from the American Academy of Neurology address use of specific drugs, but do not include comprehensive treatment protocols or benchmarks.^{3–5} Historically, patients initiated treatment for MS only after 2 separate clinical events, typically neurological symptoms such as limb weakness or blurred vision.⁶ Recent validation of the McDonald criteria in 2010, employing magnetic resonance imaging, has shortened the time from initial clinical event to diagnosis⁷ and, presumably, from diagnosis to treatment. The timing of treatment initiation is neither codified in US guidelines nor standardized across US patient populations,

in part because the benefits versus the risks of treatment initiation are assumed to vary from patient to patient.⁸ However, accumulating research has found that permanent damage occurs very early in MS,⁹ and early MS treatment can have a significant impact on the development of disability.^{10–15}

In the absence of more unified guidelines, it is important to know whether early treatment of MS is a regular occurrence in various US patient populations. One patient

¹Abbvie, Inc, North Chicago, IL, USA

²Salt Lake City Veterans Affairs Health Care System, Salt Lake City, UT, USA

³University of Utah College of Pharmacy, Salt Lake City, UT, USA

⁴Anolinx, LLC, Salt Lake City, UT, USA

⁵University of Utah School of Medicine, Salt Lake City, UT, USA

⁶Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA

⁷University of Washington School of Public Health, Seattle, WA, USA

Corresponding Author:

Richard E. Nelson, 500 Foothill Blvd, Salt Lake City, UT 84148, USA.
Email: richard.nelson@utah.edu

population for which this can be easily determined is US veterans. We found no historical cohort studies utilizing Department of Veterans Affairs (VA) databases to investigate system-wide treatment patterns of veterans with MS. Nonetheless, 2 database studies utilizing the North American Research Committee on Multiple Sclerosis (NARCOMS) database compared veterans with MS and nonveterans with MS. Both studies determined that access to care is comparable between veterans and nonveterans, but that veterans are less likely to use disease-modifying agents.^{16,17} The VA's Multiple Sclerosis Centers of Excellence, utilizing the Multiple Sclerosis National Data Repository, have also conducted numerous epidemiologic studies on varying aspects of veteran MS patient treatment,¹⁸⁻²² most involving surveys of willing participants, rather than system-wide database studies of all patients.

The objective of this study was to characterize historical treatment trends for patients with MS in the VA at various time points following diagnosis date using data from the VA electronic medical record (EMR).

Methods

This study used data from the national VA healthcare system. We identified adult patients within the VA system with a diagnosis of MS (ICD-9-CM code 340) on at least 2 occurrences from 1999 through 2010. The index date was defined as the first MS diagnosis date. Although MS can change subtype as it progresses (eg, relapsing-remitting to secondary progressive), we focused on the first diagnosis. To ensure that included patients were MS treatment naïve and were in the habit of receiving regular care at the VA, those without encounters 180 days or more before the index date and without at least 180 days of follow-up time after the index date were excluded. Patients with the ICD-9-CM code 341 (other demyelinating disease) during the study period were also excluded.

We calculated the proportion of patients in our cohort with at least one prescription for a medication used to treat MS at 6, 12, 24, 36, 48, 60, and 72 months following the index date. In order to ensure that our estimates for the percentage of patients with prescriptions were not artificially lowered due to patients not being active in the VA system or being administratively censored, patients were removed from the denominator for these calculations on the date of their last recorded encounter in the VA.

The medications included in our study were the following: amantadine, glatiramer, interferon β -1a, oral methylprednisolone, modafinil, prednisone, and all others (which included azathioprine, corticotropin, cyclophosphamide, dalfampridine, dexamethasone, fingolimod, interferon β -1b, intravenous [IV] methylprednisolone, IV corticosteroids, mitoxantrone, natalizumab, prednisolone, and valacyclovir). Medications grouped into the "other" category were those

for which few patients (<2% during the first 6-month period) had prescriptions. In addition to examining these treatments separately, we also grouped them into 3 categories based on their role within the course of the disease: disease modifying, relapse, and fatigue symptom management. Disease-modifying medications included glatiramer, interferon β -1a, interferon β -1b, azathioprine, fingolimod, mitoxantrone, cyclophosphamide, valacyclovir, and natalizumab. Relapse medications included methylprednisolone, prednisone, corticotropin, dexamethasone, IV corticosteroids, and IV prednisolone. Symptom management medications, focusing on fatigue since it occurs in 80% of MS patients,²³ included amantadine, modafinil, and dalfampridine.

Finally, we stratified our calculations of the proportion of treated patients by MS subtype as of the index date, of which there are 4: relapsing-remitting (RRMS), secondary-progressive (SPMS), primary-progressive (PPMS), and progressive-relapsing (PRMS). It is not possible to distinguish between subtypes of MS patients using structured data in an EMR because there is no ICD-9-CM code for MS subtype. Therefore, to identify subtype in our cohort of MS patients, we extracted information from patients' clinical notes using natural language processing (NLP).

The NLP subtype extraction system was built using the Unstructured Information Management Architecture Asynchronous Scaleout²⁴ as a document processing pipeline. The system used a set of libraries that enabled programmatic configuration of the pipeline and easy manipulation of text in context.²⁵ Each module in the pipeline identified keywords and phrases associated with a particular MS subtype and output structured annotations that were overlaid on the text.

Clinical experts contributed possible keywords and phrases denoting MS subtype. This list was added through multiple iterations where human reviewers examined clinical notes for visits where MS was discussed and by reviewing the context around where known MS subtype keywords were found. Because this list of keywords and phrases included terms that could have been used to identify non-MS subtype related concepts, for example, the acronym "RR" in a clinical note could mean "relapsing-remitting" but could also mean "respiratory rate," these terms were only accepted when in proximity to a reference to MS. Cases where a subtype was mentioned, but explicitly stated as not present for the patient, were also excluded (eg, "not relapsing-remitting").

To validate the NLP system, human annotators manually reviewed 1000 mentions of NLP-extracted MS subtype to determine the positive predictive value of the system. For each instance, an annotator determined whether the NLP system correctly identified and interpreted a subtype mention based on how it was documented in the text. Additionally, 150 patients were randomly selected from the cohort of MS patients where no subtypes were found, and

Table 1. Baseline Characteristics of US Veterans With MS (N = 6803).

Characteristic	N or Mean	% or SD
Age (mean)	53.9	13.3
Body mass index (mean)	35.7	181.0
Male gender	5499	80.8%
Race		
White	4805	70.6%
Black	989	14.5%
Asian	9	0.1%
Native American	23	0.3%
Hispanic	182	2.6%
Unknown	795	11.7%
Marital status		
Married	3945	58.0%
Not married	980	14.4%
Divorced	1437	21.1%
Separated	49	0.7%
Widowed	207	3.0%
Unknown	185	2.7%
MS subtype		
Relapsing remitting	1573	23.1%
Secondary progressive	429	6.3%
Primary progressive	396	5.8%
Progressive remitting	26	0.4%
Unknown	4379	64.4%

Abbreviations: MS, multiple sclerosis; SD, standard deviation.

all text notes pertaining to these patients were reviewed for possible missed subtype mentions to determine system sensitivity. In this case, an annotator carefully read through each note and identified any actual documented mentions of MS subtype. For patients that did not have a subtype mentioned in their notes, clues to which subtype was most likely were collected.²⁶

The University of Utah Institutional Review Board and the Salt Lake City VHA Research and Development office approved this study.

Results

A total of 38 234 patients had the ICD-9 code 340 during the study period, and 6803 patients remained after inclusion/exclusion criteria were applied. The mean age (SD) was 53.9 (13.3) years (Table 1). A total of 80.8% of patients were male, and 88.3% of patients had race identified, of which most were white (80.0%) or black (16.5%).

At 6 months, 1827 (26.9%) of the patients in our cohort had at least one prescription for a medication used to treat MS (Figure 1; see also Supplemental Table 1 [all Supplemental materials are available online at <http://pmt.sagepub.com/content/by/supplemental-data>]). By month 72, 1122 (55.1%) of the patients remaining in the cohort had

received at least one prescription. The rates of each individual MS treatment increased rapidly in 6 to 36 months follow-up time, and increased slightly between 36 and 72 months follow-up time. The largest increase in overall treatment occurred between 12 and 24 months (2069 to 2140 patients, or 34.4% to 44.3%). The most common treatments among MS patients from months 6 through 60 were interferon β -1a (from 9.8% in month 6 to 21.9% in month 60) and glatiramer (from 7.4% in month 6 to 17.8% in month 60), with amantadine (17.6%) and prednisone (18.2%) catching up to glatiramer (18.2%) by month 72.

Figure 2 (see also Supplemental Table 2) shows the trajectory of treatment rates by category of therapy. Disease-modifying therapies (20.2%) were more than twice as common as treatments for relapse (7.5%) or symptoms (6.7%) in month 6. By month 72, the rate of treatment with disease-modifying therapies was still approximately 50% more common than treatments for relapse (26.4%) or symptoms (25.2%). More than half (879 of 1448; 60.7%) of RRMS patients received treatment within the first year (Figure 3; see also Supplemental Table 3). The next most common subtype to receive treatment at 12 months was PRMS (12 of 25; 48.0%) followed by SPMS (135 of 354; 38.1%) and PPMS (141 of 379; 37.2%).

Discussion

In a cohort of VA patients with a formal MS diagnosis in the years 1999 to 2010, only 27.4% of patients receiving regular care at the VA had started therapy 6 months after diagnosis. By month 72, 6 years after diagnosis, 56.7% had started therapy. The most common drug class was the disease modifiers, as might be expected since the majority of our cohort with known subtype was relapsing-remitting. Within that class, the most common therapy was interferon β -1a.

Although other studies have documented treatment patterns generally for MS patients, ours is the first to use an observational study design to report rates of treatment starting from identification of MS within a specific health care system. One study using the NARCOMS patient registry found that approximately 52% of veterans were on immunomodulatory agents, compared to approximately 73% of nonveterans.¹⁷ This same study also found an increased use of symptom-managing drugs, such as modafinil, in veterans (approximately 72% to 82%) compared to nonveterans (approximately 57% to 71%).¹⁷ In a second study of MS patients using a commercial insurance database, treated patients initiated therapy an average of 5.3 months after diagnosis.²⁷ Identifying MS subtype as soon as possible after diagnosis may influence a doctor's initial treatment decisions and may determine how well a patient responds to treatment (eg, knowing that primary progressive MS is less likely to respond to the disease modifying class).^{28,29} The presumed effectiveness of varying treatment by subtype is

Figure 1. Frequency of prescriptions by time from first diagnosis in the VA.

supported by our own data, as illustrated in Supplemental Figures 1 and 2.

Damage to the central nervous system occurs early in the course of MS. Axonal damage, brain atrophy, and central nervous system tissue atrophy can occur prior to the clinical onset of MS and are predictive of long-term disability.⁹ Advocates of early treatment for MS cite evidence from clinical trials that treatment during the clinically isolated syndrome stage (ie, after the first neurologic episode lasting at least 24 hours) can be more effective than in the relapsing remitting stage and that treatment in the relapsing remitting stage is more effective than in the secondary progressive stage.¹⁰⁻¹⁵

Nearly a decade of evidence (though few comprehensive guidelines) has indicated that early treatment, particularly with disease-modifying agents, provides the best outcomes for MS patients, depending on subtype.¹⁰⁻¹⁵ To some extent, our results suggest recognition of this trend, as our high proportion of RRMS patients aligns well with our relatively high proportion of patients on disease-modifying therapies. However, our cohort only partially overlaps with the publication of the early treatment evidence, as well as precedes the McDonald criteria for diagnosis, which may explain

why our treatment rates lag compared to the ever more common practices of using the McDonald criteria and presumably earlier treatment. Notably, our treatment rates seem to have improved after 2008, which likely was partially due to the increased practice of early treatment prior to publication of the McDonald criteria. Disease-modifying therapies such as natalizumab and rituximab are not represented among the drugs of our 1999 to 2010 cohort because their use was infrequent.

Partially to account for the earlier diagnostic criteria of requiring 2 MS-associated clinical events,⁸ our cohort of MS patients consisted of veterans who had an ICD-9 code 340 on 2 or more separate encounter dates. Alternatively, other researchers have utilized VA data to identify a veteran as having MS based on a pharmacy record for a disease-modifying agent, evidence of MS-related service-connected disability through the Veterans Benefit Administration (VBA), or an average of at least one inpatient or outpatient encounter each year during the study time window in which the principal ICD-9 code was 340.³⁰ While we did not feel that this cohort definition algorithm was appropriate for our primary analysis because it included our outcome measure of interest (disease-modifying agents), as a sensitivity analysis, we

Figure 2. Frequency of prescription type by time from first diagnosis in the VA.

implemented a revised version of this algorithm (we did not have access to VBA data; see Supplemental Tables 4 through 6). We found that 4742 of the 6803 patients in our study met the definition of MS with these new criteria. We conducted our analyses on this cohort and found similar results (see Supplemental Figures 3 through 5).

This study is subject to several limitations, particularly related to cohort definition and inclusion criteria. Prior evidence favoring early treatment has focused on treating after onset of MS symptoms. However, given the difficulty in identifying symptoms of MS in the EMR, our index date is the first ICD-9 code in the VA. Second, we used the previously commonly accepted method of identifying MS patients based on the presence of 2 ICD-9 codes.⁸ However, it is possible that some patients with 2 ICD-9 codes for MS did not, in fact, have MS. Furthermore, veterans often receive health care outside the VA system.^{16,17} Patients may have received prescriptions outside the VA that we did not capture here. They may also have been diagnosed initially with MS outside of the VA, although we tried to minimize that likelihood by requiring an encounter within 180 days of the index date. Beyond applying this inclusion criterion, it was not possible for us to control which of our patients had their initial diagnosis in the VA and which did not. On the

other hand, our stringent inclusion criteria also resulted in our capture of only a very small proportion of the people in the VA system who received a diagnosis of MS; approximately five-sixths of those with an ICD-9 code for MS did not meet study criteria. These additional excluded MS patients continued to be treated and monitored at the VA. However, these excluded MS patients are not likely to differ in any clinically meaningful way from included patients, except in the criteria used for this study. Additionally, while we assumed that the date on which the first ICD-9 code for MS was seen for a patient in our cohort was the initial diagnosis for MS, there is reason to believe that this was not always the case in reality. A sizable portion of our patients received treatment for relapses and symptoms early in our observation period despite the fact that MS often progresses quite slowly. One possible explanation for this is that our pre-index period of 180 days was simply not long enough to capture previous MS diagnoses in the VA. Another is that some of the veterans in our cohort were diagnosed in a non-VA setting but sought treatment in the VA. An additional limitation is that it was not possible for us to determine whether some medications identified in this study were used for MS or for other conditions. Finally, it was not possible to identify a subtype using NLP in nearly two thirds of

Figure 3. Frequency of any MS treatment by MS subtype and time from first diagnosis in the VA.

our cohort of MS patients. Reasons for this may be that the patient received most of his/her care outside the VA, that the patient had the much-debated “benign” MS diagnosis, or that MS subtype is simply known by clinicians by not well documented in the free text of the EMR.

Conclusions

We found that roughly one third of our 1999 to 2010 cohort of MS patients received treatment during the first 12 months after diagnosis in the VA. That proportion rose to only half, at 36 months. Clinical trial evidence now suggests that early treatment can prevent neurological damage and slow progression of the disease. VA patients newly diagnosed with MS should be treated as soon as possible, ideally within 6 months of diagnosis.

Authors' Note

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