Characterizing Long-term Disability Progression and Employment in NARCOMS Registry Participants with Multiple Sclerosis Taking Dimethyl Fumarate

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Practice Points

- In the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry, most participants treated up to 5 years with dimethyl fumarate remained free from 6-month confirmed disability (Patient-Determined Disease Steps scale score) progression and conversion to secondary progressive MS.

- Disability and employment status remained stable in participants treated with dimethyl fumarate.
Abstract

**Background:** Delayed-release dimethyl fumarate (DMF) is effective in relapsing-remitting multiple sclerosis (RRMS), but long-term effects of DMF on disability and disease progression in clinical settings are unknown. We evaluated disability and employment outcomes in persons with RRMS treated with DMF for up to 5 years.

**Methods:** This longitudinal study included US North American Research Committee on Multiple Sclerosis (NARCOMS) Registry participants with RRMS reporting DMF initiation in fall 2013 through spring 2018 with 1 year or more of follow-up. Time to 6-month confirmed disability progression (≥1-point increase in Patient-Determined Disease Steps [PDDS] scale score) and change in employment status were evaluated using Kaplan-Meier analysis. Participants were censored at last follow-up or at DMF discontinuation, whichever came first.

**Results:** During the study, 725 US participants with RRMS had at least 1 year of DMF follow-up data, of whom most were female and White. At year 5, 69.9% (95% CI, 65.4%-73.9%) of these participants were free from 6-month confirmed disability progression, and 84.7% (95% CI, 78.6%-89.2%) were free from conversion to secondary progressive MS. Of 116 participants with data at baseline and year 5, most had stable or improved PDDS scale and Performance Scales scores over 5 years. Of 322 participants 62 years and younger and employed at the index survey, 66.0% (95% CI, 57.6%-73.1%) were free from a negative change in employment type over 5 years.

**Conclusions:** Most US NARCOMS Registry participants treated up to 5 years with DMF remained free from 6-month confirmed disability progression and conversion to secondary progressive MS and had stable disability and employment status. These results support the long-
term stability of disability and work-related outcomes with disease-modifying therapy. Int J MS Care.
Introduction

In the past several years, multiple new therapies have emerged for the treatment of relapsing-remitting multiple sclerosis (RRMS), including delayed-release dimethyl fumarate (DMF; also known as gastroresistant DMF). The pivotal DEFINE and CONFIRM clinical trials and the ENDORSE extension trial\(^1\)-\(^5\) demonstrated the benefits of DMF with respect to reduction in relapse rate, magnetic resonance imaging outcomes, and disability progression. Health-related quality of life measures improved during 2 years of DMF treatment but worsened with placebo treatment,\(^3\) suggesting that DMF improves patient-perceived health status.

As of December 31, 2020, more than 500,000 patients have been treated with DMF, representing more than 1,000,000 patient-years of exposure. Of these, 6,335 patients (14,241 patient-years) were from clinical trials. Although clinical trials provide a high level of evidence regarding the efficacy of a treatment, there are several potentially important limitations. The populations enrolled may differ from those observed in routine clinical practice. The duration of follow-up is short, limiting inference about medium- and long-term outcomes, particularly related to disability progression. The assessment of patient-reported outcomes and of meaningful functional and participatory outcomes is often limited.

Studies based on real-world data have the potential to address these gaps and provide additional, clinically meaningful evidence to guide treatment decisions made by persons with MS and their health care providers through a shared decision-making model.\(^6\) In previous real-world studies, patients treated with DMF had a low annualized relapse rate and risk of relapse, consistent with clinical trial findings.\(^7\)-\(^9\) Real-world studies also demonstrated that patients
treated with DMF maintained clinical stability or showed improvement after 12 months of DMF treatment versus baseline with respect to fatigue, activities of daily living, and work impairment.\cite{8,9} To date, however, most real-world studies have examined outcomes over periods of 2 years or less only. Thus, there is a lack of data regarding the long-term effects of DMF on disability outcomes, rate of conversion to secondary progressive MS (SPMS), and common symptoms that adversely affect quality of life (eg, cognition, fatigue, depression).

Data are also relatively limited regarding the long-term effects of DMF on employment outcomes. Often, MS is diagnosed between ages 20 and 50 years,\cite{10} in the prime of career development; up to half of individuals with MS exit the workforce within 5 years of diagnosis, and two-thirds are unemployed within 15 years.\cite{11} Such changes in employment status are associated with reduced quality of life.\cite{12} Absenteeism is also an issue for those who remain employed; for example, one study demonstrated that individuals with MS missed four times more workdays in a 1-year period as employees who did not have MS.\cite{13} Work productivity improvements have been observed after 12 to 24 months of treatment with DMF.\cite{3,8,9,12,14} However, there is little information on the probability of maintaining employment in persons with MS treated with DMF over the long-term.

We aimed to determine the effects of DMF on disability progression, symptom domains, and employment status in persons with RRMS treated for up to 5 years.

**Methods**

**Study Design and Source Population**
We conducted a longitudinal cohort study using the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry. Initiated in 1996, the NARCOMS Registry is a voluntary self-report registry for people diagnosed as having MS. Participants confidentially provide information about their demographic characteristics, medical history, and disease and treatment characteristics at enrollment and every 6 months thereafter, either online or on paper, per their preference. The NARCOMS Registry is approved by the Washington University in St. Louis institutional review board.

**Inclusion Criteria**

Participants were eligible for inclusion if they reported initiating DMF on a survey between fall 2013 and spring 2018, completed at least one semiannual follow-up survey approximately 1 year after DMF initiation, and were US residents (Figure S1, which is published in the online version of this article at ijmsc.org). The first survey on which the participant indicated taking DMF was considered the index survey. Participants were excluded if they had SPMS or primary progressive MS at the time of the index survey. This group of participants constituted the overall population; participants were censored at last follow-up or at DMF discontinuation, whichever came first.

We also studied two subpopulations (Figure S1): 1) a 5-year completer population of participants who initiated DMF between fall 2013 and spring 2014 and completed a survey at year 5 reporting that they were still receiving DMF treatment and 2) an employment population...
of participants who reported being employed full-time or part-time at the index survey and were 62 years and younger. Because the study spans 5 years and the average retirement age in the United States is 62 years, the change in employment status in people older than 62 years may more likely be driven by reasons unrelated to MS.

Measures

The Patient-Determined Disease Steps (PDDS) scale is a self-report measure for characterizing MS-associated disabilities and disability progression that was adapted from the physician-administered Disease Steps scale. The PDDS scale is an ordinal scale with scores ranging from 0 (normal) to 8 (bedridden). Results from the PDDS scale are highly correlated with the clinician-measured Expanded Disability Status Scale (EDSS) scores. The Performance Scales (PS) is a self-report measure for MS-associated disability assessing eight domains: mobility, bladder/bowel, fatigue, sensory, vision, cognition, spasticity, and hand. Scores for all domains except mobility range from 0 (normal) to 5 (total disability); scores for the mobility domain range from 0 to 6. Both the PDDS scale and the PS have good internal consistency and reliability and adequate test-retest reliability. The PS mobility, bladder/bowel, fatigue, vision, and hand subscales have each been validated against their clinical criterion measures (Timed 25-Foot Walk test, Nine-Hole Peg Test, low-contrast visual acuity, Modified Fatigue Impact Scale, and Bladder Control Scale). In addition, the NARCOMS depression scale was used to assess depression.
Demographic information was captured from the participant enrollment survey. Participants reported their sex, date of birth, race (categorized as White, Black, or other), and year of diagnosis on their enrollment survey. Age was calculated as age at the time of the index survey. Each semiannual update used a single question to assess whether the participant had a relapse in the past 6 months (yes/no/unsure). Participants reported their clinical course of MS by responding to the question, “What type of MS has your doctor said you have now?” with possible responses being clinically isolated syndrome, relapsing-remitting, secondary progressive, primary progressive, and don’t know/unsure. Previous use of disease-modifying therapies (DMTs) was determined based on respondents reporting past use of DMTs, including the following: cyclophosphamide, glatiramer acetate, intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b, teriflunomide, fingolimod, or natalizumab. Employment status was reported as full-time, part-time, or unemployed. Participants also reported the number of workdays missed and whether the hours they worked had decreased (yes/no).

Outcomes

Outcomes of interest differed by study population. For the overall population, we focused on time to 6-month confirmed disability progression and proportion of participants who converted to SPMS. Time to 6-month confirmed disability progression was defined as a 1-point or more increase in PDDS scale score sustained for 6 months or longer. For the 5-year completer
analysis, the outcomes included change from baseline in PDDS scale score, the eight PS domain scores, and the NARCOMS depression scale score.

Employment outcomes included time to negative change in employment status, reduction in work hours, missed workdays, and positive employment change. Negative change in employment status was categorized as change from employed full-time at the index survey to part-time; employed full-time at the index survey to unemployed; or employed full- or part-time at the index survey to unemployed. For analysis of missed workdays, we included participants who reported being employed at the index survey and who responded to the survey question regarding missed workdays. The analysis of positive employment change included participants who reported being unemployed at the index survey to determine the proportion of patients who changed from unemployed to employed (part-time or full-time).

**Statistical Analysis**

We summarized demographic and clinical characteristics for the cohort using descriptive statistics. Continuous variables were summarized using mean (SD) or median (minimum, maximum), as appropriate. Categorical variables were summarized using frequency (percentage). Time to 6-month confirmed PDDS scale score progression, conversion to SPMS, negative change in employment, and reduction in work hours were analyzed using the Kaplan-Meier method. Participants were censored at last follow-up or at the time of DMF discontinuation, whichever came first. Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc).
Results

Overall Population

**Demographics and Baseline Characteristics**

During the study period, 1,058 US NARCOMS Registry participants with RRMS initiated DMF therapy; 725 had at least 1 year of follow-up data (Figure S1). Of these 725 participants, 366 (50.5%) remained on DMF treatment at the time of the analysis. Most participants were female and White, with a median (interquartile range [IQR]) age of 53 (46-59) years and disease duration of 14 (8-19) years. More than half of the participants reported previous treatment with a DMT, and one-quarter had experienced a relapse in the 6 months before the index survey. Median DMF treatment duration and follow-up was 3 years (Table S1).

**Disability Outcomes**

Of the 725 participants assessed, 69.9% (95% CI, 65.4%-73.9%) were free from 6-month confirmed disability (PDDS scale score) progression at year 5 and 84.7% (95% CI, 78.6%-89.2%) were free from conversion to SPMS (Figure 1).

**5-Year Completer Subgroup**
Participants

From the overall population (N = 725), we identified 116 participants for inclusion in the 5-year completer population (Figure S1). Demographic and baseline characteristics of this subgroup were similar to those of the overall population (Table S1). Compared with the overall population, 15% more participants were treated previously with a DMT in the 5-year completer population.

Outcomes

Median PDDS scale and PS scores for each individual domain remained stable over 5 years. The median (IQR) PDDS scale score was 2 (0-3) at year 0 and 2 (1-4) at year 5. Median (IQR) scores at both time points were as follows: mobility, 1 (0-3); hand, 1 (0-2); vision, 1 (0-2); fatigue, 2 (1-4); cognition, 1 (1-3); bladder/bowel, 1 (0-2); sensory, 1 (1-2); spasticity, 1 (0-2); and depression, 1 (0-2). After 5 years of DMF treatment, 58% to 69% of participants had PDDS scale and PS scores that either remained stable or improved across all functional domains (Figure 2).

Employment Subgroup

Participants
Of the 322 participants 62 years and younger who were employed at the index date, 250 (78%) reported their employment as full-time and 72 (22%) reported their employment as part-time. At DMF initiation (index date), employed participants were younger than the overall population, with a median (IQR) age of 48 (42-54) years. Compared with the overall population, employed participants had a shorter disease and treatment duration; median (IQR) disease duration was 12 (7-16) years and DMF treatment duration was 3.5 (2.0-4.5) years (Table S1).

**Employment Status and Work Productivity Outcomes**

Of the participants who were employed at the index survey, 66.0% (95% CI, 57.6%-73.1%) were estimated to be free from a negative change in employment type over 5 years of DMF treatment (Figure S2). Similarly, 69.5% (95% CI, 62.8%-75.2%) were estimated to be free from needing to reduce work hours. At the time of the index survey, participants reported missing an average of 2 workdays in the past 6 months before DMF initiation. After initiating DMF treatment, the median (IQR) number of workdays missed per year was 1.0 (0.0-1.0). In the employed subgroup, 54 of 322 participants (16.8%) reported 5 or more missed workdays in any given year during the 5-year study.

Of the 294 participants who were not employed at the index survey, 109 (37.1%) had a positive change in employment status while being treated with DMF: 83 changed from unemployed to employed full-time and 26 changed from unemployed to employed part-time.
Discussion

In this cohort study, we assessed longer-term outcomes of participants treated with DMF than are routinely assessed in clinical trials. Most US NARCOMS Registry participants who were treated with DMF for up to 5 years remained free from 6-month confirmed disability (PDDS scale score) progression. In the ENDORSE clinical trial extension study, EDSS scores remained stable over 9 years of DMF treatment, and most participants remained free from EDSS score progression over those 9 years. The ENDORSE study did not collect data on whether participants converted from RRMS to SPMS.

In the present study, considering that the average MS disease duration before starting DMF treatment was 14 years, we found a low rate of conversion to SPMS over the additional 5-year DMF treatment period. Similarly, a large observational cohort study found that 10% of patients converted to SPMS, with a median time to conversion to SPMS of 32.4 years. The longer time to onset was likely related to use of DMTs. A large (n = 517) prospective study that followed more than 90% of patients for 10 years found that 18% of patients converted from relapsing MS to SPMS, with a median time of 16.8 years after disease onset. In the subgroup of participants who completed 5 years or more of DMF treatment and responded to at least one survey every year, most participants had PDDS scale and PS scores that either improved or remained stable.

Treatment with DMF was associated with stability or improvement across a wide range of outcomes, including PDDS scale scores, as well as measures of individual symptom domains such as cognition, depression, spasticity, and fatigue. Many of these domains are associated with...
employment status and work productivity.\textsuperscript{12,24-26} Cognitive impairment, disability, and fatigue negatively affect employment status and absenteeism.\textsuperscript{27}

Symptoms of MS, most commonly fatigue, are major reasons why patients with MS leave the workforce or reduce their work hours.\textsuperscript{12,24} Employment rates across other registries range from 43\% to 66\%, with rates in patients with MS generally lower than those in the general population.\textsuperscript{28} Previous studies suggest that up to half of patients with MS may exit the workforce within 5 years. Most participants in the present study with an average disease duration of 9 years before starting DMF remained employed after 5 years of DMF treatment, and many also were able to maintain their baseline level of employment. In other studies, work productivity (as measured by the Work Productivity and Activity Impairment Questionnaire–MS) also improved with DMF treatment, although most included 12 to 24 months of follow-up.\textsuperscript{3,8,9,12,14} Different DMTs have different effects on work attendance and productivity; DMF performed better or equally as well as injectable DMTs in previous studies.\textsuperscript{14,29}

There are several limitations associated with this analysis, commonly noted in most analyses of registry data, including the lack of a placebo group or active comparator. Although there is no comparison arm for employment in the present study, a recent study in the NARCOMS Registry that included participants 62 years and younger irrespective of DMT use found that the percentage of patients free from a negative change in employment across 1 year was 97.7\%,\textsuperscript{30} which is similar to the percentage of 94.1\% (95\% CI, 90.9\%-96.2\%) in this study. There is a lack of longer-term employment data available for comparison. The NARCOMS Registry participants are volunteers and may not fully represent the MS population. For the 5-year completer subgroup, there is the potential for bias because those who stay on DMF
treatment for several years are more likely to be doing well compared with those who discontinue. However, this bias is mitigated in the analyses of the overall population because the Kaplan-Meier method uses data from all patients.

Due to the self-reported nature of the data, some of the outcomes in the present analysis may be prone to recall bias,\textsuperscript{31} as well as clinician-assessed or performance-based assessments for some outcomes, such as disability status. For example, the reported conversion to SPMS was not verified against a health care provider–confirmed diagnosis of SPMS. However, previous work suggests that persons with MS can accurately report their clinical course.\textsuperscript{32} In addition, we captured a broad range of patient-reported outcomes that are not often captured in other types of registries.

In this longitudinal assessment of outcomes in NARCOMS Registry participants treated for up to 5 years, most participants remained free from 6-month confirmed disability (PDDS scale score) progression and free from conversion to SPMS. Median PDDS and PS scores remained stable, and most participants had scores that either improved or remained stable across all functional domains. In addition, most NARCOMS Registry participants treated with DMF maintained their baseline level of employment and stable levels of work productivity. Among participants who were unemployed before initiating DMF, 37\% became employed after starting DMF treatment. Overall, these results support the long-term efficacy profile of DMF on measures of disability and work-related outcomes.
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Figure 1. Freedom from 6-month confirmed disability (Patient-Determined Disease Steps scale score) progression (A) and freedom from conversion to secondary progressive multiple sclerosis (B) in overall population (N = 725)

Data were calculated as a product-limit survival estimate, with number of participants at risk calculated using Kaplan-Meier method.
Figure 2. Stable or improved Patient-Determined Disease Steps (PDDS) scale and Performance Scales domain scores at 5 years in 5-year completer subgroup (n = 93)
Table S1. Demographic and baseline characteristics of study population

| Characteristic                              | Overall Population, N = 725 | 5-year Completer Subgroup, n = 116 | 5-year Completer Subgroup, n = 322 |
|--------------------------------------------|-----------------------------|------------------------------------|-------------------------------------|
| Female, n (%)                              | 622 (86)                    | 102 (88)                           | 280 (87)                            |
| White, n (%)                               | 591 (82)                    | 91 (78)                            | 256 (80)                            |
| Age, years, median (IQR)                   | 53 (46-59)                  | 52 (45-59)                         | 48 (42-54)                          |
| <55                                        | 411 (57)                    | 75 (65)                            | 243 (75.5)                          |
| ≥55                                        | 314 (43)                    | 41 (35)                            | 79 (24.5)                           |
| Age, years, at diagnosis, median (IQR)     | 38 (30-45)                  | 36 (30-43)                         | 36 (30-41)                          |
| Disease duration, years, median (IQR)      | 14 (8-19)                   | 14 (11-20)                         | 12 (7-16)                           |
| Relapses in last 6 months, n (%)           | 159 (22)                    | 23 (20)                            | 60 (19)                             |
| PDDS, median (IQR)                         | 2 (1-4)                     | 2 (0-3)                            | 1 (0-2)                             |
| DMF treatment duration/follow-up, years, median (IQR) | 3.0 (2.0-4.5) | 5.0 (5.0-5.0) | 3.5 (2.0-4.5) |
| Previous exposure to DMTs, n (%)a          | 511 (70)                    | 99 (85)                            | 231 (72)                            |
| MS treatment reported prior to DMF, n (%)b |                             |                                    |                                    |
| Interferon-beta                            | 235 (32)                    | 39 (34)                            | 112 (35)                            |
| Glatiramer acetate                         | 163 (22)                    | 36 (31)                            | 72 (22)                             |
| Natalizumab                                | 72 (10)                     | 17 (15)                            | 27 (8)                              |
| Fingolimod                                 | 22 (3)                      | 5 (4)                              | 8 (2)                               |
| Teriflunomide                               | 14 (2)                      | 2 (2)                              | 8 (2)                               |
| Other                                      | 5 (<1)                      | 0 (0)                              | 4 (1)                               |

Note: The overall RRMS cohort included all US RRMS registry participants reporting DMF initiation between fall 2013 and spring 2018 with ≥1 year of follow-up. The 5-year completer cohort included patients treated with DMF for ≥5 years and had survey data available at baseline and year 5.

Abbreviations: DMF, delayed-release dimethyl fumarate; DMT, disease-modifying therapy; IQR, interquartile range; MS, multiple sclerosis; PDDS, Patient-Determined Disease Steps; RRMS, relapsing-remitting multiple sclerosis.

aBased on participants who reported change to treatment prior to DMF initiation.
bParticipants could have had multiple prior MS treatments.
Figure S1. Study populations

DMF, dimethyl fumarate; PS, Performance Scales; RRMS, relapsing-remitting multiple sclerosis.

Proportions were calculated in employed participants ≤62 years of age (n = 322) as a product-limit survival estimate, with number of participants at risk calculated using the Kaplan-Meier method.
Figure S2. Proportion of employed participants free from a decrease in type of employment (employment subgroup, N = 322)

Proportions were calculated in employed participants ≤62 years of age (n = 322) as a product-limit survival estimate, with number of participants at risk calculated using the Kaplan-Meier method.