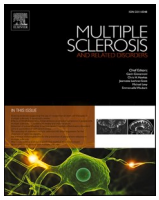
Multiple Sclerosis and Related Disorders 67 (2022) 104080

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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



Adherence and discontinuation rates in patients on Tecfidera™ (dimethyl fumarate): Long-term Canadian experience from the Biogen ONE™ support program

Mattea Tan Thompson [a], Virginia Devonshire [b], Nick Belviso [c], Melissa Gillen [a], Noella Engineer [a], Changyu Shen [c], Scott Reedie [a,*]

[a] Biogen Canada Inc., 3250 Bloor Street West, East Tower, Suite 1200, Toronto, ON M8X 2X9, Canada
[b] University of British Columbia, 2211 Wesbrook Mall, Vancouver, BC, Canada
[c] Biogen, 225 Binney Street, Cambridge, MA, USA

ARTICLE INFO

Keywords:
Multiple sclerosis
Disease-modifying therapy
Adherence
Patient-support program
Real-world evidence

ABSTRACT

Background: Tecfidera™ (dimethyl fumarate [DMF]; Biogen) is an oral disease-modifying therapy (DMT) indicated in Canada for the treatment of relapsing-remitting multiple sclerosis (MS). Biogen ONE™, an ongoing Canadian support program, facilitates access to DMF for patients with MS and maintains a database for the purposes of service provision. These data were utilized to assess adherence, persistence, discontinuations, and other outcomes between 2013 and 2021.

Methods: This non-interventional, retrospective study examined real-world use of DMF prescribed to patients with MS in Canada who were enrolled in the program and received their first dose between April 1, 2013, and June 30, 2021. Follow-up visits and laboratory monitoring occurred based on local standards and per the Canadian product monograph. For adherence and persistence assessments, patients must have had DMF dispensed by specialty pharmacies. Data were collected at patient enrollment, program exit, and throughout the duration of the program.

The primary objective was to assess treatment adherence rates to DMF. Secondary objectives included treatment persistence rates, reasons for discontinuation, absolute lymphocyte counts (ALCs), and patient characteristics throughout the duration of the program.

Results: Overall, 12,608 DMF patients from the program were included between April 1, 2013, and June 30, 2021. At enrollment, mean (standard deviation [SD]) age was 40.6 (10.7) years and mean (SD) Expanded Disability Status Scale (EDSS) score was 2.2 (1.4). DMF was initiated as first-line DMT in 48.8% of patients.

Of patients assessed ($n = 6{,}848$), 90.4% were adherent to DMF (based on medication possession ratio [MPR] $\geq$ 80%). Adherence (mean MPR) was marginally greater in DMT-naïve than switch patients, and in younger ($<$ 40 years) than older ($\geq$ 40 years) patients (both $p < 0.001$). Overall persistence on DMF at 24 months was 57.0%. Greater proportions of DMT-naïve patients persisted on DMF versus switch patients at all time points assessed. Persistence rates were comparable between female and male patients for up to 24 months, and between younger ($<$ 40 years) and older ($\geq$ 40 years) patients for up to 36 months.

Older patients were more likely to discontinue for reasons related to lymphocytes ($\geq$ 40 years, 16.1% vs. $<$ 40 years, 6.1%) while efficacy reasons were reported with greater frequency in younger patients ($\geq$ 40 years, 10.5% vs. $<$ 40 years, 16.0%). Discontinuations due to gastrointestinal and flushing events occurred most frequently during the first month of treatment and decreased thereafter. Mean ALC decreased during the first year on treatment and subsequently plateaued.

Abbreviations: ALC, absolute lymphocyte count; DMF, dimethyl fumarate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; GI, gastrointestinal; HCP, healthcare professional; HR, hazard ratio; LLN, lower limit of normal; MPR, medication possession ratio; MS, multiple sclerosis; PDC, proportion of days covered; PSP, patient-support program; RCT, randomized controlled trial; SD, standard deviation.

* Corresponding author.
E-mail address: scott.reedie@biogen.com (S. Reedie).

https://doi.org/10.1016/j.msard.2022.104080
Received 28 February 2022; Received in revised form 25 May 2022; Accepted 27 July 2022
Available online 28 July 2022

Over successive years, changes were observed in characteristics of patients starting on DMF, including decreases in EDSS score, age, and time since diagnosis. The proportion of DMT-naïve patients increased over the years (2013–2014, 26%–27%; 2018–2021, 62%–67%).
Conclusions: High adherence was found in patients on DMF treatment within the Biogen support program with access to specialty pharmacies. The evolution of the patient population throughout the years suggests a shift towards earlier treatment. These real-world data may support the value of a support program in optimizing the management of patients on DMF treatment. Support programs provide personalized treatment monitoring, which can help minimize early discontinuations and improve adherence to treatment.

1. Introduction

Real-world studies can provide valuable data on the effectiveness and safety of treatments given in routine clinical care, complementing the evidence generated by randomized controlled trials (RCTs). In addition, real-world studies may capture use of treatments over longer durations than in RCTs, and in larger and more representative patient populations. Such data can be beneficial to clinical decision-making and contribute towards improving treatment adherence and achieving better disease management. There are an estimated 90,000 people in Canada living with multiple sclerosis (MS) and a further 4377 new diagnoses every year (Multiple Sclerosis International Federation, 2020). By 2031, this total has been projected to surpass 130,000 (Amankwah et al., 2017).

In Canada, the oral disease-modifying therapy (DMT) Tecfidera™ (dimethyl fumarate [DMF]; Biogen) is indicated for the treatment of relapsing-remitting MS (Biogen Canada Inc., 2013). The Canadian Biogen ONE™ support program facilitates access to DMF for patients with MS and maintains a database for the purposes of service provision of patient education, financial assistance, pharmacy services, and clinic support services all through the patients' journey. All safety events have been reported as per local regulatory requirements. Since the inception of the support program in 2013, the database has collected data for at least 90% of Canadian patients with MS treated with DMF, representing approximately 12,000 patients.

We report a retrospective analysis of the support program database to evaluate the long-term use of DMF in patients with MS, by assessing adherence to DMF, treatment persistence, discontinuation rates, lymphocyte counts, and patient characteristics between 2013 and 2021.

2. Methods

2.1. Study design

This was a non-interventional, clinical study examining the real-world use of DMF for the treatment of patients with MS in Canada based on a retrospective review of data captured as part of Biogen's support program database. Patients were treated with DMF as part of their routine clinical care. Follow-up visits occurred based on local standards of care, and additional points of contact could occur if required by the patient or prescribed by their physician. Laboratory monitoring was conducted as per the DMF Canadian product monograph, including a complete blood count (including lymphocytes), urinalysis, and liver transaminases within 6 months before treatment, 6 months after treatment, then every 6–12 months thereafter and as clinically indicated.

2.2. Patients

For inclusion in these analyses, patients must have received at least one dose of DMF and been enrolled in Biogen's support program from April 1, 2013, to June 30, 2021. Patients were excluded from the analysis if they did not have first-dose data, or if enrollment or their first dose occurred after June 30, 2021. For all measures of treatment adherence and persistence, patients must have had DMF dispensed by Biogen's program specialty pharmacies; patients were excluded from all treatment adherence and persistence analyses if DMF was dispensed by retail pharmacies.

2.3. Data collection

Data were collected at patient enrollment, program exit, and throughout the duration of the program. Data for the analyses reported here were collected between April 1, 2013, and June 30, 2021. Drug fill data was collected at the specialty pharmacy level through Biogen's support program. Lymphocyte counts were collected during routine and physician-prescribed blood monitoring. The Biogen ONE™ Lab Assist+ Program for in-house bloodwork monitoring started in 2018; the data for lymphocyte counts reported here were collected between April 17, 2018, and July 19, 2021, for eligible patients on DMF treatment. Lymphocyte counts were only available for DMF patients within the support program who opted into the blood monitoring program.

Reasons for discontinuation were either patient-reported or reported by healthcare professionals (HCPs). The data were only available if the information was disclosed to the support program. If multiple reasons were provided, only the primary reason for discontinuation was recorded.

2.4. Objectives

The primary objective of this study was to assess adherence rates to DMF treatment in patients with MS enrolled in Biogen's Canadian support program. Secondary objectives were to assess treatment persistence, evaluate long-term absolute lymphocyte counts (ALCs) in the overall population, assess rates of and reasons for discontinuation of DMF treatment, and observe any evolution in the types of patients on DMF treatment over successive years of the program.

2.5. Assessments

Adherence to DMF was based on medication possession ratio (MPR), calculated as the total number of days treated divided by the total number of days from first treated day until last treated day. The threshold for adherence was MPR $\geq$ 80%.

Overall persistence rates were assessed as percentages of the patient population who had remained on DMF at 90 days, 180 days, 12 months, 24 months, and 36 months after the start of treatment, with an allowable gap of 30 days. Patients were not included in the persistence calculation for *x* months if they had not been enrolled to receive DMF as part of the support program at least *x* months beforehand. For example, patients must have been enrolled for at least 12 months prior to be included in the persistence calculation for 12 months.

Mean ALC trends were assessed in the overall population throughout long-term follow-up. Reasons for discontinuation (termination or withdrawal from the support program) at all time points were stratified by patient population for characteristics including age ($<$ 40 and $\geq$ 40 years), gender, and prior DMT status. Evolution of patient type was determined by assessment of patient characteristics at program enrollment over the years of the support program, including Expanded Disability Status Scale (EDSS) score, age, and time since diagnosis.

2.6. Statistical analysis

T-test was applied for comparisons of means for continuous variables; Chi-square test was applied for categorical variables. For analyses of time to discontinuation, Cox proportional hazards model was applied to derive hazard ratios (HRs), and Kaplan-Meier product limit method was used to estimate proportions of patients discontinued.

3. Results

3.1. Patient demographics

A total of 12,608 patients were included in the overall population of the support program. The program comprised over 1800 patients in 2013, between 4000 and 6000 patients during 2014 to 2017, and over 6000 patients from 2018 onwards (Fig. 1).

In the overall population, the mean (standard deviation [SD]) age at enrollment was 40.6 (10.7) years and the mean (SD) EDSS score at enrollment was 2.2 (1.4) (Table 1). Almost half (48.8%) of the patient population were new to treatment with DMTs and initiated DMF as first-line therapy. Among the patients who switched to DMF from another DMT (n = 6343), the most common previous treatments were interferons (48.2%), glatiramer acetate (35.7%), teriflunomide (6.3%), natalizumab (4.7%), and fingolimod (4.0%). Most patients resided in the provinces of Ontario (32.5%), Quebec (21.8%), Alberta (13.8%), British Columbia (10.8%), Saskatchewan (6.2%), and Nova Scotia (4.8%); the remainder were in New Brunswick, Manitoba, Newfoundland & Labrador, Prince Edward Island, Yukon, Northwest Territories, and Nunavut.

3.2. Adherence and persistence rates

Overall, 6848 patients within the support program had prescriptions filled at specialty pharmacies. Therefore, prescription fill data for treatment adherence and persistence analyses were available for this cohort, representing 54% of the total support program population. Of this patient cohort, 90.4% were adherent to DMF treatment (based on MPR ≥ 80%). Mean (SD) MPR was 93.9% (13.4%) in the overall population. Adherence was greater in DMT-naïve patients compared with switch patients based on all measures (mean MPR, $p < 0.001$; MPR ≥ 80%, $p = 0.003$) (Table 2). Younger patients (< 40 years old) demonstrated greater adherence to DMF treatment than older patients (≥ 40 years old) as measured by mean MPR and MPR ≥ 80% ($p < 0.001$ for both). Comparisons between female and male patients showed no significant difference in adherence rates based on mean MPR or MPR ≥ 80%.

Persistence rates for the overall population and for subgroups (DMT-naïve and switch patients; female and male patients; patients of age < 40 years and ≥ 40 years) are presented in Table 2. Overall persistence on DMF at 24 months was 57.0%. Greater proportions of DMT-naïve patients persisted on DMF treatment at all time points assessed (90 days, 180 days, 12 months, 24 months, and 36 months) compared with switch patients (< 0.001 for all comparisons) (Table 2). Persistence rates were comparable between female and male patients for up to 24 months, and between younger (< 40 years) and older (≥ 40 years) patients from 180 days up to 36 months.

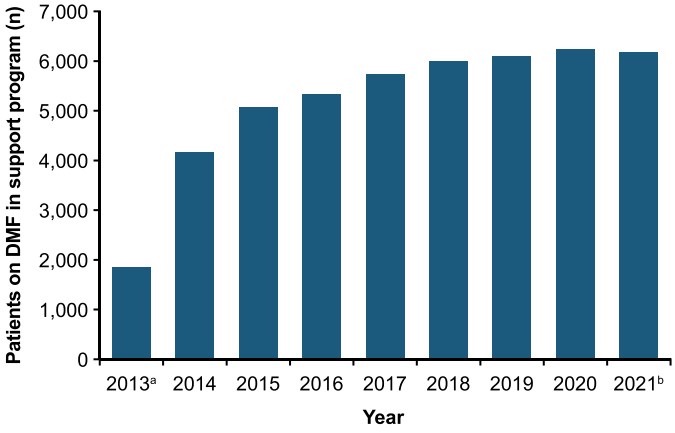


Fig. 1. Numbers of patients on DMF in Biogen's support program between 2013 and 2021. [a]From April 1, 2013. [b]Until June 30, 2021. DMF: dimethyl fumarate; DMT: disease-modifying therapy.

Table 1
Baseline demographics and clinical characteristics of patients enrolled in Biogen's support program.

	Overall population (N = 12,608)	Newly diagnosed population (n = 5977)
Mean (SD) age at enrollment,[a] years	40.6 (10.7)	38.4 (10.5)
Female,[b] n (%)	8292 (73.0)	3590 (69.0)
Mean (SD) EDSS score at enrollment,[c]	2.2 (1.4)	1.9 (1.2)
Mean (SD) time since diagnosis,[d] months	132.7 (94.2)	77.3 (67.7)
Number of prior DMTs,[e] n (%)		
0	6026 (48.8)	–
1	4307 (34.9)	–
2	1452 (11.8)	–
≥3	572 (4.6)	–

[a] Data available for 11,368 patients in the overall population and 5213 in the newly diagnosed subgroup.
[b] Data available for 11,363 patients in the overall population and 5207 in the newly diagnosed subgroup.
[c] Data available for 6688 patients in the overall population and 3236 in the newly diagnosed subgroup.
[d] Data available for 9806 patients in the overall population and 4358 in the newly diagnosed subgroup.
[e] Data available for 12,357 patients in the overall population.
DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; SD: standard deviation.

3.3. Discontinuation rates

In a plurality of cases of discontinuation, no reason for discontinuation was provided (32.4%); the next most common reasons given for discontinuation were efficacy (13.2%), lymphocytes (11.1%), and other adverse event (10.4%) (Table 3).

The frequencies of the different reasons provided for discontinuation varied with increasing follow-up time (Fig. 2). Among reasons of special interest, gastrointestinal (GI) and flushing events were given as a reason for discontinuation more frequently during the first month of DMF treatment and decreased thereafter (Supplementary Fig. 1).

Reasons for discontinuation varied in frequency and ranking between different patient subgroups. Older patients (≥ 40 years old, 16.0%) were more likely to discontinue for reasons related to lymphocytes than younger patients (< 40 years old, 6.1%) (Supplementary Table 1). However, it should be acknowledged that although these reports captured the reasons for discontinuation only as "lymphocytes," these discontinuations were not necessarily all due to cases of low lymphocyte counts where interruption of DMF should be considered as defined by the product monograph (< 0.5×10^9/L persisting for > 6 months. Discontinuations for efficacy reasons were reported with greater frequency in younger patients (< 40 years old, 16.0%) than in older patients (≥ 40 years old, 10.5%).

As of July 1, 2021, there were 49 patients actively on DMF treatment who had remained on treatment for a minimum of 8 years (≥ 96 months).

Table 2
Adherence on DMF treatment in Biogen's support program based on MPR, and persistence rates at 90 days, 180 days, 12 months, 24 months, and 36 months.

	Overall (n = 6848)	Population		Sex		Age	
		DMT-naïve (n = 3852)	Switch (n = 2996)	Female (n = 4912)	Male (n = 1936)	< 40 years (n = 3235)	≥ 40 years (n = 3613)
Adherence rates							
Mean (SD) MPR,[a] %	93.9 (13.4)	94.5 (13.0)	93.2 (13.7)	93.9 (13.3)	93.9 (13.4)	94.9 (12.0)	93.1 (14.4)
p-value	–	< 0.001		0.837		< 0.001	
MPR ≥ 80%, %	90.4	91.4	89.2	90.5	90.3	92.8	88.3
p-value	–	0.003		0.924		< 0.001	
Persistence rates							
90 days,[b] %	71.1	75.9	64.8	70.6	72.4	69.7	72.4
p-value	–	< 0.001		0.203		0.023	
180 days,[c] %	68.3	73.3	61.8	68.0	68.9	67.5	68.9
p-value	–	< 0.001		0.529		0.275	
12 months,[d] %	63.2	69.1	56.0	63.5	62.5	63.6	62.9
p-value	–	< 0.001		0.565		0.661	
24 months,[e] %	57.0	62.4	51.2	58.0	54.9	57.7	56.4
p-value	–	< 0.001		0.133		0.496	
36 months,[f] %	51.5	56.3	46.8	53.2	47.5	52.4	50.5
p-value	–	< 0.001		0.026		0.425	

[a] MPR = sum of days' supply ÷ number of days from first fill to (last fill + last fill days' supply) × 100.
[b] Based on p90 = proportion of patients persistent at 90 days (without gap in therapy > 30 days).
[c] Based on p180 = proportion of patients persistent at 180 days (without gap in therapy > 30 days).
[d] Based on p365 = proportion of patients persistent at 365 days (without gap in therapy > 30 days).
[e] Based on p730 = proportion of patients persistent at 730 days (without gap in therapy > 30 days).
[f] Based on p1095 = proportion of patients persistent at 1095 days (without gap in therapy > 30 days).
DMF: dimethyl fumarate; DMT: disease-modifying therapy; MPR: medication possession ratio; SD: standard deviation.

Table 3
Most common reasons (occurring in ≥ 5% of discontinuations) for discontinuation of treatment with DMF in Biogen's support program.

	Population		Sex		Age	
Reason,[a] n (% of total discontinuations)	Overall (n = 5481)	DMT-naïve (n = 2430)	Male (n = 1445)	Female (n = 4032)	< 40 years (n = 2704)	≥ 40 years (n = 2774)
No reason provided	1775 (32.4)	740 (30.5)	513 (35.5)	1260 (31.3)	932 (34.5)	842 (30.4)
Efficacy	724 (13.2)	343 (14.1)	232 (16.1)	492 (12.2)	433 (16.0)	291 (10.5)
Lymphocytes[b]	608 (11.1)	277 (11.4)	163 (11.3)	445 (11.0)	164 (6.1)	444 (16.0)
Other adverse event	568 (10.4)	247 (10.2)	117 (8.1)	451 (11.2)	231 (8.5)	337 (12.2)
Alternative therapy	474 (8.7)	230 (9.5)	132 (9.1)	342 (8.5)	283 (10.5)	191 (6.9)
Gastrointestinal	383 (7.0)	180 (7.4)	60 (4.2)	322 (8.0)	164 (6.1)	218 (7.9)
Lost to follow-up	301 (5.5)	137 (5.6)	90 (6.2)	210 (5.2)	180 (6.7)	120 (4.3)

[a] Reasons for discontinuations are patient-/HCP-reported reasons. Percentages reported are of total discontinuations. If multiple reasons were provided, only the primary reason for discontinuation was recorded.
[b] "Lymphocytes" was a patient-/HCP-reported reason and may not necessarily follow the product monograph's guidance for DMF discontinuation.
DMF: dimethyl fumarate; DMT: disease-modifying therapy; HCP: healthcare professional.

3.4. Time to discontinuation

Kaplan-Meier analyses in the overall population indicated that 18.1% of patients had discontinued 12 months after the start of treatment, and 44.4% had discontinued after 48 months (Fig. 3A). Based on further Kaplan-Meier analyses, DMT-naïve patients were more likely than switch patients to have discontinued (HR [95% CI] = 1.20 [1.14, 1.27]; $p < 0.0001$; Fig. 3B), and patients aged < 40 years were more likely to have discontinued than patients aged ≥ 40 years (HR [95% CI = 1.17 [1.11, 1.24]; $p < 0.0001$; Fig. 3C).

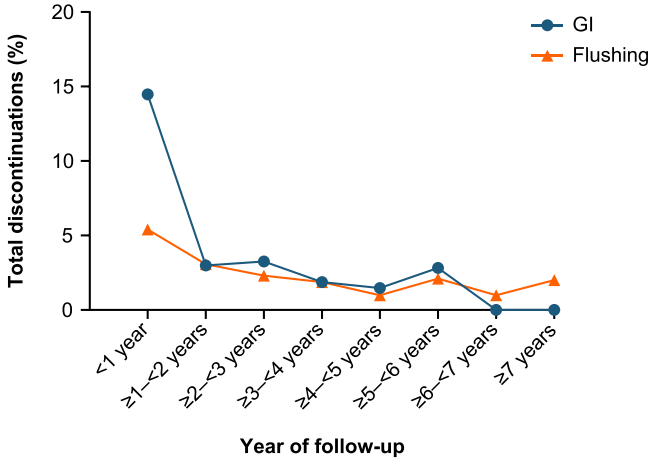


Fig. 2. Frequencies of GI and flushing being provided as reasons for discontinuation by years of follow-up. GI, gastrointestinal.

3.5. Absolute lymphocyte counts

ALC data were available for a subset of 1443 patients. There was a mean (95% CI) decrease in ALC of 29.2% (15.1%–43.3%) during the first year on DMF treatment, followed by a plateauing after year 1 (Fig. 4). Greater variation in ALC was observed in later months, likely due to smaller sample sizes. Of the 1443 patients, 51 patients discontinued for reasons related to lymphocytes after the first year of DMF treatment. Of these 51 patients, 38 had a last ALC count that was < 0.9 × 10^9/L before DMF discontinuation and eight had an ALC count that was < 0.5 × 10^9/L before DMF discontinuation (data not shown).

3.6. Changes in population characteristics over time

Mean EDSS scores of patients initiating DMF treatment decreased over the years of the support program, from 2.3 in 2013 to 1.9 in 2021 (Fig. 5A). A decrease was also observed in mean age at enrollment, from

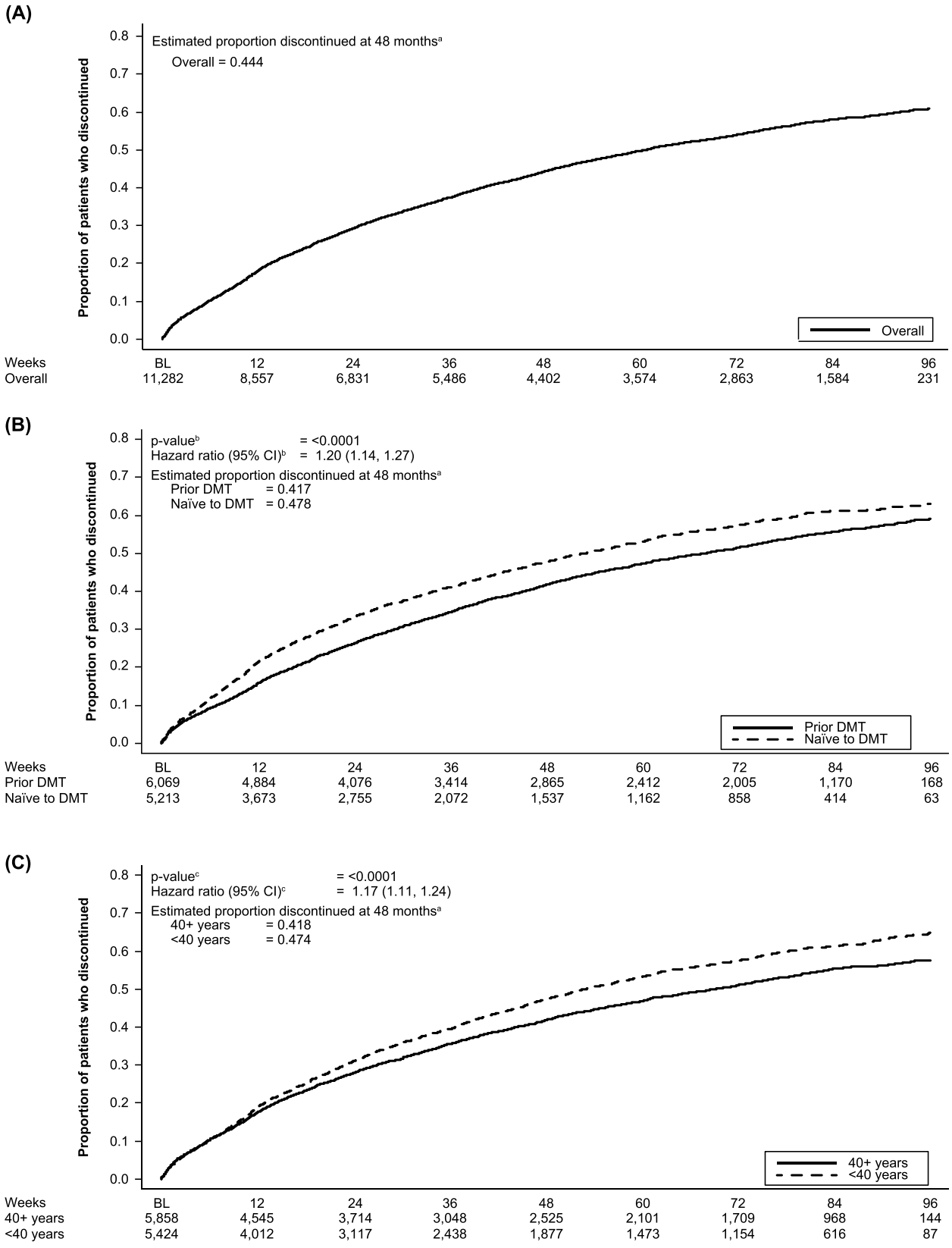


Fig. 3. Time to DMF discontinuation in the overall population (**A**), in DMT-naïve versus switch patients (**B**), and patients aged < 40 years old versus ≥ 40 years old (**C**).

[a]Based on Kaplan-Meier product limit method. [b]Based on unadjusted Cox proportional hazards model. HR < 1 favors DMT-naïve group. [c]Based on unadjusted Cox proportional hazards model. HR < 1 favors < 40 years age group. BL: baseline; DMF: dimethyl fumarate; DMT: disease-modifying therapy; HR: hazard ratio.

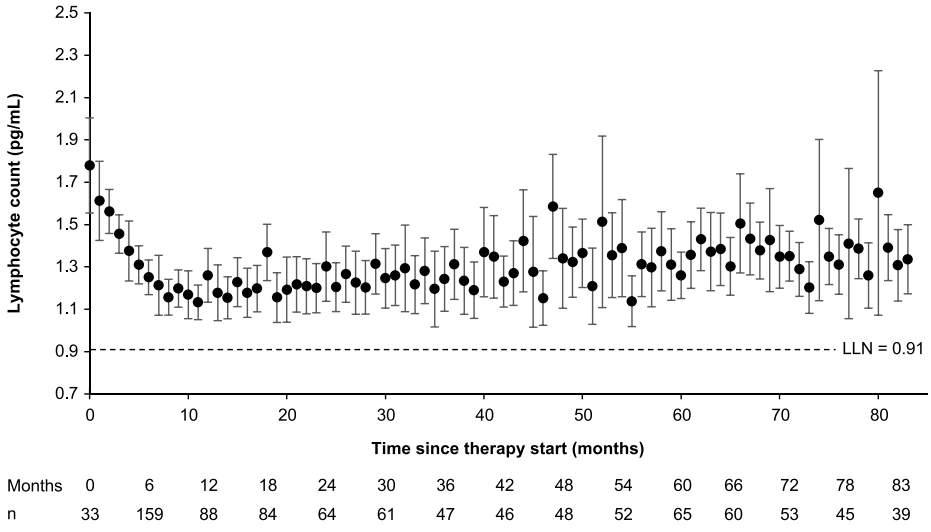


Fig. 4. Mean ALC observed in patients in Biogen's support program by months since start of therapy. Error bars represent 95% confidence intervals. ALCs are reported based on data being collected for a sufficient number of patients ($n > 30$). ALC: absolute lymphocyte count; LLN: lower limit of normal.

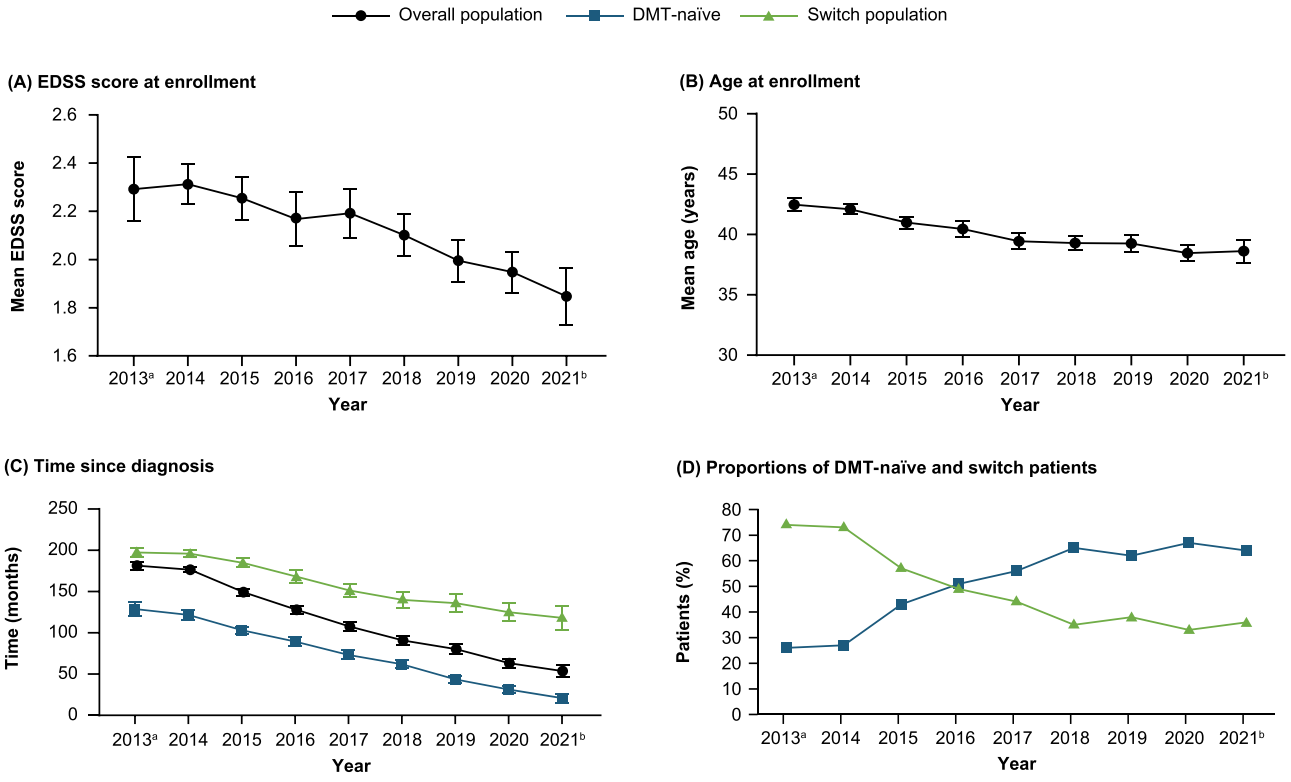


Fig. 5. . Characteristics at enrollment for patients in Biogen's support program showing mean EDSS scores (**A**), mean age (**B**), time since diagnosis (**C**), and proportion of patients who were DMT-naïve or who switched to DMF (**D**). Error bars represent 95% confidence intervals. [a]From April 1, 2013. [b]Until June 30, 2021. DMF: dimethyl fumarate; DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; PSP: patient-support program.

42.5 years in 2013 to 38.6 years in 2021 (Fig. 5B).

Mean time to treatment initiation since patient diagnosis decreased from 182.1 months in 2013 to 53.8 months in 2021 in the overall population, and these decreases were also reflected in the DMT-naïve and switch patient subgroups (Fig. 5C). Throughout the years of the program, mean time since diagnosis to treatment initiation was lower for DMT-naïve patients compared with switch patients. Over successive years, the proportion of patients who were DMT-naïve when starting DMF treatment increased from 26% to 27% during 2013–2014 to 62%–67% during 2018–2021 (Fig. 5D).

4. Discussion

In this retrospective analysis of real-world data from a long-term Biogen support program, 90.4% of DMF patients in Canada were adherent (MPR $\geq$ 80%) to treatment. Adherence rates remained high

when stratified by patient characteristics (DMT-naïve or switch patients; female or male; younger [<40 years] or older [≥ 40 years old] patients).

While previous studies have assessed adherence to other DMTs, direct comparisons between adherence rates cannot be made with the current study due to differences in the types and designs of the studies. Adherence rates (based on MPR ≥ 80%) have been reported elsewhere for fingolimod (DMT-naïve: 87.4%; prior DMT: 90.5%) (Agashivala et al., 2013), glatiramer acetate (74.3%) (Jones et al., 2013), and collectively for oral DMTs (53.0%) and self-injectable DMTs (54.1%) (Munsell et al., 2017). A previously published Canadian retrospective claims analysis reported MPR ≥ 80% over 24 months for fingolimod (70%), DMF (56%), teriflunomide (68%), and natalizumab (56%), as well as for grouped injectables (35%; including interferon beta-1a, interferon beta-1b, and glatiramer acetate) (Duquette et al., 2019).

In this study, adherence rates were assessed based on MPR, although adherence based on proportion of days covered (PDC) had also been considered. For the calculation of both MPR and PDC, the numerator is the total number of days treated. However, while the time period for calculation of MPR extends from the start of the first prescription fill to the end of the last fill, PDC includes the entire duration from the first prescription fill until the end of follow-up time. Based on this, a patient remaining in the support program but no longer receiving DMF would lower overall adherence assessed by PDC but not by MPR. As such, MPR may be a more accurate measure of treatment adherence within this patient population, given the design of the support program; therefore, PDC measures were not included here.

Persistence rates were evaluated at several time points for up to 3 years on treatment, demonstrating overall persistence on DMF of 63.2% after 12 months and 57.0% after 24 months. Previously, a Canadian support program for fingolimod reported a 12-month persistence rate of 80.7% (Lapierre et al., 2016). In the current analysis, persistence was also assessed between different patient subgroups. Patients who were naïve to DMTs demonstrated significantly greater persistence on DMF at all time points assessed than patients who had received DMTs previously; other subgroup comparisons between female and male patients and between younger and older patients did not show such distinct differences.

The overall 12-month discontinuation rate for DMF was 18.1% within Biogen's support program. Other studies have reported discontinuation rates at 12 months for fingolimod in a retrospective cohort study of 31.3% (DMT-naïve patients) and 25.7% (prior DMT patients) (Agashivala et al., 2013). An analysis of a claims database reported 12-month discontinuation rates for ocrelizumab (8%) and for other DMTs grouped as other intravenous (28%), oral (32%), and injectable (43%) (Engmann et al., 2021). A previously published meta-analysis derived a 12-month discontinuation rate for oral DMTs of 25.4% based on 20 real-world studies, including DMF, fingolimod, and teriflunomide (Nicholas et al., 2020).

The reasons reported for discontinuations in the present study were profiled across the different patient subgroups to identify specific causes for discontinuations that may occur with greater frequency in some groups than in others. This analysis indicated that younger patients (age < 40 years) were more likely to report efficacy as a reason for discontinuation than older patients (age ≥ 40 years), while among older patients, discontinuations due to lymphocyte-related reasons were reported with a greater incidence. Since exact reasons for lymphocyte-related discontinuations were neither captured nor verified by the program, these do not necessarily all represent cases of low lymphocyte counts where interruption of DMF should be considered as defined by the product monograph.

For discontinuations of special interest, including those due to GI reasons and flushing, rates were similar to or lower than those observed in comparable real-world studies of DMF (Min et al., 2019; Sabin et al., 2020; Sejbaek et al., 2018). Reasons for discontinuation demonstrated trends based on the duration of follow-up; GI events were cited more commonly during the first month of treatment and decreased in frequency thereafter. Flushing leading to discontinuation also showed a decline after a peak in the first month of DMF treatment. Awareness of the most frequent reasons for discontinuation of DMF may support better management of them and minimize the probability of premature discontinuations. A limitation of the data for reasons for discontinuation was the proportion of discontinuations for which no reason had been provided (32.4%). However, this is not uncommon for patient-support programs, which are non-interventional in nature and in which data are provided voluntarily by patients and/or HCPs. Despite this, data were available for discontinuations in a substantial number of patients, given the large study population.

ALCs were also assessed through Biogen's support program, demonstrating an initial decline of mean counts for the first 12 months on treatment and subsequent plateauing, consistent with previous understanding of DMF from clinical trials and other real-world studies (Buckle et al., 2020; Gold et al., 2021; Mehta et al., 2019). Patient characteristics at enrollment into the support program evolved throughout the years. EDSS scores at time of enrollment, time since diagnosis, and age at enrollment decreased over the years of the program; these outcomes may be indicative of a shift to earlier prescribing of DMF during a patient's course of disease. The proportion of patients who were DMT-naïve when starting on DMF treatment increased over the years, although this may in part be driven by first-line access to DMF and the evolving reimbursement profile within the various provinces and territories in Canada.

This study of adherence and persistence on DMF based on the routine clinical care of patients with MS in Canada has limitations that are commonly associated with analyses of real-world data. These include challenges with regular data collection, variable follow-up times, and the absence of blinding or randomization. However, registry studies can provide valuable data on the routine use of treatments in real-world clinical care that cannot be delivered by RCTs; in addition, they allow observations to be made over longer treatment durations and in more heterogeneous and representative patient populations. This present study of the support program did not assess a comparator arm; however, analyses that incorporate such a comparator arm of patients receiving DMF but not enrolled on a support program may allow the evaluation of the effect of participation in a support program on treatment adherence.

While previous studies have reported increased adherence to treatment for patients enrolled in support programs (Sato et al., 2018; Zhou et al., 2018), the potential benefits of support programs extend further. Participation in support programs has been associated with increases in quality of life and functional status, and reductions to overall costs of health care, while some evidence suggests improvements in clinical outcomes (Brixner et al., 2019; Ganguli et al., 2016; Rubin et al., 2017). The use of support services is also associated with higher patient satisfaction (Wolcott et al., 2009).

This analysis of a long-term support program provides valuable data on the real-world outcomes of DMF including adherence and persistence rates, the most frequent reasons for discontinuing treatment, and evolution of the patient population over an extensive time period. This population comprised a substantial number of patients and represented the vast majority of patients who received DMF in Canada since 2013. These data support the use of DMF as an option for patients with MS, with the potential for remaining on treatment long-term.

CRediT authorship contribution statement

Mattea Tan Thompson: Investigation, Formal analysis, Data curation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Virginia Devonshire:** Conceptualization, Writing – review & editing. **Nick Belviso:** Data curation, Formal analysis, Visualization, Writing – review & editing. **Melissa Gillen:** Writing – review & editing. **Noella Engineer:** Writing – review & editing. **Changyu Shen:** Writing – review & editing. **Scott Reedie:** Writing – review & editing.

Declaration of Competing Interest

MT: employee of Biogen Canada Inc. when this work was conducted.
VD: has received speaker fees and advisory board honorarium from Biogen Inc.
NB: employee of Biogen.
MG: employee of Biogen Canada Inc.
NE: employee of Biogen Canada Inc. when this work was conducted.
CS: employee of Biogen.
SR: employee of Biogen Canada Inc.

Acknowledgments

The authors thank the patients who participated in the Biogen ONE™ support program. Biogen provided funding for medical writing support in the development of this manuscript; David Pertab, Ph.D., from Excel Medical Affairs (Glasgow, UK) wrote the first draft of the manuscript based on input from authors, and copyediting and styling of the manuscript per journal requirements was provided by Excel Medical Affairs. The authors had full editorial control of the manuscript and provided their final approval of all content.

Funding

Biogen ONE™ Support Program was planned, coordinated, and funded by Biogen. Funding for writing and editorial support was provided by Biogen.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104080.

References

Agashivala, N., Wu, N., Abouzaid, S., Wu, Y., Kim, E., Boulanger, L., Brandes, D.W., 2013. Compliance to fingolimod and other disease modifying treatments in multiple sclerosis patients, a retrospective cohort study. BMC Neurol. 13, 138. https://doi.org/10.1186/1471-2377-13-138.

Amankwah, N., Marrie, R.A., Bancej, C., Garner, R., Manuel, D.G., Wall, R., Fines, P., Bernier, J., Tu, K., Reimer, K., 2017. Multiple sclerosis in Canada 2011 to 2031: results of a microsimulation modelling study of epidemiological and economic impacts. Health Promot. Chronic Dis. Prev. Can. 37 (2), 37–48. https://doi.org/10.24095/hpcdp.37.2.02.

Biogen Canada Inc., 2013. Tecfidera™ product monograph. https://www.biogen.ca/content/dam/corporate/en_CA/pdfs/products/TECFIDERA/TECFIDERA_PM_EN_07Oct2021.pdf (accessed 13 December 2021).

Brixner, D., Rubin, D.T., Mease, P., Mittal, M., Liu, H., Davis, M., Ganguli, A., Fendrick, A.M., 2019. Patient support program increased medication adherence with lower total health care costs despite increased drug spending. J. Manag. Care Spec. Pharm. 25 (7), 770–779. https://doi.org/10.18553/jmcp.2019.18443.

Buckle, G., Bandari, D., Greenstein, J., Gudesblatt, M., Khatri, B., Kita, M., Repovic, P., Riser, E., Weinstock-Guttman, B., Thrower, B., Loring, S., Riester, K., Everage, N., Prada, C., Koulinska, I., Mann, M., 2020. Effect of dimethyl fumarate on lymphocyte subsets in patients with relapsing multiple sclerosis. Mult. Scler. J. Exp. Transl. Clin. 6 (2), 2055217320918619 https://doi.org/10.1177/2055217320918619.

Duquette, P., Yeung, M., Mouallif, S., Nakhaipour, H.R., Haddad, P., Schecter, R., 2019. A retrospective claims analysis: compliance and discontinuation rates among Canadian patients with multiple sclerosis treated with disease-modifying therapies. PLOS One 14 (1), e0210417. https://doi.org/10.1371/journal.pone.0210417.

Engmann, N.J., Sheinson, D., Bawa, K., Ng, C.D., Pardo, G., 2021. Persistence and adherence to ocrelizumab compared with other disease-modifying therapies for multiple sclerosis in U.S. commercial claims data. J. Manag. Care Spec. Pharm. 27 (5), 639–649. https://doi.org/10.18553/jmcp.2021.20413.

Ganguli, A., Clewell, J., Shillington, A.C., 2016. The impact of patient support programs on adherence, clinical, humanistic, and economic patient outcomes: a targeted systematic review. Patient Prefer Adherence 10, 711–725. https://doi.org/10.2147/PPA.S101175.

Gold, R., Arnold, D.L., Bar-Or, A., Fox, R.J., Kappos, L., Mokliatchouk, O., Jiang, X., Lyons, J., Kapadia, S., Miller, C., 2021. Long-term safety and efficacy of dimethyl fumarate for up to 13 years in patients with relapsing-remitting multiple sclerosis: final ENDORSE study results. Mult. Scler. https://doi.org/10.1177/13524585211037909, 13524585211037909.

Jones, J.L., Scheidt, D.J., Kaushal, R.S., Carroll, C.A., 2013. Assessing the role of patient support services on adherence rates in patients using glatiramer acetate for relapsing-remitting multiple sclerosis. J. Med. Econ. 16 (2), 213–220. https://doi.org/10.3111/13696998.2012.744316.

Lapierre, Y., O'Connor, P., Devonshire, V., Freedman, M.S., Kremenchutzky, M., Yeung, M., Schecter, R., 2016. Canadian experience with fingolimod: adherence to treatment and monitoring. Can. J. Neurol. Sci. 43 (2), 278–283. https://doi.org/10.1017/cjn.2015.325.

Mehta, D., Miller, C., Arnold, D.L., Bame, E., Bar-Or, A., Gold, R., Hanna, J., Kappos, L., Liu, S., Matta, A., Phillips, J.T., Robertson, D., von Hehn, C.A., Campbell, J., Spach, K., Yang, L., Fox, R.J., 2019. Effect of dimethyl fumarate on lymphocytes in RRMS: implications for clinical practice. Neurology 92 (15), e1724–e1738. https://doi.org/10.1212/WNL.0000000000007262.

Min, J., Cohan, S., Alvarez, E., Sloane, J., Phillips, J.T., van der Walt, A., Koulinska, I., Fang, F., Miller, C., Chan, A., 2019. Real-world characterization of dimethyl fumarate-related gastrointestinal events in multiple sclerosis: management strategies to improve persistence on treatment and patient outcomes. Neurol. Ther. 8 (1), 109–119. https://doi.org/10.1007/s40120-019-0127-2.

Multiple Sclerosis International Federation, 2020. Atlas of MS –3rd Edition. https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms (accessed 13 December 2021).

Munsell, M., Frean, M., Menzin, J., Phillips, A.L., 2017. An evaluation of adherence in patients with multiple sclerosis newly initiating treatment with a self-injectable or an oral disease-modifying drug. Patient Prefer Adherence 11, 55–62. https://doi.org/10.2147/PPA.S118107.

Nicholas, J.A., Edwards, N.C., Edwards, R.A., Dellarole, A., Grosso, M., Phillips, A.L., 2020. Real-world adherence to, and persistence with, once- and twice-daily oral disease-modifying drugs in patients with multiple sclerosis: a systematic review and meta-analysis. BMC Neurol. 20 (1), 281. https://doi.org/10.1186/s12883-020-01830-0.

Rubin, D.T., Mittal, M., Davis, M., Johnson, S., Chao, J., Skup, M., 2017. Impact of a patient support program on patient adherence to adalimumab and direct medical costs in Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, psoriatic arthritis, and ankylosing spondylitis. J. Manag. Care Spec. Pharm. 23 (8), 859–867. https://doi.org/10.18553/jmcp.2017.16272.

Sabin, J., Urtiaga, S., Pilo, B., Thuissard, I., Galan, V., Sainz de la Maza, S., Costa-Frossard, L., Gómez-Moreno, M., Díaz-Díaz, J., Oreja-Guevara, C., Martínez-Ginés, M.L., Lozano, A., Borrega, L., Ayuso, L., Castro, A., Sanchez, P., Meca-Lallana, V., Muñoz, C., Casanova, I., López de Silanes, C., Martín, H., Rodriguez-García, E., Moreno, I., García-Merino, J.A., Aladro, Y., DMF Study Group, 2020. Tolerability and safety of dimethyl fumarate in relapsing multiple sclerosis: a prospective observational multicenter study in a real-life Spanish population. J. Neurol. 267 (8), 2362–2371. https://doi.org/10.1007/s00415-020-09848-7.

Sato, M., Tsujimoto, M., Kajimoto, K., Uetake, H., Shimoda, H., Fujiwara, S., 2018. Effect of a patient-support program on once-daily teriparatide adherence and persistence in the Japan Fracture Observational Study (JFOS). Arch. Osteoporos. 13 (1), 74. https://doi.org/10.1007/s11657-018-0487-8.

Sejbaek, T., Nybo, M., Petersen, T., Illes, Z., 2018. Real-life persistence and tolerability with dimethyl fumarate. Mult. Scler. Relat. Disord. 24, 42–46. https://doi.org/10.1016/j.msard.2018.05.007.

Wolcott, D., Woloson, R.J., Macdonald, J.S., 2009. Patient support services & patient satisfaction: can increased use of these services increase patient satisfaction? Oncol. Issues 24 (1), 42–44. https://doi.org/10.1080/10463356.2009.11883750.

Zhou, F.L., Yeaw, J., Karkare, S.U., DeKoven, M., Berhanu, P., Reid, T., 2018. Impact of a structured patient support program on adherence and persistence in basal insulin therapy for type 2 diabetes. BMJ Open Diabetes Res. Care 6 (1), e000593. https://doi.org/10.1136/bmjdrc-2018-000593.