Examining Real World Treatment Patterns and Outcomes with Oral Disease Modifying Therapy Use in the Treatment of Relapsing Forms of Multiple Sclerosis: A Retrospective Study to Evaluate Adherence, Outcomes, and Utilization of Treatment

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BACKGROUND

- Multiple sclerosis (MS) is a progressive neurodegenerative disease affecting nearly one million people in the United States, with over 85% of patients diagnosed with relapsing-remitting disease[1]
- MS is typically diagnosed among adults ages 20-50 and affects women three times more often than men with prevalence higher among areas further away from the equator[2]
- Primary treatment goals are to prevent disease progression by reducing progressive neurological impairment, disability, and incidence of relapse; within the past few years, oral MS disease modifying therapies (DMTs) have come to market, providing more treatment options
- Patient-specific factors such as comorbidities, adverse drug events (ADEs), cost, breakthrough disease progression, and ineffectiveness of therapy strongly influenced adherence, with approximately one-fifth of patients taking oral DMTs non-adherent and one-fourth of patients discontinuing oral DMTs within one year[3]

OBJECTIVE

- To evaluate oral DMT utilization, switching trends, medication adherence, and patient-reported side effects

METHODS

- Data source: AllianceRx Walgreens Prime specialty pharmacy records
- Inclusion criteria: Patients taking an FDA-approved oral DMT for relapsing forms of MS from July 1, 2019 to December 31, 2020
- Exclusion criteria: Use of a third-party payer with research exclusion contractual agreements, <18 years of age, did not meet PDC calculation criteria (defined below), did not have either an ICD-10 code reflective of MS or Clinically Isolated Syndrome (CIS) or a confirmed MS diagnosis with the patient.
- Data collected: Demographic information, prescription history, patient profile notes, and survey responses from pharmacy dispensing software and clinical patient management applications/programs as part of normal pharmacy operating procedures
- Patients were separated into six categories based on medication or if they switched oral DMT therapy during the study period; for analysis purposes, medications were then categorized by drug class, including:*
  - Dihydroorotate dehydrogenase inhibitors (DHODHI): teriflunomide
  - Nuclear factor activators (Nrf2): dimethyl fumarate, diroximel fumarate
  - Sphingosine 1-phospahte receptor modulators (S1P): fingolimod, siponimod
- Adherence was measured by using proportion of days covered (PDC), requiring:
  - At least two fills on two separate dates, at least a 56-day supply of medication, and an index date that did not occur within the last 90 days of the study period
  - Switchers were defined as meeting the above criteria and switching from one medication to another in a different drug class or within the same drug class during the study period
- ADEs reported by patients were defined as side effects reported in a clinical assessment conducted upon patient initiation and every refill
  - Mean time to report an ADE was calculated by averaging the time of each of the three most common patient reported ADEs across each drug class
- Analyses were completed using Microsoft Excel Office 2016®, SAS Enterprise Guide 7.12® ,and RapidMiner® Studio Version 9.8 software
- Study approval was obtained from the Duquesne University Institutional Review Board

*Cladribine was excluded due to its unique dosing schedule and difficulty calculating PDC. Ozanimod was excluded due to limited data since its approval was halfway through the study period.

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All researchers have no conflicts of interest to disclose. For more information please contact: rich.t.miller@alliancerxwp.com.
Presented at the Academy of Managed Care Pharmacy (AMCP) 2021 Annual Meeting – April 12-16, 2021.

RESULTS

Table 1: Demographics

	Teriflunomide	Fingolimod	Siponimod	Dimethyl fumarate	Diroximel fumarate	Switched therapy
Patients, n (%)	2,930 (28.3)	2,199 (21.2)	226 (2.2)	4,700 (45.3)	58 (0.6)	257 (2.5)
Female sex, n (%)	2,280 (77.8)	1,637 (74.4)	170 (75.2)	3,435 (73.1)	48 (82.8)	198 (77.0)
Age, n (% of patients per drug)						
18 to 29 years	89 (3)	177 (8)	13 (5.6)	281 (6)	7 (12.1)	17 (6.6)
30 to 39 years	342 (11.7)	496 (22.6)	28 (12.4)	879 (18.7)	17 (29.3)	46 (17.9)
40 to 49 year	740 (25.3)	730 (33.2)	61 (27)	1407 (30)	13 (22.4)	65 (25.3)
50 to 59 years	1028 (35.1)	598 (27.2)	79 (35)	1409 (30)	16 (27.6)	93 (36.2)
60 to 69 years	624 (21.3)	181 (8.23)	39 (17.3)	644 (13.7)	5 (8.6)	31 (12.1)
70+ years	107 (3.7)	17 (.7)	6 (2.7)	80 (1.6)	0 (0)	5 (1.9)
Mean age, years	52	45	50	48	44	48
Geographic region, n (%)*						
Northeast	451 (15.4)	339 (15.4)	42 (18.6)	849 (18.1)	10 (17.2)	29 (11.3)
Midwest	1098 (37.5)	782 (35.6)	72 (31.9)	1611 (34.3)	12 (20.7)	83 (32.3)
West	337 (11.5)	275 (12.5)	27 (12)	706 (15)	19 (32.8)	35 (13.6)
South	1044 (35.6)	803 (36.5)	85 (37.6)	1534 (32.6)	17 (29.3)	110 (42.8)

** Geographic region was classified using the US Census Bureau classification*

Table 2: Medication Switching During Study Period

Switched therapy from	Switched therapy to, n (%)		
	DHODHI	Nrf2	S1P
Dihydroorotate dehydrogenase inhibitor (DHODHI) (n=42)	0 (0)	28 (66.7)	14 (33.3)
Nuclear factor activator (Nrf2) (n=188)	41 (21.8)	131 (69.7)	16 (8.5)
Sphingosine 1-phosphate receptor (S1P) (n=27)	14 (51.9)	6 (22.2)	7 (25.9)
Total (n=257)	55 (21.4)	165 (64.2)	37 (14.4)

Table 3: Mean PDC by Drug Class and Reported ADEs

	Patients, n (%)	Mean PDC ± SD
Dihydroorotate dehydrogenase inhibitor (DHODHI) (n=2930)		
ADE reported	951 (32.5)	.82 ± .24
No ADE reported	1979 (67.5)	.81 ± .25
Nuclear factor activator (Nrf2) (n=4758)		
ADE reported	2131 (44.8)	.78 ± .24
No ADE reported	2627 (55.2)	.78 ± .25
Sphingosine 1-phosphate receptor modulator (S1P) (n=2425)		
ADE reported	494 (20.4)	.82 ± .22
No ADE reported	1931 (79.6)	.83 ± .23
Switchers (n=257)		
ADE reported	158 (61.5)	.81 ± .19
No ADE reported	99 (38.5)	.79 ± .22

RESULTS, CONTINUED

Table 4: Frequency and mean time to report of the three most common ADEs by drug class

	Patients, n (%)*	Mean ± SD time to first reported ADE, days*
Dihydroorotate dehydrogenase inhibitor (DHODHI) (n=788)		
Hair loss or thinning	177 (22.5)	101 ± 94.7
Abdominal Pain	96 (12.2)	148 ± 111.4
Diarrhea	92 (11.7)	82 ± 78.3
Nuclear factor activator (Nrf2) (n=1277)		
Flushing	1037 (54.7)	111 ± 106
Abdominal Pain	166 (8.8)	117 ± 101.8
Diarrhea	74 (4)	103 ± 132.5
Sphingosine 1-phosphate receptor modulator (S1P) (n=149)		
Abdominal Pain	72 (17.8%)	156 ± 115.6
Fatigue	39 (9.7%)	122 ± 98
Headache	38 (9.4%)	113 ± 91.1

**Patients may have reported more than one ADE*

- A total of 10,370 patients met study inclusion criteria; the sample was predominantly female, between 40 and 59 years of age, and resided in the Midwest and South
  - Dimethyl fumarate was the most used oral DMT and diroximel fumarate was the least (**Table 1**)
  - The most utilized oral DMT drug class was Nrf2 (45.4%), followed by DHODHI (28.3%) and S1P (23.4%)
- A total of 257 patients (2.48%) switched from one oral DMT to another, including 46.3% switching to a different oral DMT drug class and 53.7% switching within the same class
  - The most common switch was from one Nrf2 to another, the least common was from an S1P to an Nrf2
  - In patients who changed oral DMT drug classes, the most common switch was to a DHODHI (**Table 2**)
- PDC estimates by drug class according to ADE report are presented in **Table 3**
  - There were no significant differences in PDC for any class according to ADE report
- A greater proportion of switchers (61.5%) reported at least one ADE relative to other study groups (Nrf2=44.8%; DHODHI=32.5%; and S1P=20.4%)
- Most reported ADEs by class were hair loss/thinning (DHODIH), flushing (Nrf2), and abdominal pain (S1P) (**Table 4**)

DISCUSSION / CONCLUSIONS

- Dimethyl fumarate was the most utilized oral DMT drug and diroximel fumarate was the least. However, this may be influenced by their approval dates, as dimethyl fumarate has been on the market the longest and diroximel fumarate is the newest, with an approval date after the start of the study period (October 29th, 2019)
- Based on this data, oral DMTs are well tolerated from an ADE perspective. Even among patients who experienced an ADE, our data suggests that ADE(s) did not affect patient adherence.
- Among switchers, mean PDC was greater after the switch compared to before the switch alluding that switching from one oral DMT to another may be a viable option to address non-adherence.
- The limitations of this study include reliance upon subjective patient-reported outcomes (susceptible to recall bias), and inability to measure all factors beyond ADEs which may influence patient non-adherence and switching behavior
- The strengths of the study are the generalizability and sample size of AllianceRx Walgreens Prime data
- Patient non-adherence and switching behavior may not be solely due to ADEs. In accordance with current literature, ADEs may contribute but are not the only factors contributing to non-adherence. These other factors need to be investigated in future studies

The authors wish to acknowledge and thank Dr. Jordan Covvey, Dr. Michael Gionfriddo, Paul Hanna, Kyle Essenburg, Kelsee McDermott, Rebecca Carlson and Jeffrey Chowaniec.