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Lymphopenia in Patients With Multiple Sclerosis Treated With Delayed-Release Dimethyl Fumarate: Analysis of Two United States Electronic Health Record Databases

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INTRODUCTION

- In clinical trials, delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) significantly reduced clinical and neuroradiological disease activity and exhibited a favorable benefit-risk profile in patients with relapsing-remitting multiple sclerosis (RRMS).[1,2]
- In clinical trials, the incidence of severe (Grade 3) lymphopenia (absolute lymphocyte count [ALC] <500 cells/µL) in DMF-treated patients was 7%.[3] The incidence of severe lymphopenia persisting ≥6 months was 2.5% (please see poster P2.099).
- Further research, including data obtained in real-world settings, is needed to understand the effects of DMF on lymphocytes.

OBJECTIVE

- Evaluate ALCs in patients with MS treated with DMF using data from 2 deidentified US electronic health record (EHR) databases.

METHODS

- We identified patients with a diagnosis of MS (International Classification of Diseases, Ninth Revision, code 340) using 2 EHR databases.
  - Geisinger Health System: patients identified from January 1, 2004 through March 31, 2015.
    - A health care delivery system serving the central, south central, and northeastern regions of the US state of Pennsylvania. It comprises 9 hospital campuses, 2 research centers, and the Geisinger Health Plan.
  - Humedica: patients were obtained from a deidentified EHR database from January 1, 2007 through December 31, 2014.
    - A compilation of medical records from ~55 million patients across the United States from various private health insurance plans.
- Inclusion criteria:
  - Patients included in the analyses received ≥1 valid prescription (written prescription for DMF including quantity and number of refills)
  - Patients had ALC values available at Baseline (within 6 months before DMF initiation to 7 days post DMF initiation) and at ≥1 time points post DMF initiation.
- Total time on DMF was defined as:
  - Geisinger Health System: time from DMF initiation to the earliest of the first disease-modifying therapy (DMT) switch or the last encounter in the database
  - Humedica: time from DMF initiation to the earliest of the first DMT switch, the last encounter in the database, the end of database follow-up period, or the end of exposure.
- ALCs were assessed at 6- and 12-month windows (±1.5 months) post DMF initiation and categorized into the following:
  - ≥1000 cells/µL
  - 700–999 cells/µL
  - 500–699 cells/µL
  - <500 cells/µL (severe lymphopenia).

RESULTS

- A total of 3187 patients with MS were identified to have received a prescription for DMF during the study period (Table 1).
- A total of 1014 patients (201 Geisinger and 813 Humedica) met the inclusion criteria.

Table 1. Geisinger Health System and Humedica patient population flow

	Geisinger	Humedica
Data available through	March 31, 2015	December 31, 2014
No. of DMF[a]-exposed patients with a valid prescription[b]	478	2709
No. of DMF[a]-exposed patients with Baseline ALC (within 6 months before initiation)	298	1466
No. of DMF[a]-exposed patients with Baseline and post DMF[a] initiation ALC	201	813

[a]DMF, delayed-release DMF (also known as gastro-resistant DMF)
[b]Valid prescription defined as a written prescription for DMF including quantity and number of refills

- Demographic characteristics of patients were similar between the Geisinger Health System and Humedica databases (71% and 77% female, respectively; mean age 44 and 47 years, respectively; Table 2).

Table 2. Patient characteristics

Characteristic	Geisinger n=201	Humedica n=813
	Mean/median	
Total time in database, mo[a]	86/99	70/71
Time after DMF[b] initiation, mo[c]	13/14	11/11
Total time on DMF[b] therapy, mo	12/12	9/9
Age at DMF[b] initiation, y	44/45	47/48
No. of ALC tests during DMF[b] treatment	4/2	2/2
Time from DMF[b] initiation to first ALC, d	136/111	105/78
	n (%)	
Female	143 (71)	625 (77)
Lymphocyte tests during DMF[b] exposure		
1 only	71 (35)	356 (44)
2 only	48 (24)	216 (27)
3 only	32 (16)	104 (13)
≥4	50 (25)	137 (17)
DMF[b]-exposed patients with ALC ≥1000 at Baseline	185 (92)	677 (83)
DMF[b]-exposed patients who discontinued treatment	34 (17)	67 (8)

[a]Total time in database refers to the patient's first encounter in the database to last encounter or end of available data, whichever came first
[b]DMF, delayed-release DMF (also known as gastro-resistant DMF)
[c]Time after DMF initiation refers to the patient's time from DMF initiation to last encounter in the database or end of available data, whichever came first

- Time on DMF treatment and follow-up time vary between the 2 data sources due to the difference in the date of available data.
- Fifty-four percent (Geisinger Health System) and 62% (Humedica) of patients had Baseline ALCs before DMF initiation.
- Among patients with ALCs at Baseline and post DMF initiation, the mean time to first ALC test after DMF initiation was 105–136 days.
- Among patients who had both Baseline and 6-month ALC values:
  - Mean ALCs decreased from 1934 to 1450 cells/µL for the Geisinger Health System and from 1821 to 1371 cells/µL for Humedica, representing a 25% decrease in both cohorts
  - Few (Geisinger Health System, 4%; Humedica, 3%) developed severe lymphopenia (ALC <500 cells/µL) at 6 months (Figure 1).

Figure 1. Lymphocyte trajectory at Baseline and 6 months among patients with ALCs measured at both time points

Geisinger, n=80

		Baseline ALC ≥1000 n=73	700–999 n=3	500–699 n=3	<500 n=1
6-month ALC, n (%)	≥1000	56 (70)	2 (3)	0	0
	700–999	13 (16)	1 (1)	2 (3)	0
	500–699	1 (1)	0	0	1 (1)
	<500	3 (4)	0	1 (1)	0

Humedica, n=348

		Baseline ALC ≥1000 n=297	700–999 n=33	500–699 n=9	<500 n=9
6-month ALC, n (%)	≥1000	215 (62)	11 (3)	1 (<1)	2 (<1)
	700–999	56 (16)	13 (4)	2 (<1)	1 (<1)
	500–699	15 (4)	8 (2)	5 (1)	1 (<1)
	<500	11 (3)	1 (<1)	1 (<1)	5 (1)

- Among patients who had both Baseline and 12-month ALC values:
  - Mean ALCs decreased from 1881 to 1272 cells/µL (32% decrease) for the Geisinger Health System and from 1858 to 1339 cells/µL (28% decrease) for Humedica
  - Four percent (Geisinger Health System) and 5% (Humedica) developed severe lymphopenia (ALC <500 cells/µL) at 12 months (Figure 2).

Figure 2. Lymphocyte trajectory at Baseline and 12 months among patients with ALCs measured at both time points

Geisinger, n=49

		Baseline ALC ≥1000 n=44	700–999 n=4	500–699 n=1	<500 n=0
12-month ALC, n (%)	≥1000	27 (55)	3 (6)	0	0
	700–999	8 (16)	0	1 (2)	0
	500–699	7 (14)	1 (2)	0	0
	<500	2 (4)	0	0	0

Humedica, n=182

		Baseline ALC ≥1000 n=163	700–999 n=15	500–699 n=2	<500 n=2
12-month ALC, n (%)	≥1000	99 (54)	10 (5)	1 (<1)	2 (1)
	700–999	40 (22)	2 (1)	1 (<1)	0
	500–699	14 (8)	1 (<1)	0	0
	<500	10 (5)	2 (<1)	0	0

- Among patients who had ALC ≥1000 cells/µL at Baseline, 5–6% of patients developed severe lymphopenia (ALC <500 cells/µL at any time) while on therapy; the majority had ≥1 ALC <500 cells/µL at or after 6 months of therapy (Table 3).
- The mean time from DMF initiation to severe lymphopenia was 9–10 months.

Table 3. Description of DMF patients who had ALC ≥1000 cells/µL at Baseline and experienced ≥1 ALC <500 cells/µL at any time while on therapy

	Geisinger n=185	Humedica n=677
≥1 ALC <500 cells/µL, n (%)	12 (6)	32 (5)
Months from initiation to ALC <500 cells/µL, mean/median	10/11	9/9

Limitations

- Observational data are not systematically collected.
  - Testing of lymphocytes is subject to physician discretion, health care delivery system protocols, and insurance reimbursement.
  - Lymphocyte subtypes were not routinely performed in these health care systems and were therefore not available for analysis.
- ALC results that could have been derived (where total white blood cell counts and percent lymphocytes are known) were not included in the analysis.
- Limited follow-up was due to the relatively recent approval of DMF in the United States.
  - May lead to an underestimate of identifying patients with severe lymphopenia.
  - Does not allow for a rigorous assessment of lymphocyte recovery after DMF discontinuation.
- Prior DMTs, immunosuppressant therapies, and steroids, which may or may not predispose DMF patients to lower ALC values, were not accounted for in this analysis.

CONCLUSIONS

- Consistent with observations in pivotal clinical trials, patients treated with DMF in the real-world setting experienced an ~30% reduction in ALCs. Approximately 5–6% of patients developed severe lymphopenia (ALC <500 cells/µL at any time), and the majority of patients who developed severe lymphopenia did so after ~9–10 months.[1,2]
- Decrease in lymphocyte count is a known adverse event of DMF and can be monitored by simple blood tests (ALC).
- Additional analyses using the Geisinger Heath System and Humedica databases are being conducted to examine ALC recovery patterns in patients with severe lymphopenia after discontinuation of DMF.

References

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Disclosures

MW, TS, CL, SE, CP, and AD: employees of and hold stock/stock options in Biogen; MJ: contract employee of Biogen.

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