Lymphocyte counts after initiation of dimethyl fumarate

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BACKGROUND

- Dimethyl fumarate (DF) is a first line oral therapy for relapsing remitting multiple sclerosis (RRMS)
- Its safety and tolerability has been demonstrated in the 2 year Phase 3 studies DEFINE and CONFIRM
- The Canadian DF Product Monograph indicates that the lymphocyte count will decrease by 30% within the first year and lymphopenia will occur in <6%
- One patient in an extension study developed progressive multifocal leukoencephalopathy (PML) in the setting of prolonged lymphopenia (lymphocyte counts predominantly <0.5 x 10^9/L for 3.5 years)
- The role of lymphopenia in the case of PML is unknown

OBJECTIVES

- This quality assurance project was undertaken to determine:
  - Change in lymphocyte counts over time
  - Occurrence of Grade 2 and Grade 3 lymphopenia
  - Patient adherence to safety monitoring for lymphocyte counts

METHODS

Study Population:

- Patients with RRMS who initiated DF between July 1, 2013 and December 31, 2014 and were followed at the Calgary MS Clinic; follow-up continued to March 31, 2015
- The Calgary MS Clinic manages over 1,800 disease modifying therapy (DMT) treated patients
- DMT use is carefully tracked using administrative processes and a clinic database
- A checklist is used to support patient education and safety prior to starting DMT
- Safety monitoring for lymphopenia is done monthly for the first 6 months and then every 3 months

Data Collection:

- Demographic, clinical, and lab information collected from electronic medical records (EMRs)
- Lymphocyte counts collected at baseline, 3 (+/-1), 6 (+/-1) and 12 (+/-2) months
- Lymphopenia defined as Grade 2 (0.5-0.7 x 10^9/L) and Grade 3 (0.2-0.4 x 10^9/L)
- Type of lymphopenia defined as confirmed, recurrent, transient, and no follow-up
- Time to first occurrence of lymphopenia categorized as 0 to <3, 3 to <6, 6 to <9, 9 to <12, and ≥12 months
- Adherence to lab testing measured at 3 (+/-1), 6 (+/-1), and 12 (+/-2) months; and between 0 to 6, and 6 to 12 months

Analysis:

- Summarized lymphocyte counts using descriptive statistics (mean, SD, median, IQR, range)
- Calculated absolute and percent change in lymphocyte counts from baseline to 3, 6, and 12 months
- Compared mean lymphocyte counts at each time point using two-sided paired t-tests

RESULTS

Table 1. Characteristics of the Study Cohort (N=170)

Characteristic	Statistic	
Age (years) [mean, range]	42.5	20.8-70.3
Women [n, %]	127	74.7
Age at MS onset (years) [mean, range]	30.3	11.8-56.2
Disease duration (years) [median, range]	12.1	0.2-39.8
EDSS score [median, range]	2.0	0-8
Prior DMT* [n, %]		
Glatiramer acetate	69	40.6
Interferon beta	49	28.8
Treatment naïve	40	23.5
Follow-up time (months) [median, range]	9.3	4.5-20.7
Time on DF (months) [median, range]	8.8	0.2-20.7
Discontinued DF [n, %]	24	14.1
Time to DF stop date (months) [median, range]	3.9	0.2-15.1

*Fingolimod (n=7), Natalizumab (n=4), Teriflunomide (n=1)

Table 2. Lymphocyte Counts Over Time

Time Point	Mean (SD)	Median (IQR)	Range
Lymphocyte Count (x 10^9/L)			
Baseline	2.0 (0.7)	2.0 (1.6 to 2.4)	0.5 to 4.4
3 month	1.6 (0.6)	1.6 (1.2 to 2.0)	0.4 to 3.5
6 month	1.3 (0.5)	1.2 (0.9 to1.6)	0.4 to 2.6
12 month	1.3 (0.5)	1.2 (0.9 to1.6)	0.4 to 26.0
Absolute Change from Baseline (x 10^9/L)			
3 month	-0.5 (0.6)	-0.4 (-0.8 to -0.1)	-2.4 to 2.2
6 month	-0.7 (0.6)	-0.7 (-1.1 to -0.3)	-2.8 to 0.8
12 month	-0.7 (0.5)	-0.7 (-1.0 to -0.3)	-1.6 to 0.5
Percent Change from Baseline (%)			
3 month	-16.6 (48.5)	-22.2 (-38.2 to -3.5)	-73.3 to 400.0
6 month	-32.3 (28.5)	-37.2 (-54.2 to -15.8)	-76.9 to 71.4
12 month	-34.0 (23.4)	-38.9 (-53.8 to -15.8)	-73.3 to 33.3

Baseline (n=170), 3 month (n=131), 6 month (n=96), 12 month (n=47)

Fig 1. Lymphocyte Counts Over Time

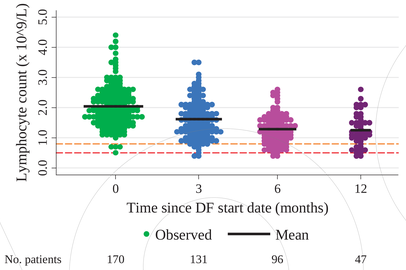


Fig 2. Change in Lymphocyte Counts from Baseline

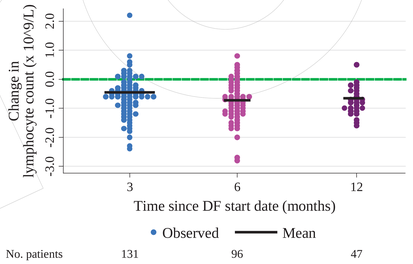


Fig 3. Increase/Decrease in Lymphocyte Counts from Baseline

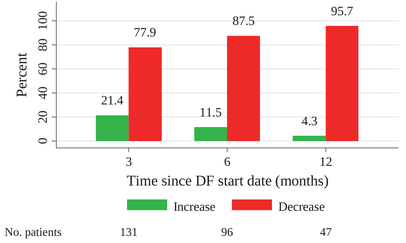


Fig 4. Time to Lymphopenia

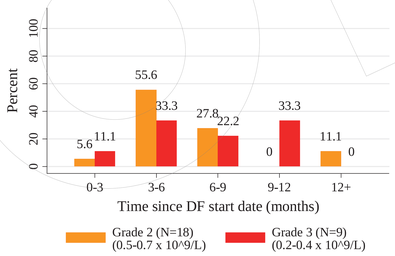
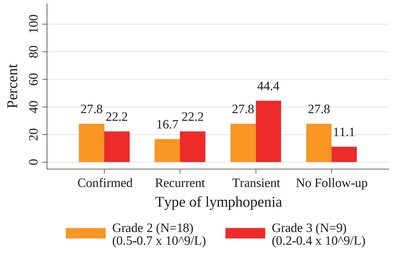
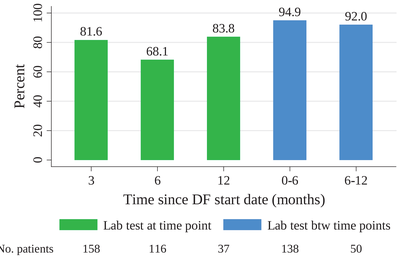


Fig 5. Type of Lymphopenia



Confirmed – lymphopenia observed on all subsequent lab tests
Recurrent – lymphopenia observed on at least one subsequent lab test
Transient – lymphopenia observed on one lab test only
No Follow-up – no subsequent lab tests available

Fig 6. Adherence to Lymphocyte Testing



- Lymphocyte counts decreased significantly from baseline to 3, 6 and 12 months; and from 3 months to 6 and 12 months (p<0.001); there was no significant difference at 6 and 12 months (p=0.09)

Grade 2 Lymphopenia (0.5-0.7 x 10^9/L)

- Occurred in 18/163 (11.0%, 95% CI: 6.2-15.9)
- Median time to first occurrence was 6.4 months (range: 3.0-13.8)
- 1/18 discontinued DF (patient decision) – patient was concerned about abnormal lab results and had flushing side effects

Grade 3 Lymphopenia (0.2-0.4 x 10^9/L)

- Occurred in 9/163 (5.5%, 95% CI: 2.0-9.1)
- Median time to first occurrence was 6.3 months (range: 2.6-11.0)
- 1/9 discontinued DF (patient decision) – patient felt unwell
- Only 1/50 (2.0%) followed for at least 12 months had no lab tests

CONCLUSIONS

- Our data are consistent with the expectation from the Canadian DF Product Monograph
- At 12 months, lymphocyte counts decreased by 34.0% from baseline, but the mean lymphocyte count remained within normal limits
- Grade 3 lymphopenia (0.2-0.4 x 10^9/L) occurred in 5.5%
- The Canadian DF Product Monograph recommends lymphocyte testing after 6 months of treatment, then every 6 to 12 months, and as clinically indicated
- Monthly lymphocyte testing in the first 6 months appears to be excessive
- Our data support lymphocyte testing every 3 months in the first year
- Adherence to safety monitoring is generally good in our population