Progressive multifocal leukoencephalopathy outcomes in patients with multiple sclerosis treated with dimethyl fumarate

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Abstract
Background and objectives: Dimethyl fumarate (DMF), an oral disease-modifying therapy with an established benefit and well-described safety profile, is among the most commonly used therapies for relapsing forms of multiple sclerosis. As of 31 December 2021, >560,000 patients have been treated with DMF, representing >1,190,000 person-years of exposure. Of these, 6413 patients (14,292 person-years) were from clinical trials.

Methods and results: Progressive multifocal leukoencephalopathy (PML) has occurred in the setting of lymphopenia (<0.91 × 10⁹/L) in patients treated with DMF. We present detailed clinical characteristics and outcomes of the 12 confirmed PML cases occurring in MS patients on DMF as of 21 July 2021. The PML incidence in DMF-treated patients is 1.07 per 100,000 person-years of DMF exposure. Lymphopenia is the common risk for PML in DMF treatment.

Discussion: DMF-related PML is rare but has occurred in the setting of lymphopenia, supporting the current recommendations for absolute lymphocyte count monitoring in all patients, regardless of age and time on therapy.

Keywords: Multiple sclerosis, progressive multifocal leukoencephalopathy, John Cunningham virus, dimethyl fumarate, immune suppression, viral infections

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of the manuscript is to describe DMF-related PML cases including outcomes post-PML and to inform on the decreased incidence of PML resulting from the implementation of absolute lymphocyte count (ALC) monitoring.

Methods
Biogen has a dedicated adverse event of special interest team for targeted and standardized clinical data collection and classification of PML reports from all sources. The cases reported in this manuscript are based on Biogen internal data and post-marketing surveillance reports, as of July 2021. Biogen PML Case Classification Criteria uses standardized criteria and case definitions to differentiate and classify reported cases of PML by levels of diagnostic certainty. Case Classification Criteria were developed using the Brighton Criteria methodology, hierarchy of diagnostic evidence approach and in collaboration with external PML experts. A confirmed case (Level 1) is defined as either (1) a brain biopsy or brain from post-mortem examination showing evidence of viral cytopathic changes on hematoxylin and eosin (H&E) stain associated with either positive immunohistochemistry for SV40 or in situ hybridization for JCV DNA or (2) cerebrospinal fluid (CSF) with evidence of JCV DNA (preferably by ultrasensitive quantitative polymerase chain reaction testing) along with detailed brain magnetic resonance imaging (MRI) findings consistent with PML and, preferably, new or progressive clinical symptoms suggestive of PML. Cases that are not confirmed are adjudicated as Levels 2–5, depending on the level of diagnostic certainty based on available information/follow-up.

The examining neurologists conducted neurologic assessments, including assessment of the Expanded Disability Status Scale (EDSS) score and Kamofsky Performance Scale score. The EDSS scores range from 0 to 10, with a higher score indicating a greater degree of disability. The Kamofsky Performance Scale Index scores range from 0 to 100, with a lower score indicating greater functional impairment.

Information about the cases has been collected during the course of Biogen’s routine pharmacovigilance data collection activities and compiled from the Biogen GSD and supplemented by published cases.

Results
Review of PML cases in DMF-treated patients
As of 31 December 2021, >560,000 patients have been treated with DMF, representing >1,190,000 person-years of exposure. During this time, a total of 12 cases of PML were confirmed (Table 1). All 12 cases were confirmed in the setting of presence of JCV DNA in CSF along with a brain MRI consistent with the diagnosis of PML. None of the 12 patients with confirmed PML underwent brain biopsy. Over half of all PML cases (nine patients) occurred in the setting of prolonged, moderate to severe lymphopenia; all PML cases occurred in the setting of lymphopenia. Three cases occurred in the setting of mild, non-prolonged (<6 months) lymphopenia. Patient age ranged from 39 to 66 years (median age: 60.5 years old), and median duration of DMF exposure prior to PML diagnosis was 42 months, ranging from 17 to 72 months. The range from first PML symptom to diagnosis date of PML is 3 weeks to 5 months, and the average is 2.16 months. Lymphocyte subset data, specifically CD4+ and CD8+ lymphocyte counts, were not available for any case prior to the time of PML diagnosis. Prior DMTs included natalizumab for two patients, injectable therapies for 8 patients, natalizumab and an injectable for one patient and none for one patient. Eleven of the 12 confirmed cases were reported in the post-marketing setting after the implementation of specific lymphocyte monitoring guidance, resulting in an incidence rate of 1.07 per 100,000 person-years of DMF exposure.

Patient outcomes
The most commonly reported PML outcome was ‘recovered with sequela’ (seven patients); three patients were reported as ‘not recovered’. The term ‘not recovered’, as defined, differs from ‘recovered with sequela’ insofar as the former refers to a disease that is ongoing, whereas the latter signifies that the disease has resolved, but there are ongoing deficits as a result of the disease. Two patients died. The majority of patients (n = 9) presented with motor symptoms, followed by speech disturbance (n = 7), cerebellar symptoms (n = 5), cognitive/behavioral disturbance (n = 4) and visual and sensory disturbance (n = 3), respectively. There were no reports of spinal cord involvement among the 12 confirmed cases. Five patients experienced immune reconstitution inflammatory syndrome (IRIS), two patients did not experience IRIS and the remaining five patients did not have information regarding IRIS provided. Of the two patients with dates recorded for IRIS onset, 1 month and 4 months after PML symptom onset were recorded. Two of five patients received steroid treatment specifically for IRIS. One patient received plasma exchange therapy (PLEX). All but two patients received one or more of the following...
Table 1. Clinical characteristics of DMF-treated patients with MS who developed PML.

| Case | Sex | Lymphocyte status | Year of Age (years) | DMF exposure (months) | Case setting | Duration of MS diagnosis (years) | Duration of lymphopenia (months) | Prior treatment for MS | Diagnosis information | MRI 6 months post-PML diagnosis | Most recent PML outcome | PML management |
|------|-----|-------------------|--------------------|----------------------|--------------|---------------------------------|--------------------------------|----------------------------|------------------------|---------------------------|------------------------|-------------------|
| 1    | F   | Prolonged, moderate to severe | 2014 | 54 | 54b | Clinical trial (ENDORSE) | Unknown | 48 | Glatiramer acetate | Gait disorder, L arm ‘weakness’, ‘difficult speech’ | L MCP and L cerebellar hemisphere | NA (fatal) | Fatal |
| 2    | M   | Prolonged moderate to severe | 2015 | 64 | 25 | Post-marketing | 3 | At least 12 months (ALC not followed per label) | None | Dizziness | L inferior frontal | PML | Not recovered |
| 3    | M   | Prolonged moderate to severe | 2015 | 59 | 17 | Post-marketing | 7 | 14 | IFN beta-1a (Rebif) | Fatigue, apathy, weight loss | Bilateral frontal | PML improved | Recovered with sequelae |
| 4    | F   | Prolonged moderate to severe | 2015 | 61 | 22 | Post-marketing | Unknown | 12 | IFN beta-1a (Avonex); Intravenous immunoglobulin; Natalizumab | L arm weakness, dressing apraxia | R parietal lobe | N/A (no imaging) | Not recovered |
| 5    | F   | Prolonged moderate to severe | 2016 | 66 | 41 | Post-marketing | 10 | 23 | IFN beta-1a (Rebif); Glatiramer acetate | Dysarthria, imbalance, ataxia | Pons, L MCP, bilateral cerebellar hemispheres, L superior and inferior frontal lobe | PML unchanged | Recovered with sequelae |
| 6    | F   | Prolonged moderate to severe | 2017 | 60 | 36 | Post-marketing | 6 | 16 | IFN beta-1a (Rebif); Corticosteroids | Dizzy, L hemianopsia, sensory loss of LE, memory loss | R TPO Area | NA (no imaging) | Recovered with sequelae |
| 7    | F   | Mild | 2018 | 66 | 52 | Post-marketing | 6 | 1 | IFN beta-1a (Avonex) | R ataxia and tremor, food intolerance/vomiting | R MCP and cerebellar hemisphere | PML improved | Recovered with sequelae |
| 8    | F   | Mild | 2018 | 39 | 42 | Post-marketing | 7 | 3 | Natalizumab | R thalamus, midbrain, pons, medulla, bilateral MCPs | New MS lesions | Recovered with sequelae |
| 9    | F   | Prolonged, moderate to severe | 2020 | 64 | 43 | Post-marketing | Unknown | NA | Rebif, IFN beta-1a | Gait instability | NA | Fatal |

(continued)
| Case | Sex | Lymphocyte status | Year of case | Age (years) | DMF exposure (months) | Case setting | Duration of MS diagnosis (years) | Duration of lymphopenia (months) | Prior treatment for MS | Diagnosis information | MRI 6 months post-PML diagnosis | Most recent PML outcome | PML management |
|------|-----|-------------------|--------------|-------------|----------------------|--------------|-------------------------------|---------------------------------|------------------------|------------------------|------------------------|------------------------|------------------|
| 10   | F   | Mild              | 2017         | 41          | 20                   | Post-marketing | 4                             | ~ 0.5                           | IFN beta-1a (Avonex, Rebif) | L inferior frontal and parietal | NA                     | Not recovered           | Steroids, mannitol |
| 11   | F   | Prolonged moderate to severe | 2020 | 66          | 69                   | Post-marketing | Unknown                      | 22                              | Natalizumab            | R posterior frontal, progressed to parietal, occipital also L parietal Bilateral frontal, R internal and external capsules, basal ganglia, parietal, bilateral thalami (R > L) | NA                     | Recovered with sequelae | Mirtazapine 15 mg HS |
| 12   | F   | Prolonged, moderate to severe | 2020 | 57          | Unknown             | Post-marketing | 17                            | At least 38                      | IFN beta-1b (Betaseron)     | L arm weakness and dysarthria | PML improved            | Recovered with sequelae | Steroids for IRIS |

Severe prolonged lymphopenia (ALC < 0.5 x 10^9/L for ≥6 months; World Health Organization [WHO] grades 3–4); moderate prolonged lymphopenia (ALC ≥ 0.5 x 10^9/L and < 0.8 x 10^9/L for ≥6 months, excluding patients with < 0.5 x 10^9/L for ≥6 months; WHO grade 2); mild lymphopenia (ALC < lower limit of normal [i.e., 0.91 x 10^9/L] any time, excluding patients with < 0.8 x 10^9/L for ≥6 months; WHO grade 1).

*This patient was treated with 240 mg of DMF TID for 2 years in DEFINE, followed by 240 mg of DMF BID for 2.5 years in ENDORSE. All other patients were treated with 240 mg DMF B.

ALC, absolute lymphocyte count; DMF, dimethyl fumarate; IRIS, immune reconstitution inflammatory syndrome; L, left; MS, multiple sclerosis; MCP, middle cerebellar peduncle; MRI, magnetic resonance imaging; NA, information not available; PML, progressive multifocal leukoencephalopathy; PLEX, plasma exchange therapy; R, right; TPO, temporal/parietal/occipital.
experimental therapies throughout the course of their PML: mirtazapine, mefloquine, or corticosteroids. Of the 10 patients who survived PML, 4 went on to receive a new MS DMT post-PML diagnosis: glatiramer acetate \((n=2)\), peginterferon beta-1a \((n=1)\) and teriflunomide \((n=1)\). Two patients did not start a new DMT, and in four patients, the follow-up therapy status is unknown. MRI findings varied in terms of lesion location and lesion evolution.

Follow-up EDSS and Karnofsky Assessment Scores post-PML diagnosis were reported in seven patients, with three patients having \(\geq 3\) scores reported over the follow-up time period (3, 6, 12 and 24 months) (Figure 1(a) and (b)). Of those, scores rose or remained stable post-PML diagnosis. Of those, scores rose or remained stable post-PML diagnosis. Of the two patients with a modified Rankin Score reported, both had a score of 4, at 5 months and 2 years after PML diagnosis, respectively.

Among the 12 reported PML cases, 2 deaths have been reported, both in the setting of PML with prolonged, severe lymphopenia. The first fatal case was a 54-year-old woman with MS who was treated with DMF and who died from complications related to aspiration pneumonia and PML.\(^{12}\) The patient had received DMF 240 mg three times daily for 2 years in the DEFINE clinical trial and was exposed to DMF 240 mg twice daily for 2.5 years in the ENDORSE open-label extension of the DEFINE clinical trial, for a total of 4.5 years of DMF treatment. After 12 months of DMF treatment, the patient developed severe lymphopenia persisting for 3.5 years. The patient is the only DMF-PML case known to have been treated with PLEX. Following this case, the ENDORSE clinical trial protocol was updated to monitor ALC more closely and to withhold treatment in patients with lymphocyte counts \(<0.5 \times 10^9/mL\) for more than 6 months. The second PML fatality was a woman with MS who had received treatment with DMF for more than 3 years in a post-marketing setting. This patient experienced prolonged grade 2 lymphopenia (ALK 0.6 \(\times 10^9/L\)). Ten out of the 12 reported cases are known to have survived PML (7 have recovered with sequelae, while 3 have not recovered).

**Discussion**

As of 21 July 2021, PML in DMF-treated patients remains a very rare event, with an estimated reporting rate of 1.07 cases per 100,000 person-years of post-marketing exposure (Biogen data on file). This is a similar PML risk to that reported for ocrelizumab (0.37 per 100,000 person-years as of March 2022 for ‘non-carry-over cases’, or 2.24 per 100,000 person-years including ‘carry-over’ cases from previous natalizumab or fingolimod use);\(^{19, 20}\) about three times less PML risk than that reported for fingolimod (3.12 per 100,000 person-years as of 31 August 2017),\(^{7}\) and \(~300\) times less than natalizumab (402 per 100,000 person-years as of December 2019).\(^4\) Compared to fingolimod and natalizumab, the small number of cases of PML in DMF-treated patients allowed us to include data for all 12 cases. Overall, DMF has demonstrated efficacy for the treatment of MS with long-term sustained clinical benefits.\(^{10}\) The risks of DMF use, including the risk of PML, must continue to be weighed against the potential for benefit in the consideration of its use.

In patients treated with natalizumab, the presence of serum anti-JCV antibodies, immunosuppressant use prior to natalizumab initiation and natalizumab treatment duration of \(\geq 2\) years are the primary risk factors for developing PML and these risk factors can be used to assess benefit–risk ratio for individual patients.\(^{21}\) In fingolimod-treated patients, PML has occurred primarily in the setting of \(\geq 2\) years on treatment. These risk factors have not been identified to date as being risk factors for PML with DMF. ALC

![Figure 1. Scores for (a) EDSS and (b) Karnofsky in individual patients with PML. EDSS, Expanded Disability Status Scale; PML, progressive multifocal leukoencephalopathy. The timeframe for the measurement pre-PML diagnosis is an estimate.](http://www.sagepub.com/msjetc)
is the most commonly used metric for identifying DMF-treated patients who are at risk of developing PML.1, 22, 23 Age (≥54 years) has also been hypothesized as a potential risk factor for PML in DMF-treated patients,1 but this is not supported by this analysis.

All 12 confirmed cases of PML in DMF treatment were symptomatic. Two patients had fatal outcomes and 10 survived. All cases occurred in the setting of lymphopenia, and all occurred after the timing of the expected lymphocyte nadir of about 12 months on therapy.9 Therefore, monitoring for lymphopenia and being vigilant for signs and symptoms of PML throughout treatment in all patients treated with DMF is important for risk reduction.

Importance of ALC monitoring
Following the initial report of PML in ENDORSE, occurring in the setting of prolonged, severe lymphopenia that persisted for ≥3 years with a fatal outcome, lymphopenia was identified as a risk factor for PML.12 Pursuant to this case, more stringent lymphocyte monitoring and stopping criteria for prolonged, severe lymphopenia were implemented for the ENDORSE study.10 Additionally, prescribing information globally was updated.22, 23

Clinicians are recommended to consider DMF treatment interruption in patients with ALCs <0.5 × 10^9/L persisting for ≥6 months as per the US DMF label guidance.23 Monitoring ALC remains an effective way for identifying patients at risk of subsequently developing prolonged lymphopenia, a risk factor for PML in DMF-treated patients.

At the present time, ALC is the recommended monitoring tool to identify MS patients treated with DMF at risk for developing PML, as all DMF-treated patients who developed PML had lymphopenia. Further, an analysis found no genetic predictors of severe or moderate prolonged lymphopenia factors using the DEFINE/CONFIRM dataset.24 Globally, the DMF labels include a recommendation for clinicians to discontinue or consider treatment interruption in patients with ALCs <0.5 × 10^9/L that persists for more than 6 months to minimize the risk of subsequently developing prolonged, severe lymphopenia and its potential complications.22, 23

In an integrated analysis of phase 3, and long-term extension studies of DMF in patients with MS (DEFINE, CONFIRM and ENDORSE), mean ALCs decreased by 28% over the first year, then remained generally stable for the duration of the study, remaining above the lower limit of normal (0.91 × 10^9/L) for the majority of patients (59%) at Year 2.10 The overall incidence of prolonged, severe lymphopenia (ALC <0.5 × 10^9/L persisting for more than 6 months) was very small, occurring in 53 (2.8%) of all DMF-treated patients. Consistent with the overall ALC dynamics, the majority of patients who developed prolonged, severe lymphopenia did so within the first 3 years of treatment. Late-onset prolonged, severe lymphopenia (onset after Year 3) was very rare but occurred in 9 of 2513 patients (<1%).25 In the majority of this small subset of patients, their ALC dropped below 0.8 × 10^9/L within the first year of treatment and remained low for several years until they eventually developed prolonged, severe lymphopenia.26 Most patients’ ALCs were always ≥0.8 × 10^9/L within the first year of treatment (83% [2050/2470]; of those, few (0.1% [2/2050]) developed prolonged, severe lymphopenia.26 Our review of patient cases supports previous reports showing lymphopenia as the common risk factor for PML development in MS patients treated with DMF and that vigilant and consistent ALC monitoring throughout DMF use can provide an effective method of early identification of patients at risk of developing prolonged, severe lymphopenia.

In summary, DMF is an oral DMT that is efficacious and has a favorable safety profile in patients with MS. The risk for the development of PML in a DMF-treated MS patient is rare, and the incidence rate is estimated at 1.07 per 100,000 person-years. DMF-related PML has occurred in the setting of lymphopenia, supporting the current recommendations for ALC monitoring in all patients, regardless of age and time on therapy. Future real-world data are needed to further identify the risk factors of lymphopenia in all patients, including patients of different ethnic groups and different genetic backgrounds.

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References

1. Jordan AL, Yang J, Fisher CJ, et al. Progressive multifocal leukoencephalopathy in dimethyl fumarate-treated multiple sclerosis patients. *Mult Scler* 2022; 28(1): 7–15.
2. Kartau M, Sipila JO, Auvinen E, et al. Progressive multifocal leukoencephalopathy: current insights. *Degener Neurol Neuroradiol* 2019; 9: 109–121.
3. Patel A, Sul J, Gordon ML, et al. Progressive multifocal leukoencephalopathy in a patient with progressive multiple sclerosis treated with ocrelizumab monotherapy. *JAMA Neurol* 2021; 78: 736–740.
4. Giovannoni GKL, Berger J, Cutter G, et al. Updated incidence of natalizumab-associated progressive multifocal leukoencephalopathy (PML) and its relationship with natalizumab exposure over time. In: Paper presented at: American Academy of Neurology 2020–22nd Annual Meeting, 2020.
5. Berger JR, Cree BA, Greenberg B, et al. Progressive multifocal leukoencephalopathy after fingolimod treatment. *Neurology* 2018; 90: e1815–e1821.
6. Klotz L, Havla J, Schwab N, et al. Risks and risk management in modern multiple sclerosis immunotherapeutic treatment. *Ther Adv Neurol Disord* 2019; 12: 175628641983657.
7. Cohan SL, Moses H, Calkwood J, et al. Clinical outcomes in patients with relapsing-remitting multiple sclerosis who switch from natalizumab to delayed-release dimethyl fumarate: a multicenter retrospective observational study (STRATEGY). *Mult Scler Relat Disord* 2018; 22: 27–34.
8. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012; 367: 1087–1097.
9. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012; 367: 1098–1107.
10. Gold R, Arnold DL, Bar-Or A, et al. 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* 2022; 28(5): 801–816.
11. Kresa-Reah K, Repovic P, Robertson D, et al. Effectiveness of delayed-release dimethyl fumarate on clinical and patient-reported outcomes in patients with relapsing multiple sclerosis switching from glatiramer acetate: RESPOND, a prospective observational study. *Clin Ther* 2018; 40: 2077–2087.
12. Rosenkranz T, Novas M and Terborg C. PML in a patient with lymphocytopenia treated with dimethyl fumarate. *N Engl J Med* 2015; 372: 1476–1478.
13. Baharnoori M, Lyons J, Dastagir A, et al. Nonfatal PML in a patient with multiple sclerosis treated with dimethyl fumarate. *Neurol Neuroimmunol Neuroinflamm* 2016; 3: e274.
14. Diebold M, Altersberger V, Decard BF, et al. A case of progressive multifocal leukoencephalopathy under dimethyl fumarate treatment without severe lymphopenia or immunosenescence. *Mult Scler* 2019; 25: 1682–1685.
15. Garcia JCBH, Chavez Baroni H, Dubessy AL, et al. Progressive multifocal leukoencephalopathy in a patient treated by dimethyl fumarate for multiple sclerosis with no lymphopenia but exhausted T lymphocyte subpopulations. In: 35th congress of the European committee for treatment and research in multiple sclerosis and 24th annual conference of rehabilitation in MS, Stockholm, Sweden, 2019.
16. Gieselbach RJ, Muller-Hansma AH, Wijburg MT, et al. Progressive multifocal leukoencephalopathy in patients treated with fumaric acid esters: a review of 19 cases. *J Neurol* 2017; 264: 1155–1164.
17. Lehmann-Horn K, Penkert H, Grein P, et al. PML during dimethyl fumarate treatment of multiple sclerosis: how does lymphopenia matter? *Neurology* 2016; 87: 440–441.
18. Dong-Si TWT, Richert N, Quinn G, et al. Classification of natalizumab case reports with progressive multifocal leukoencephalopathy. In: Paper presented at: 64th Annual meeting of the American Academy of Neurology, New Orleans, Louisiana, 2012.
19. Genentech USA Inc. Ocrevus (ocrelizumab) for US healthcare professionals; additional information on topics of interest, https://www.ocrelizumabinfo.com/ocrelizumab-safety-resources.html#additional-information (2022, accessed 24 August 2022).
20. Clifford DB GA, Richert N, Tornatore C, et al. Cases reported as progressive multifocal leukoencephalopathy in ocrelizumab-treated patients with multiple sclerosis. In: Presented at the 35th Congress of the European committee for treatment and research in multiple sclerosis (ECTRIMS), Stockholm, Sweden, 2019.
21. Ho PR, Koendgen H, Campbell N, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. *Lancet Neurol* 2017; 16: 925–933.
22. European Medicines Agency. Tecfidera 120 mg gastro-resistant hard capsules [online], ema.europa.eu/documents/product-information/tecfideraepar-product-information_en.pdf (2021, accessed 13 August 2021).

23. Biogen Inc. Tecfidera® prescribing information (dimethyl fumarate) delayed-release capsules, for oral use [online], tecfidera.com/content/dam/commercial/multiple-sclerosis/tecfidera/pat/en_us/pdf/full-prescribing-info.pdf (2021, accessed 13 August 2021).

24. Sangurdekar D, Sun C, McLaughlin H, et al. Genetic study of severe prolonged lymphopenia in multiple sclerosis patients treated with dimethyl fumarate. *Front Genet* 2019; 10: 1039.

25. Chan AFR, Bar-Or A, Gold R, et al. Lymphocytes increase and disease activity remains stable in patients who discontinue dimethyl fumarate with lymphopenia. In: Paper presented at: ECTRIMS (2019) European committee for treatment & research in multiple sclerosis – 35th Congress, Stockholm, Sweden, 2019.

26. Fox RJCA, Gold R, Phillips JT, et al. Lymphocyte decline and reconstitution after discontinuation in patients with severe, prolonged lymphopenia treated with delayed-release dimethyl fumarate. In: Paper presented at: American Academy of Neurology, Los Angeles, CA, 2018.