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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 ($<0.91 \times 10^9$/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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Introduction

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by reactivation and viral replication of the John Cunningham virus (JCV) in glial cells that can lead to death or severe disability.[1] Originally described in patients with hematologic malignancies, PML typically occurs in patients with reduced cell-mediated immunity, such as advanced HIV infection or patients who have undergone immune suppression in the setting of organ transplantation or chemotherapy.[2] PML has also been described in patients treated with disease-modifying therapies (DMTs) for multiple sclerosis (MS) with a range of clinical outcomes from asymptomatic cases to those with fatal outcomes.[2–6]

Dimethyl fumarate (DMF) is an oral DMT approved for treating relapsing forms of MS (RMS). DMF has demonstrated significant, clinically meaningful, sustained efficacy and a favorable benefit–risk profile in the pivotal phase 3 studies DEFINE and CONFIRM and in real-world studies of patients with RMS.[7–11] PML has been reported in patients treated with DMF for MS.[1,12–17] The first case of PML with DMF use occurred in ENDORSE, the extension study of the pivotal phase 3 DEFINE and CONFIRM clinical trials designed to evaluate long-term safety and efficacy of DMF in patients with MS.[12]

This manuscript presents the latest data on the clinical characteristics and outcomes of MS patients who developed PML while treated with DMF. The aim

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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.[18] A confirmed case (Level 1) is defined as either (1) a brain biopsy or brain from postmortem 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 Karnofsky Performance Scale score. The EDSS scores range from 0 to 10, with a higher score indicating a greater degree of disability. The Karnofsky 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.[12–15]

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 sequelae' (seven patients); three patients were reported as 'not recovered'. The term 'not recovered', as defined, differs from 'recovered with sequelae' 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 case	Age (years)	DMF exposure (months)	Case setting	Duration of MS diagnosis (years)	Duration of lymphopenia (months)	Prior treatment for MS	Diagnosis information			Most recent PML outcome	PML management
										Clinical symptoms	Lesion location on MRI	MRI 6 months post-PML diagnosis		
1[12]	F	Prolonged, moderate to severe	2014	54	54[a]	Clinical trial (ENDORSE)	Unknown	48	Glatiramer acetate	Gait disorder, L arm 'weakness' 'difficult speech'	L MCP and L cerebellar hemisphere	NA (fatal)	Fatal	PLEX and steroids
2[13]	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 improved	Not recovered	Mirtazapine 30 mg HS
3[17]	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	Mefloquine and mirtazapine
4[16]	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	NA
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	Mirtazapine 30 mg, steroids
6	F	Prolonged moderate to severe	2017	60	36	Post-marketing	6	16	IFN beta-1[a] (Rebif); Corticosteroids	Dizzy, L hemianopsia, sensory loss of LE, memory loss	R TPO Area	NA (no imaging)	Recovered with sequelae	Steroids
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	Steroids
8	F	Mild	2018	39	42	Post-marketing	7	3	Natalizumab	L hand tremor	R thalamus, midbrain, pons, medulla, bilateral MCPs	New MS lesions	Recovered with sequelae	Nothing
9	F	Prolonged, moderate to severe	2020	64	43	Post-marketing	Unknown	NA	Rebif: IFN beta-1a	Gait instability	Bilateral cerebellum and bilateral MCP	NA	Fatal	Mirtazapine (for 1 week) then mefloquine and steroids

(continued)

Table 1. 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			Most recent PML outcome	PML management
										Clinical symptoms	Lesion location on MRI	MRI 6 months post-PML diagnosis		
10	F	Mild	2017	41	20	Post-marketing	4	~ 0.5	IFN beta-1a (Avonex, Rebif)	Temporal and spatial disorientation, nystagmus, memory issues, tremor, dysmetria, speech disorder	L inferior frontal and parietal	NA	Not recovered	Steroids, mannitol
11	F	Prolonged moderate to severe	2020	66	69	Post-marketing	Unknown	22	Natalizumab	L hemiparesis and falls	R posterior frontal, progressed to parietal, occipital also L parietal	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	Bilateral frontal, R internal and external capsules, basal ganglia, parietal, bilateral thalami (R > L)	PML improved	Recovered with sequelae	Steroids for IRIS

Severe prolonged lymphopenia (ALC $<0.5\times10^9$/L for ≥6 months; World Health Organization [WHO] grades 3–4); moderate prolonged lymphopenia (ALC $\geq0.5\times10^9$/L and $<0.8\times10^9$/L for ≥6 months, excluding patients with $<0.5\times10^9$/L for ≥6 months; WHO grade 2); mild lymphopenia (ALC < lower limit of normal [i.e., 0.91×10^9/L] any time, excluding patients with $<0.8\times10^9$/L for ≥6 months; WHO grade 1).

[a]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 ≥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 (ALC 0.6×10^9/L). Ten out of the 12 reported cases are known to have survived PML (7 have recovered with sequelae, while 3 have not recovered).

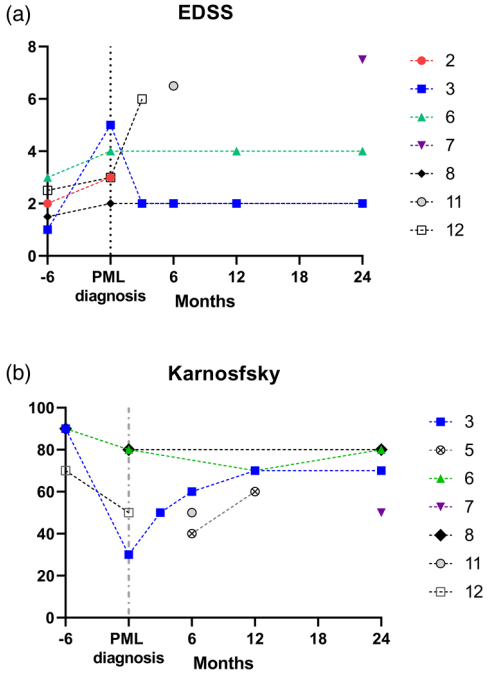

Figure 1. Scores for (a) EDSS and (b) Karnofsky in individual patients with PML.
EDSS, Expanded Disability Status Scale; PML, progressive multifocal leukoencephalopathy. The timeframe for the measurement pre-PML diagnosis is an estimate.

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),[5] 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 ≥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 >2 years on treatment. These risk factors have not been identified to date as being risk factors for PML with DMF. ALC

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 $<0.5 \times 10^9$/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 $<0.5 \times 10^9$/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 $<0.5 \times 10^9$/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.[25] Most patients' ALCs were always $\geq 0.8 \times 10^9$/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.

Author's contribution

Biogen provided funding for medical writing support in the development of this paper. Karen Spach, from Excel Scientific Solutions, wrote the first draft of the manuscript based on input from the authors, and copyedited and styled the manuscript per journal requirements. Biogen reviewed and provided feedback on the paper. The authors had full editorial control of the paper and provided their final approval of all content.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or

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