Dimethyl fumarate treatment shifts the immune environment toward an anti-inflammatory cell profile while maintaining protective humoral immunity

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Abstract

Background: Delayed-release dimethyl fumarate (DMF) demonstrates sustained efficacy and safety for relapsing forms of MS. Absolute lymphocyte count (ALC) is reduced initially, then stabilizes on treatment.

Objective: PROCLAIM, a 96-week, prospective, open-label, phase 3b study, assessed lymphocyte subsets and immunoglobulin (Ig) levels during 48 and 96 weeks (W) of DMF treatment.

Methods: Patients received 240 mg DMF BID. Endpoints: lymphocyte subset count changes (primary); Ig isotypes and ALC changes (secondary); adverse events and relationship between ALC changes and ARR/EDSS (exploratory); and neurofilament assessment (ad hoc).

Results: Of 218 patients enrolled, 158 (72%) completed the study. Median ALC decreased 39% from baseline to W96 (BL–W96), stabilizing above the lower limit of normal (baseline: 1.82 × 10⁹/L; W48: 1.06 × 10⁹/L; W96: 1.05 × 10⁹/L). CD4⁺ and CD8⁺ T cells correlated highly with ALC from BL–W96 (p < 0.001). Relative to total T cells, naive CD4⁺ and CD8⁺ T cells increased, whereas CD4⁺ and CD8⁺ central and effector memory T cells decreased. Total IgA, IgG, IgM, and IgG1–4 subclass levels remained stable. Adverse event rates were similar across ALC subgroups. ARR, EDSS, and neurofilament were not correlated with ALCs.

Conclusion: Lymphocyte decreases with DMF were maintained over treatment, yet immunoglobulins remained stable. No increase in infection incidence was observed in patients with or without lymphopenia.

Support: Biogen

Keywords: Delayed-release dimethyl fumarate, multiple sclerosis, lymphocytes, B cells, immunoglobulin
vaccination, including both T-cell–dependent and T-cell–independent antigens, comparable to interferon (IFN)-treated patients.13 Although ALC does not appear to directly correlate with clinical response, functional shifts in circulating lymphocyte subsets favoring naive and anti-inflammatory phenotypes likely contribute to the effect of DMF.1,2,14,15

Previous immunophenotyping studies have been either cross-sectional6,9 or longitudinal, with few patients10 or minimal data-collection time points.16 PROCLAIM, the first large longitudinal study designed to assess the effects of DMF on lymphocyte subset counts and immunoglobulin (Ig) isotypes, may provide greater insight into DMF’s therapeutic benefit and inform the safety profile.

Methods

Study design

PROCLAIM (EUDRA CT 2015-001973-42) was a prospective, open-label, multicenter, phase 3b study assessing changes in immune cell compartments through 2 years of DMF treatment. The study period consisted of a screening visit, a 96-week treatment period, and a final follow-up visit 4 weeks after the last dose of DMF. All patients received 120 mg twice daily (BID) for the first 7 days, followed by a maintenance dose of 240 mg BID thereafter (approved dosing regimen for MS). Temporary dose reduction to 120 mg BID through 4 weeks was permitted for individuals who did not tolerate the maintenance dose due to flushing or gastrointestinal disturbance. Treatment compliance was monitored by study personnel via capsule counting at visits. Blood samples were collected at baseline and Weeks 4, 8, 12, 24, 36, 48, 72, and 96.

Patients

Eligible patients were aged 18–65 years with a confirmed diagnosis of RMS.17 Key exclusion criteria were positive serology for HIV or hepatitis B/C; history of drug or alcohol abuse within 1 year before screening; clinically significant comorbid disorders or conditions, including infectious illness; leukocytes < 3.5 × 10⁹/L; ALC values ≤ LLN (0.91 × 10⁹/L); or prior treatment with cladribine, mitoxantrone, total lymphoid irradiation, alemtuzumab, T-cell or T cell–receptor vaccination, or any therapeutic monoclonal antibody (except natalizumab or daclizumab). Concomitant treatment with alternative MS drugs or systemic steroid therapy was not allowed unless approved by the medical monitor for treatment of a protocol-defined relapse.

Study objectives and endpoints

The study objectives were to evaluate the effect of DMF on lymphocyte subset counts (primary) and the pharmacodynamic effect of DMF on ALCs and Ig isotypes (secondary) in patients with RMS during the first 48 weeks of treatment. Exploratory study objectives included evaluation of safety and tolerability over 96 weeks; lymphocyte subset counts through 96 weeks of DMF treatment; the relationship between changes in ALC and lymphocyte subsets and MS disease activity (measured by clinical relapse; annualized relapse rate (ARR)) or sustained clinical disease progression (CDP) (measured by the Expanded Disability Status Scale (EDSS)); and ad hoc evaluations of hypothesis-driven biomarker analyses, including neurofilament light chain (NFL).

ALC, immune cell phenotyping, and Igs

ALC was measured using complete blood cell differential. Changes in lymphocyte subsets were assessed by flow cytometry utilizing cell surface markers (Supplementary Table 1). Serum Ig levels (total IgA, IgG, IgM, and subclasses IgG1, IgG2, IgG3, and IgG4) were measured using an immunoturbidimetric method on the Integra/Plus (Roche Diagnostics, Basel, Switzerland) or by immunologic methods (LOINC®, LabCorp, Burlington, North Carolina).

Clinical assessments

Safety outcomes were monitored throughout the study and safety assessments were performed at the post-treatment follow-up visit. Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting ≥ 24 hours, accompanied by objective neurological findings and confirmed by a neurologist. Sustained CDP was defined as ≥ 1.0-point increase on the EDSS from a baseline score of ≥ 1.0, sustained for 24 weeks, or ≥ 1.5-point increase on the EDSS from a baseline EDSS score of 0, sustained for 24 weeks.

ALCs were categorized as follows: always > LLN, 0.91 × 10⁹/L; mild lymphopenia, < 0.91 × 10⁹/L anytime, excluding patients with ALC < 0.8 × 10⁹/L for ≥ 6 months; moderate prolonged lymphopenia, ≥ 0.5 × 10⁹/L to < 0.8 × 10⁹/L for ≥ 6 months; and severe prolonged lymphopenia, < 0.5 × 10⁹/L for ≥ 6 months.

ALCs were stratified by age at baseline; younger patients (<50 years) versus older patients (≥ 50 years). This cutoff was selected in order to explore the immune function in patients who may be prone to decreased immune function and immunosenescence based on age, while maintaining a sufficient sample size.18,19
Sera NfL (sNfL) levels were measured using single molecule array (Simoa™ NF-light® Advantage assay, Quanterix, Billerica, MA). Two patients with extremely high (> 10 standard deviations (SDs)) baseline sNfL values were excluded.

### Statistical analyses

All patients who received ≥ 1 dose of study treatment were included in safety and relapse assessments. All patients who received ≥ 1 dose of study treatment and had ≥ 1 post-baseline pharmacodynamic measurement were included in the immune cell phenotyping analysis; EDSS was assessed in those with ≥ 1 post-baseline EDSS measurement. For the primary endpoint, the actual value, change, and percent change from baseline (CFB) were descriptively summarized. The Wilcoxon signed-rank test was used to assess if changes were different from zero. For secondary analyses, changes in levels of Ig isotypes and ALCs were descriptively summarized. Mixed-effect model repeated measurement assessed CFB in the Ig isotypes, and ALC CFB to Week 96 as the dependent variable. The model included visit, corresponding baseline value, age, and sex as fixed effects, and an unstructured variance-covariance matrix structure. Least squares mean, standard error, and 95% confidence intervals were reported for each visit.

ARR was estimated from a negative binomial regression model, adjusted for baseline covariates. No imputation was used for missing data; the missing values were skipped. The observed data were used for all analyses. EDSS metrics and the proportion of patients with CDP were descriptively summarized. All adverse events (AEs) were included.

### Results

#### Study population

A total of 218 patients were enrolled from six countries (Table 1 and Supplementary Figure 1); 158 (72%) patients completed the study and 60 (28%) withdrew, primarily due to withdrawn consent (n=22) and AEs (n=17). Five patients withdrew due to lymphopenia: one with severe lymphopenia and four with moderate. The mean (SD) age in PROCLAIM was 42 (11) years and 69% of patients were female (Table 1). Patients were older in PROCLAIM than in the pivotal phase 3 clinical trials DEFINE/CONFIRM (NCT00420212/NCT00451451): 27% were aged ≥ 50 years in PROCLAIM (Table 1) compared with 13% in the DMF 240 mg group in DEFINE/CONFIRM.1,2 Other demographic variables were consistent with the phase 3 studies.1,2

### DMF treatment reduced lymphocyte subset counts together with temporal changes in ALC

ALC decreases were evident as early as 8 weeks after DMF treatment initiation, continuing to decline for 6-12 months, then stabilizing; median ALC CFB was −41% by Week 48 and −39% by Week 96 (baseline, 1.82 × 10^9/L; Week 48, 1.06 × 10^9/L; and Week 96, 1.05 × 10^9/L) (Figure 1(a)). When stratified by younger patients (<50 years) versus older patients (≥50 years) at baseline, median ALC CFB was −38%...
and –51% by Week 96, respectively. After 2 years of DMF treatment, 110/218 (50%) patients had never developed lymphopenia (all ALCs remained > LLN), 69 (32%) had mild lymphopenia, 32 (15%) had moderate prolonged lymphopenia, and 1 (<1%) had severe prolonged lymphopenia.

The degree of change in lymphocyte subset counts correlated with changes in ALC; CD4+ and CD8+ T, CD19+ B, and NK cell median CFB to Week 48 were –42%, –55%, –30%, and –26% (all p < 0.0001), respectively (Figure 1(b)). The changes were sustained through Week 96 (Figure 1(a)). Using a sequential, cross-sectional analysis of correlations over 2 years, changes in T-cell, B-cell, and NK cell subsets generally correlated with changes in ALC; the strongest correlations were observed in T cells (Pearson’s correlation coefficient range, 0.798–0.911; p < 0.001), though all correlations reached statistical significance. Among T cells, both CD4+ and CD8+ T cells correlated highly with ALC from baseline through Week 96 (Pearson’s correlation coefficient range, 0.559–0.880; p < 0.001) (Figure 2(a)). The correlations remained strong when stratified by age < 50 and ≥ 50 years at baseline (Figures 2(b) and (c)).

DMF drives a general shift toward a naive/anti-inflammatory repertoire
Decreased total CD19+ B-cell counts were observed at Week 4 after treatment initiation (–10% CFB; p < 0.001), whereas reductions were observed for ALCs and CD4+ and CD8+ T-cell subsets by Week 8. Total B cells reached nadir at Week 24 (–31% CFB; p < 0.0001). After Week 48, a gradual increase in total B cells was observed, though levels did not return to baseline, remaining decreased through Week 96 (–13% CFB; p < 0.05). Total CD14+ monocytes appeared stable during DMF treatment, with modest reductions during Year 2 (median CFB at Week 96: –11.6%, p = 0.005). Circulating classical monocytes (CD14+CD16-) remained generally stable during the treatment period (–0.88%, p = 0.948 median CFB to Week 96) while the nonclassical (CD14+CD16+) monocyte numbers declined beginning at Week 12 (median CFB: –25.5%, p < 0.0001) and remained at a lower level for the duration of the treatment period. As measured by flow cytometry, granulocytes slightly increased at Week 96 (median CFB: 13% (p < 0.001). When assessed by hematology, neutrophil shifts of potential clinical significance were infrequently reported (<1.5 cells × 10⁹/L: 11/218 patients; ≤ 1.0 cell × 10⁹/L: 0 patients; ≥ 12.0 cells × 10⁹/L: 10/218 patients).

At Week 96, the memory compartment was selectively reduced compared with naive cells for CD4+ and CD8+ T cells and B cells. CFB: CD4+CD45RA-CCR7+ (p < 0.0001), versus naive CD4+CD45RA-CCR7+ T cells, –16% (p < 0.005); CD8+CD45RA-, –85% (p < 0.0001), versus naive CD8+CD45RA-CCR7+ T cells, –55% (p < 0.0001); and CD27+IgD-B cells (non-class switched) –53% (p < 0.0001), and CD27+IgD-/B cells (class switched), –71% (p < 0.0001), versus naive CD27-IgD+B cells, –16% (p < 0.05) (Figure 1(b)).

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**Figure 1.** Median percentage change in ALC and major lymphocyte subsets with DMF treatment over time. For (a), ALC is from the CBC, with unit × 10⁹/L. For both (a) and (b), data were collected by flow cytometry. (a) Median ALC is shown for all patients in the analysis population (N=218) and median percent change is shown. (b) Median percent change is shown. ALC: absolute lymphocyte count; DMF: delayed-release dimethyl fumarate; Ig: immunoglobulin; NK: natural killer; Q: quartile; Th: T helper. ****p < 0.0001; ***p < 0.001; **p < 0.01; *p < 0.05.
CD4⁺ populations demonstrated a relative increase, whereas stable populations during the study whether patients experienced of DMF treatment (Figure 4(a)). IgG levels remained stable over 2 years (233) mg/dL, respectively. Total IgM, IgA, IgG, and IgA-4 subclass levels remained stable during DMF treatment. Total IgM, IgA, IgG, and IgG1-4 subclass levels reached a normal value during DMF treatment. In general, when patients were stratified by ALC category, baseline Ig concentrations and median CFB to Weeks 48 and 96 were similar across categories. Data were available for only one patient with severe prolonged lymphopenia and therefore this category was not included in the analysis.

Compartmental relative shifts within lymphocyte subsets
When relative changes were assessed within the total T-cell compartment, naïve CD4⁺ and CD8⁺ T-cell populations demonstrated a relative increase, whereas CD4⁺ and CD8⁺ central memory and effector memory populations decreased (Figure 3). Within T helper (Th) cell subsets, there was a relative decline in pro-inflammatory Th1 and Th17 cells, a relative increase in anti-inflammatory Th2 cells, and stable total regulatory T cells. The relative proportion of regulatory T cells remained stable compared with effector T cells. The relative proportion of the naïve and transitional B-cell populations increased, compared with a decrease in the proportion of memory B cells (Figure 3). There was a relative increase in the immunoregulatory CD56bright NK cell population.

Igs remain stable during DMF treatment
At baseline, mean (SD) total IgM, IgA, and IgG levels were 133 (71) mg/dL, 212 (91) mg/dL, and 1051 (233) mg/dL, respectively. Total IgM, IgA, IgG, and IgG1-4 subclass levels remained stable over 2 years of DMF treatment (Figure 4(a)). Ig levels remained stable during the study whether patients experienced relapses (n = 41) or not (n = 170) while on DMF treatment (Figure 4(b)). Baseline serum IgM, IgA, or IgG levels were below the LLN in 7% (16/218) of patients. Most of these patients had been previously treated with ≥1 DMTs, although three had no previous DMT exposure. Seven of the 16 patients with low baseline Ig levels reached a normal value during DMF treatment. In general, when patients were stratified by ALC category, baseline Ig concentrations and median CFB to Weeks 48 and 96 were similar across categories. Data were available for only one patient with severe prolonged lymphopenia and therefore this category was not included in the analysis.

Safety outcomes
AEs and serious AEs were reported in 185/218 (85%) and 26/218 (12%) patients, respectively (Table 2), consistent with the known safety profile of DMF; flushing was the most common (46%). Treatment-emergent infections were reported in 89/218 (41%) patients. When stratified by ALC subgroup, a similar percentage of infections were reported across subgroups: 0.5 ≤ ALC < 0.8 × 10⁹/L (14/32 (44%) patients); 0.8 × 10⁹/L ≤ ALC < LLN (29/69 (42%) and ALC ≥ LLN (43/110 (39%)). No infections were reported in the patient with severe, prolonged lymphopenia.

Serious treatment-emergent infections (nasopharyngitis and cellulitis) were reported in two patients, neither considered related to study treatment. Nasopharyngitis
occurred in a patient with mild lymphopenia (ALC $0.8 \times 10^{9}/L$ to $< LLN$) and cellulitis occurred in a patient without lymphopenia (ALC $\geq LLN$); IgG concentrations were $> LLN$ (700 mg/dL) for both patients. A malignancy, stage 1 breast cancer, was reported in one patient, considered unrelated to study treatment. No deaths or treatment-emergent opportunistic infections were reported.

**ALC is not a marker of treatment response**

The overall unadjusted ARR was 0.153. When patients were stratified into quartiles by percentage CFB in ALC over 96 weeks, ARR for each quartile was generally consistent, relapse rates were low across all groups, and there were no patterns associating ALC change with relapse rate (Figure 5(a)). Similarly, changes in EDSS score and the proportion of relapse-free patients were not associated with ALC quartiles (Figure 5(b) and (c)). The low rate of disability progression observed in this study (13 patients with CDP events) prevented assessment of CDP by ALC quartile.

**Discussion**

The PROCLAIM study results demonstrate that DMF treatment of up to 2 years produced temporal changes in ALC and lymphocyte subsets, consistent with the known effect of DMF treatment. A median 39% ALC reduction from baseline to Week 96 and stabilization $\geq LLN$ for
most patients were observed; this decline is slightly higher than that observed in previous phase 3 and extension studies but is similar to an observational study of patients who were also older at baseline.20 The number of circulating lymphocytes within most major subsets, including CD4+ and CD8+ T, CD19+ B, and CD56+ NK cells, declined following DMF initiation, consistent with overall ALC. Overall, monocytes were generally stable, which is expected given that classical monocytes, which comprise the majority of the compartment, were not changed with treatment. Interestingly, the nonclassical monocytes, which have been implicated in various inflammatory autoimmune disorders, declined and remained low. While likely not a primary driver of DMF efficacy, this change may be another reflection of the mechanism by which DMF shifts circulating cells from an inflammatory to an anti-inflammatory repertoire. Granulocytes, specifically neutrophils, were generally not decreased. These findings are consistent with clinical observations of DMF-treated patients in that the rate of serious and opportunistic infection is generally low. The relative proportion of regulatory T cells remained stable compared with effector T cells, suggesting immune tolerance mechanisms were maintained. Increased immunoregulatory CD56bright NK cells with DMF treatment confirm previous observations. Overall, DMF treatment induced a general shift toward a circulating naive/anti-inflammatory cell profile and away from memory/pro-inflammatory phenotypes, in both the T-cell and B-cell compartments. Similar reductions in memory B cells have been previously observed including concomitant reductions in the pro-inflammatory cytokines granulocyte macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF)-α, and IL-6. This shift was established within the first 3–6 months of treatment and maintained over 2 years.

Total IgA, IgG, IgM, and subclass IgG1–4 levels remained stable over 96 weeks of DMF treatment, regardless of ALCs, and were similar to Ig levels in healthy adult and MS populations. This is consistent with prior studies demonstrating that DMF-treated patients mount an effective T cell–independent and T cell–dependent immune response to recall and neoantigens comparable with that of IFN-treated patients. Previous IFN studies have shown no decrease in serological response to vaccination when vaccines were co-administered during treatment with IFN; therefore, the similar rise in immunoglobulin levels in patients who were vaccinated while treated with IFN or DMF suggests similar seroprotection potential for the two agents. In PROCLAIM, which included patients slightly older at baseline than pivotal trials and those previously treated with DMTs, there was no change in serum IgG levels, in contrast to the decrease noted during treatment with other DMTs.

These data do not support changes in ALC as a biomarker of treatment efficacy, consistent with previous reports. Although T-cell numbers, specifically CD8+ T cells, are impacted by DMF treatment, the magnitude of the reduction does not correlate with relapse rate or changes in EDSS score. This prospective study and prior observational studies agree that relapse status, unadjusted ARRs, and change in EDSS scores were similar across ALC subgroups. Ig isotypes were also not differentially affected by relapse.

### Table 2. Adverse events.

| Patients, n (%) | PROCLAIM N=218 |
|----------------|----------------|
| **Treatment-emergent adverse events** | 185 (85) |
| Treatment-emergent infections | 89 (41) |
| Nasopharyngitis | 33 (15) |
| Upper respiratory tract infection | 28 (13) |
| Sinusitis | 10 (5) |
| Bronchitis | 8 (4) |
| Urinary tract infection | 8 (4) |
| Influenza | 7 (3) |
| Gastroenteritis viral | 6 (3) |
| Pharyngitis | 6 (3) |
| **Most common adverse event (≥10%)** |
| Flushing | 100 (46) |
| MS relapse | 48 (22) |
| Nasopharyngitis | 33 (15) |
| Diarrhea | 28 (13) |
| Upper respiratory tract infection | 28 (13) |
| Fatigue | 27 (12) |
| Abdominal pain | 22 (10) |
| Upper abdominal pain | 22 (10) |
| Nausea | 22 (10) |
| **Adverse events leading to study drug discontinuation** | 28 (13) |
| Deaths | 0 |
| Serious adverse events | 26 (12) |
| **Most common serious adverse events (≥1%), n (%)** |
| MS relapse | 16 (7) |
| **Adverse events of special interest** |
| Serious infections | 2 (<1) |
| Malignancies | 1 (<1) |
| Opportunistic infections | 0 |
| Progressive multifocal leukoencephalopathy | 0 |

*Treatment-emergent events by preferred term.*
The exploratory marker sNfL was decreased by DMF treatment, similar to other studies, but the magnitude of reduction was not associated with ALC. Only younger age was associated with higher baseline ALC. Despite ALC changes not being indicative of the magnitude of treatment response, it is purported that changes in the peripheral lymphocyte compartment toward an anti-inflammatory phenotype may contribute to reducing disease activity in DMF-treated patients with RMS. In addition, a decrease in interleukin-17–producing CD8+ T cells in DMF-treated patients, together with the reduced IFN-gamma production by CD4+ T cells, dendritic cells, and monocytes, and greater reduction of CD8+ T cells, suggests DMF impacts MS through multiple mechanisms.

The PROCLAIM dataset provides additional context for the safety implications of T-cell subset changes in...
DMF-treated patients. No deaths or treatment-emergent opportunistic infections were reported over the 2-year study period. Rates of AEs were similar across all ALCs, consistent with the known safety profile of DMF; rates of serious AEs were low. Taken together with the strong correlation between ALC and T-cell subsets, these data continue to support that additional monitoring of T-cell subsets is not required for safety surveillance in routine clinical practice for DMF-treated patients. However, the correlation coefficient is not 1.0; therefore, a small proportion of patients will have lower than expected T-cell subset counts despite normal ALCs.

To our knowledge, PROCLAIM is the first large prospective longitudinal study evaluating immunophenotypic changes among patients treated with DMF. Exclusion criteria for this study were limited, allowing enrollment of patients of a wider age spectrum with prior exposure to DMT. The study population therefore more closely reflects clinical practice, and the data reported here correspond well with the observational data previously reported. The discontinuation rate (28%) in PROCLAIM was higher than the assumption of 10% but in line with the pivotal clinical trials (31% and 30%).

This study was not powered to assess changes that occur in only a small percentage of patients, for example, 2%–3% of patients with severe prolonged lymphopenia; this population has been assessed in other studies. Moreover, this open-label prospective study did not include a comparator group, limiting the interpretation of some results. Disease activity at baseline was not controlled for in this study and only 13 patients experienced disability progression, limiting conclusions for changes in ALC in relation to disease activity. The clinical significance of this study is also limited by the lack of MRI data.

Conclusion
DMF modulates a shift in circulating lymphocytes away from memory cells and toward a naive repertoire that does not impair protective humoral immunity. This may contribute to the therapeutic benefits of DMF in MS. Overall, the relative proportion of naive and anti-inflammatory–type (Th2-enriched) cells increase, whereas central and effector memory and pro-inflammatory–type (Th17) cells decrease over 2 years of DMF treatment. These shifts do not affect Ig isotype concentrations. The magnitude of DMF-mediated changes in ALC were not associated with greater efficacy or increases in serious infections, as similarly noted in patients treated with DMF over many years. Additional T-cell subset monitoring is not required for safety surveillance in routine clinical practice based on the longitudinal correlation between T cells and ALC, regardless of T-cell subset type or

Figure 5. (a) Adjusted ARR, (b) change in EDSS score, and (c) patients with zero relapses by ALC change, from baseline to Week 96. (a) Both protocol-defined and non-protocol–defined relapses are included in the analysis. Based on negative binomial regression, adjusted for baseline EDSS score (≤ 2.0 vs > 2.0) and baseline age (<40 vs ≥ 40 years). If the negative binomial regression model did not converge, a Poisson regression model with the same covariates was used. (b) Includes patients in the clinical assessment population with a baseline EDSS score (n = 183). (c) Percentage of patients with 0 relapses from baseline to Week 96. ALC: absolute lymphocyte count; ARR: annualized relapse rate; CI: confidence interval; EDSS: Expanded Disability Status Scale; Q: quartile; RR: rate ratio; SD: standard deviation.
Overall, the lymphocyte subset changes and Ig stability observed, together with the safety profile, indicate that DMF is generally well tolerated as evidenced by 72% of patients remaining on the study at 2 years. Protective humoral immune function is maintained over 96 weeks of treatment.

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Data Sharing Statement

The datasets used and/or analyzed during the study are available from the corresponding author upon reasonable request. Requests for data supporting this manuscript should be submitted to the Biogen Clinical Data Request Portal (www.biogenclinicaldatarequest.com).

Declaration of Conflicting Interests

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Research Ethics and Patient Consent

The PROCLAIM study was conducted in accordance with The International Conference on Harmonization Guidelines on Good Clinical Practice, the ethical principles outlined in the Declaration of Helsinki, and all applicable local laws and regulations. Written informed consent was obtained from each patient prior to eligibility evaluations.

Trial Registration

2015Clinical trial registration: EudraCT-001973-42

Supplemental Material

Supplemental material for this article is available online.

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