Safety and efficacy of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis: 9 years' follow-up of DEFINE, CONFIRM, and ENDORSE

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Abstract

Introduction: We report safety and efficacy in patients treated with dimethyl fumarate (DMF) for ~9 years in ENDORSE. Lymphocyte analysis data are also reported.

Methods: Incidence of serious adverse events (SAEs), discontinuations due to adverse events (AEs), annualized relapse rate (ARR) and Expanded Disability Status Scale (EDSS) score were assessed. Patients were treated with DMF 240 mg twice daily (BID): placebo (PBO)/DMF (PBO for years 0–2 /DMF for years 3–9) or continuous (DMF/DMF) treatment; newly diagnosed patients were included. Annual magnetic resonance imaging (MRI) was evaluated in patients from the MRI cohort of DEFINE/CONFIRM. For the lymphocyte analysis, data from first DMF exposure were analyzed.

Results: Of 2079 DEFINE/CONFIRM completers, 1736 enrolled and received ⩾1 dose of DMF. The MRI cohort included 530 patients. In the overall population, 527 (30%) patients experienced SAEs; most were fall and urinary tract infection. Over 9 years on DMF treatment, adjusted ARR remained low (⩽0.20). In patients treated with PBO in years 0–2, decreased ARR was apparent as early as year 3. Of DMF/DMF and PBO/DMF patients, 73% and 74%, respectively, had no 24-week confirmed disability progression. Most patients (~70%) had no new T1 or new/newly enlarging T2 lesions compared with previous MRI scans after 7 years treatment with DMF; the annual number of new T1 hypointense lesions and new/newly enlarging T2 hyperintense lesions were 0.6–0.8 and 0.9–2.0, respectively. Mean percentage brain volume change from ENDORSE baseline (6 years treatment in ENDORSE) was –1.32% (range –1.60% to –1.05%). Of the 2513 patients with lymphocyte assessments, 2470 had ⩾1 post-baseline measurement, 53 developed severe prolonged lymphopenia and were followed for up to 11 years; incidence of serious infection was not higher than in patients with absolute lymphocyte count (ALC) always ⩾ lower limit of normal (LLN). In patients with lymphopenia while on DMF and ALC $< 0.91 \times 10^9$/L at discontinuation ($n = 138$), median time to ALC ⩾ LLN was 7 weeks post-discontinuation.

Conclusions: Sustained safety and efficacy of DMF was observed in patients continuing on treatment for up to 11 years, supporting DMF as a long-term treatment option for patients with RRMS.

Trial registration: ClinicalTrials.gov identifiers, NCT00835770 (ENDORSE); NCT00420212 (DEFINE); NCT00451451 (CONFIRM).

Keywords: delayed-release dimethyl fumarate, efficacy, multiple sclerosis, newly diagnosed, safety

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Introduction

Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) is an oral treatment approved for use in patients with relapsing forms of multiple sclerosis (MS), including relapsing-remitting MS (RRMS),[1,2] clinically isolated syndrome and active secondary progressive MS.[1] As of 31 January 2020, >445,000 patients have been treated with DMF, representing >875,000 patient-years of exposure. Of these, 6335 patients (14,241 patient-years) were from clinical trials. DMF has demonstrated efficacy and a favorable benefit-risk profile in patients with RRMS in the phase III DEFINE and CONFIRM studies and in ENDORSE.[3–5]

ENDORSE is an ongoing extension study of DEFINE and CONFIRM to evaluate long-term safety and efficacy of DMF in patients with RRMS.[5] Long-term extension studies provide crucial information for characterization of safety and tolerability of disease-modifying therapies in treatment of patients with RRMS, and additional information on efficacy. In particular, these studies allow for robust assessment of safety, particularly events that are expected to occur rarely and after a long duration of exposure. Patients followed in extension studies also represent an aging patient population that may be more generalizable for the real-world population.

We report a median of approximately 9 years' follow-up of clinical and radiological safety and efficacy outcomes observed in patients treated for 2 years in DEFINE/CONFIRM and for a median of approximately 7 years in ENDORSE, including a subgroup analysis of patients newly diagnosed at enrolment in DEFINE/CONFIRM. In total, some patients were treated for up to 11 years in these phase III studies. We also report findings from a lymphocyte analysis in patients with RRMS using integrated clinical trial data from the phase IIb study and phase III studies (DEFINE, CONFIRM, and ENDORSE), where follow-up ranged from <1 month to up to 11 years.

Methods

Study design

ENDORSE (NCT00835770)[5] is an ongoing extension of DEFINE (NCT00420212)[3] and CONFIRM (NCT00451451),[4] with a minimum of 10 years of planned follow-up [2 years in DEFINE/CONFIRM, plus ≥8 years (up to 12 years) in ENDORSE]. Details have been reported previously.[5] The study was approved by central and local ethics committees (see supplementary file for approval numbers), and conducted in accordance with International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

Patients randomized in DEFINE/CONFIRM to DMF 240 mg twice daily (BID) or thrice daily (TID) initially continued on the same dosage at the start of ENDORSE; patients randomised to placebo (PBO) or glatiramer acetate (GA) (CONFIRM only) were re-randomised 1:1 to DMF BID or TID. Following marketing authorization of DMF in the United States (effective March 2013), all patients receiving DMF TID switched to DMF BID (approved dosage) at their next study visit. Patients who received at least one dose of DMF in ENDORSE and were previously treated with DMF 240 mg BID, DMF 240 mg TID or PBO in the parent studies (DEFINE and CONFIRM) were included in the analysis of safety outcomes. Patients who were initially randomized to DMF BID or PBO in DEFINE/CONFIRM and continued on DMF BID (continuous DMF; DMF/DMF) or were re-randomized to DMF BID (delayed DMF; PBO/DMF) were included in the efficacy analysis reported herein. An analysis of newly diagnosed patients was also performed. Newly diagnosed patients were defined as those diagnosed with MS within a year before DEFINE/CONFIRM study entry and who were either treatment naïve or previously treated with corticosteroids alone.

Patient populations. Patient populations are depicted in Figure 1.

For the safety analysis, the total number of patients in the overall safety population are included, that is, all patients who received DMF, regardless of dose, in ENDORSE, after receiving DMF or PBO in DEFINE and CONFIRM. Of note, the patient population within the CONFIRM study who received GA were excluded from this analysis, due to the potential for confounding effects.

In the efficacy population, again, only patients who received DMF in ENDORSE and had received
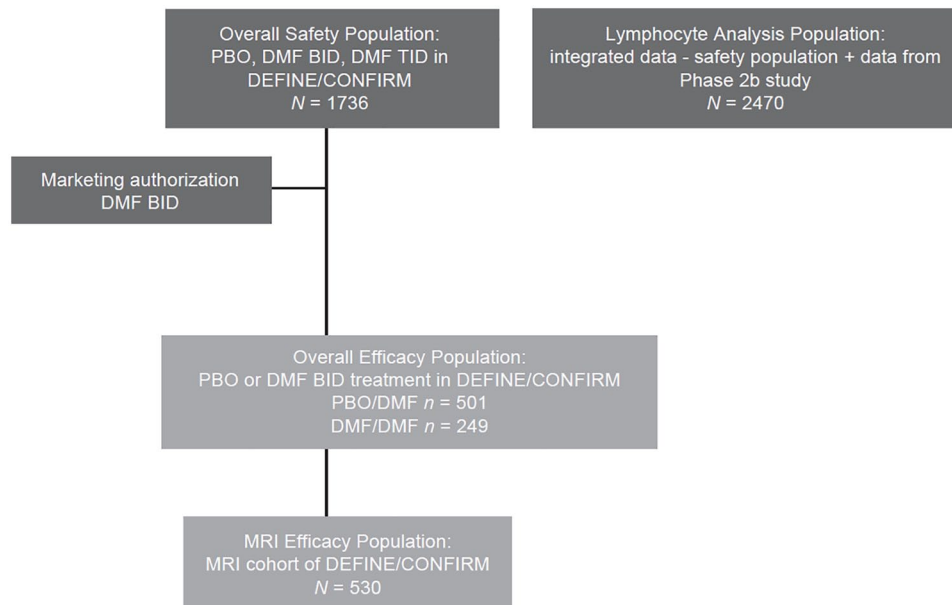
Figure 1. Patient populations for safety, efficacy, and lymphocyte analysis.
DMF, dimethyl fumarate; BID, twice daily; TID, three times daily; MRI, magnetic resonance imaging; PBO, placebo.

either DMF or PBO in DEFINE and CONFIRM were included. However, because the marketing authorization is for DMF 240 mg BID, patients who received DMF 240 mg TID at any time during these three studies were excluded.

Magnetic resonance imaging (MRI) assessment of efficacy was performed in a subset of patients who were included in the MRI cohort of DEFINE/CONFIRM. Details have been reported previously.[6]

Pharmacodynamics of changes in absolute lymphocyte count (ALC) and associated clinical implications were analyzed in a separate analysis of data from the integrated data of clinical trials (phase IIb, DEFINE, CONFIRM, and ENDORSE) and methods and results have been previously reported.[7]

Safety assessments
Adverse events (AEs) and concomitant medications were monitored and recorded continuously throughout the study. Laboratory assessments were performed on a schedule: blood and urine samples at baseline and then every 4 weeks until week 24, and then every 12 weeks thereafter; hematologic parameters at baseline and at least every 12 weeks thereafter. AEs are reported for

the newly diagnosed and overall DMF treatment group (intent-to-treat population). Data were not stratified by treatment assignment at the start of ENDORSE, as no major differences were observed, likely due to duration of treatment with DMF BID following the switch after marketing authorization.

Efficacy assessments
Annualized relapse rate (ARR) at years 0–2 (DEFINE/CONFIRM) and years 3–9 (ENDORSE) were assessed. Relapse (confirmed by an independent neurologic evaluation committee) was defined as new or recurrent neurologic symptoms lasting ⩾24 h, accompanied by new objective neurologic findings. Disability progression was measured every 24 weeks on the Expanded Disability Status Scale (EDSS). An EDSS score of 4 has been used as a milestone marker for onset of ambulation impairment.[8–10] Time to 24-week confirmed disability progression (CDP) was defined as a ⩾1.0-point increase from a baseline EDSS score ⩾1 confirmed for 24 weeks, or a ⩾1.5-point increase from a baseline EDSS score of 0 confirmed for 24 weeks.

To assess efficacy using MRI end points included numbers of new T1 hypointense and new or newly enlarging T2 hyperintense lesions and

annual changes in brain volume in patients. Data are reported by year of exposure to DMF due to some patients previously receiving DMF in the parent studies. For analysis of new T1 hypointense and T2 hyperintense lesions, lesion analysis was performed only for patients who completed a yearly scan for the first 5 years of DMF treatment. Due to sample size restrictions, it was not possible to perform the analysis beyond 5 years. For the percentage brain volume change (PBVC) analysis, MRI scan readings were restricted to those collected in the ENDORSE study and performed at a single center. The first ENDORSE MRI was performed at the end of year 1; therefore, only data from year 1 forward were analyzed. Changes in PBVC from DEFINE/CONFIRM have been previously reported.[11,12]

Lymphocyte analysis

Pharmacodynamics of changes in ALC and associated clinical implications were analyzed in a separate analysis of data from the integrated data of clinical trials (phase IIb, DEFINE, CONFIRM, and ENDORSE) and methods and results have been previously reported.[7] ALC was characterized by CTCAE grade: $<0.5 \times 10^9$/L (severe lymphopenia), $\geqslant 0.5$ to $<0.8 \times 10^9$/L (moderate lymphopenia) and $\geqslant 0.8$ to <0.91 (LLN) $\times 10^9$/L (mild lymphopenia).

Patients with an ALC $<$ LLN at DMF discontinuation and $\geqslant 1$ post-DMF ALC value were included in an analysis of lymphocyte reconstitution after DMF discontinuation. Patients with severe prolonged lymphopenia, defined as $<0.5 \times 10^9$/L for $\geqslant 6$ months, were excluded from the post-DMF lymphocyte reconstitution analyses due to the prolonged duration of on-treatment lymphopenia ($N = 38$). This patient population has been previously described.[7] This exclusion permits the evaluation of a patient population expected to be representative of real-world patients treated with DMF, as the current label recommendations state clinicians should consider discontinuation of DMF if a patient develops persistent severe lymphopenia >6 months. In addition, it has been demonstrated that reconstitution rate is dependent upon duration of lymphopenia, specifically if lymphopenia persists >6 months, the estimated rate of reconstitution is significantly slower compared with patients with less persistent lymphopenia.[7]

Statistical analysis

ARR was defined as the total number of relapses divided by the number of patient-years in the study, using a negative binomial regression model adjusted for age, number of relapses in the year prior to study entry, baseline EDSS score and region. Cox proportional hazards model estimated time to 24-week confirmed EDSS progression, adjusted for baseline EDSS score, region and number of relapses in the year prior to study entry. Negative binomial regression was used for analysis of the total number of new or enlarging hyperintense T2 lesions and the total number of new hypointense T1 lesions at 5 years. Safety parameters were tabulated and summarized using descriptive statistics. To assess slope of ALC reconstitution after DMF discontinuation, a linear mixed-effect model with random intercept and random slope of time (in weeks), adjusted for age, ALC groups at DMF discontinuation and an interaction between time and ALC category, was used.

Results

Patients

Of the 2079 patients who completed DEFINE/CONFIRM, 1736 enrolled and received at least one dose of DMF in ENDORSE (Table 1). As of 1 September 2017, the median follow-up from the combined 2-year parent studies and ENDORSE was approximately 9 years (median 8.5; range 2.0–11.3), representing >10,348 patient-years of follow-up. The newly diagnosed population comprised 470 patients (Table 1) with a total follow-up time (including DEFINE/CONFIRM) of ~9 years (median 8.6; range 2.1–10.8 years) for patients on continuous (DMF/DMF) and delayed (PBO/DMF) DMF treatment.

The ENDORSE MRI cohort included 530 patients; mean [standard deviation (SD)] age was 40 (9) years (Table 2). Patients included in this radiological analysis had a median of one (range 0–4) relapse in the year before starting DMF treatment; median EDSS score was 2 (range 0–7.5). Median (min, max) time on study was similar between total population and the newly diagnosed population (Table 3).

Safety

The incidence of serious adverse events (SAEs), discontinuations due to adverse events (AEs)

Table 1. Baseline demographics and disease characteristics in ENDORSE or parent studies.

Characteristic[a]	Overall population (*N* = 1736)	Newly diagnosed population (*n* = 470)
Age, years	39.8	38.0
Female, *n* (%)	1212 (70)	330 (70)
Time since first MS symptoms, years	9.6 (6.3)	6.1 (5.1)
Time since diagnosis of MS, years	6.7 (5.1)	2.4 (0.5)
Relapses in prior year (parent studies baseline)	1.3 (0.7)	1.4 (0.6)
EDSS score (parent studies baseline)	2.5 (1.2)	2.1 (1.1)

[a]Values are mean (SD) unless otherwise stated.
BID, twice daily; DMF, delayed-release dimethyl fumarate; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; SD, standard deviation.

Table 2. Analysed MRI cohort: demographics and baseline characteristics at first exposure to DMF.

Characteristic[a]	Analyzed MRI cohort (*N* = 530)
Mean (SD) age, years[b]	40 (9)
Female, *n* (%)	379 (72)
Median (range) number of relapses in prior year	1 (0–4)
Median (range) EDSS score	2.0 (0–7.5)

[a]For patients in the GA-DMF and PBO-DMF group, ENDORSE baseline values are shown; for patients in the DMF/DMF group, DEFINE or CONFIRM baseline values are shown.
[b]Age based on ENDORSE baseline values for all patients.
BID, twice daily; DMF, delayed-release dimethyl fumarate; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; MRI, magnetic resonance imaging; PBO, placebo.

(Table 3) and AEs of interest (Table 4), were generally similar regardless of prior treatment history [overall safety population (*n* = 1736) or newly diagnosed patient population (*n* = 470)].

Treatment discontinuation due to disease activity (MS relapse and progression) occurred in 3–5% of patients in both the overall safety population and newly diagnosed population (Table 3). Nasopharyngitis and flushing were the most common AEs after MS relapse (Table 5).

The incidence of SAEs was 30% in the overall safety population and 27% in the newly diagnosed population. The most common SAEs were MS relapse, fall, and urinary tract infection. Serious infections occurred in ≤5% of patients in each group analyzed (Table 3). One opportunistic infection [a fatal case of progressive multifocal leukoencephalopathy (PML)] in a patient with ~3.5 years of severe lymphopenia was confirmed in the safety population (DMF TID group). Details of this case have been reported elsewhere.[13] Of the total of nine deaths reported in the study, this was the only death considered related to study drug, and it occurred after study drug discontinuation.

Potential hepatic disorders occurred in 11% of the DMF/DMF treated patients (Table 4), including one patient with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) occurring more than three times the upper limit of normal and total bilirubin more than twice the upper limit of normal concurrently. Consistent with the parent studies, proteinuria, microalbuminuria, and hematuria were the most common (incidence ≥5% in any treatment group) renal AEs reported (Table 4). Renal or urinary disorders led to ≤2%

Table 3. Overall disposition, AEs, SAEs, and discontinuations in ENDORSE.

n (%)	Overall safety population (N = 1736)	Newly diagnosed population (n = 470)
Median (min, max) time on study, years	5.74 (0.03, 8.25)	5.75 (0.09, 8)
Time on study, n (%)		
≥1 year	1542 (89)	430 (91)
≥3 years	1256 (72)	350 (74)
≥5 years	1093 (63)	308 (66)
≥7 years	199 (11)	61 (1)
≥8 years	2 (<1)	1 (<1)
Patients ongoing on treatment	797 (46)	230 (49)
Treatment discontinuation	817 (47)	207 (44)
MS relapse	36 (2)	12 (3)
MS progression	24 (1)	9 (2)
AE	234 (13)	48 (10)
AE leading to discontinuation of study drug	271 (16)	58 (12)
Gastrointestinal disorder	62 (4)	10 (2)
Nervous system disorder	52 (3)	14 (3)
Lost to follow-up	34 (2)	7 (1)
Consent withdrawn	210 (12)	54 (11)
Investigator decision	65 (4)	17 (4)
Subject non-compliance	18 (1)	4 (<1)
Death	7 (<1)	0
Other	189 (11)	56 (12)
Any AE	1633 (94)	435 (93)
SAE	527 (30)	125 (27)

AE, adverse event; ALC, absolute lymphocyte count; BID, twice daily; DMF, dimethyl fumarate; SAE, serious adverse event.

of study drug discontinuations in the overall safety population. This is consistent with DEFINE and CONFIRM, and these data do not appear to indicate any increased risk of renal injury after long-term treatment with DMF.

The incidence of malignancies remained low in both treatment groups (3%) in the overall safety population (Table 4); the rate of malignancy reported in this population was 461.8 per 100,000 patient-years' follow up, which was generally consistent with the expected background rate for the general United States population of 442 per 100,000 persons per year based on Surveillance, Epidemiology and End Results Program database analysis; 2012–2016 cases and deaths).

Table 4. AEs of interest in ENDORSE.

AE, *n* %	Overall safety population (*N* = 1736)	Newly diagnosed population (*n* = 470)
GI disorders	735 (42)	206 (44)
Flushing	332 (19)	107 (23)
Anaphylactic reaction	1 (<1)	1 (<1)
Potential hepatic disorders	189 (11)	46 (10)
ALT increased	163 (9)	24 (5)
AST increased	108 (6)	16 (3)
Renal and urinary disorders	431 (25)	120 (26)
Proteinuria	151 (9)	44 (9)
Microalbuminuria	116 (7)	29 (6)
Hematuria	110 (6)	29 (6)
Serious infections	79 (5)	24 (5)
Potential opportunistic infection	7 (< 1)	0
Opportunistic infections	1 (< 1)	0
Malignancy	45 (3)	16 (3)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal.

Table 5. Most common AEs (≥10%) in ENDORSE.

AEs, *n* (%)	Overall safety population (*N* = 1736)	Newly diagnosed population (*n* = 470)
Any AE	1633 (94)	435 (93)
MS relapse	655 (38)	169 (36)
Nasopharyngitis	437 (25)	130 (28)
Flushing	332 (19)	107 (23)
Urinary tract infection	350 (20)	85 (18)
Upper respiratory tract infection	272 (16)	88 (19)
Headache	269 (15)	76 (16)
Back pain	242 (14)	71 (15)
Diarrhea	224 (13)	66 (14)
Fatigue	198 (11)	63 (13)
Arthralgia	202 (12)	52 (11)
Pain in extremity	184 (11)	51 (11)
Depression	181 (10)	48 (10)
Bronchitis	170 (10)	51 (11)

AE, adverse event; MS, multiple sclerosis.

Lymphocyte analysis

The lymphocyte analysis population comprised 2470 patients (10,971 patient years of follow-up) for patients with at least one post-baseline ALC reading.[5] The majority (70%) of these patients were female, mean (SD) age was 38.4 (9.2) years, and mean (SD) baseline ALC was 2.0 (0.6). Declines in ALC were observed as early as 4 weeks after DMF initiation. ALC declined 30%, on average, but remained above the lower limit of normal (LLN; i.e., ALC $\leqslant 0.91 \times 10^9$/L) for the majority of patients (~60%). Severe prolonged lymphopenia developed in 2% of patients; moderate prolonged lymphopenia developed in 10% of patients. When stratified by patient age, severe prolonged lymphopenia occurred at a higher incidence in patients who were age >50 years [4.2% (13/310)] and 40–50 years [3.3% (28/837)] compared with <40 [0.9% (12/1323)] years. Similar patterns were observed when stratified by baseline ALC; lower baseline ALC was associated with higher incidence of severe prolonged lymphopenia compared with those with higher baseline ALC. Notably, severe prolonged lymphopenia occurred across all age categories and baseline ALC categories, supporting the recommendation to monitor ALC for all patients treated with DMF. Importantly, regardless of baseline ALC, patient age, or the magnitude of lymphocyte decline while on treatment, the pattern of ALC decline was similar, occurring within the first 1–2 years followed by stabilization, with most patients remaining above LLN. No unexpected changes in the pattern of ALC were observed with up to 11 years of treatment.

Lymphopenia and AEs. In patients followed for up to 11 years, development of severe prolonged lymphopenia ($n = 53$) or moderate prolonged lymphopenia ($n = 238$) was not associated with increased incidence of infection (12.5 cases per 100 patient-years, and 12.2 cases per 100 patient-years, respectively) or serious infection (1.6 cases per 100 patient-years, and 0.8 cases per 100 patient-years, respectively) when compared with the incidence reported in patients with ALC always $\geqslant$ LLN ($n = 1475$; 1 case per 100 patient years; Table 6). Aside from one fatal case of PML (details reported separately),[13] no other opportunistic infections were confirmed in DEFINE/CONFIRM or ENDORSE, regardless of ALC.

Lymphocyte reconstitution after DMF discontinuation. Of 138 patients with lymphopenia at any time while on DMF, and with an ALC < LLN (0.91×10^9/L) at DMF discontinuation, 62% (86/138) patients reached an ALC threshold of at least LLN after DMF discontinuation. The median time to reach an ALC threshold of $\geqslant$ LLN was 7 weeks after discontinuation. Of the 52 patients who did not reach LLN, 39 (75%) discontinued the study before achieving LLN and follow-up did not continue.

Rate of reconstitution is estimated at approximately 0.04×10^9/L cells per week, regardless of ALC at time of discontinuation when stratified by median at discontinuation (above or below 0.73×10^9/L): (slope 0.035 *versus* 0.043; $p = 0.504$; Figure 2).

Patients with severe prolonged lymphopenia (i.e., severe lymphopenia that lasted for $\geqslant$ 6 months) were analyzed separately ($N = 38$) as this cohort is not considered representative of current DMF use based on current ALC monitoring recommendations; these data have been previously presented.[7]

Efficacy

Clinical end points

Overall efficacy patient population. Overall, for patients continuously treated with DMF BID (DMF/DMF) up to 9 years, the adjusted ARR [95% confidence interval (CI)] remained low, ranging from 0.20 (0.17, 0.25) in the first year to as low as 0.09 (0.05, 0.13) in years 8–9 (Figure 3a). In the PBO/DMF group, adjusted ARR (95% CI) was 0.35 (0.29–0.43) during the PBO treatment period (years 0–2 [DEFINE/CONFIRM]) and decreased to less than 0.16 during the DMF treatment period (years 3–9 [ENDORSE]; Figure 3b). A decreased ARR was apparent as early as year 3–4, and some reduction in ARR continued year-over-year throughout the treatment period. By years 8–9, after 7 years of DMF treatment, unadjusted ARR (95% CI) was 0.09 (0.05, 0.16). Importantly, over ~9 years, 53% of DMF/DMF and 47% of PBO/DMF patients remained free from relapses; the majority (86%) of patients had two or fewer relapses.

At the start of ENDORSE (year 2), mean (SD) EDSS scores were 2.3 (1.3) for the DMF/DMF group and 2.5 (1.3) for the PBO/DMF group. After ~7 years of DMF treatment in ENDORSE (year 9), mean (SD) EDSS scores remained stable and were 2.4 (1.6) for the DMF/DMF group and 2.6 (1.5) for the PBO/DMF group. The

**Table 6.** Incidence of infection and malignancy by ALC level.

	Severe prolonged lymphopenia (n = 53)	Moderate prolonged lymphopenia (n = 238)ᵃ	Mild lymphopenia (n = 686)ᵇ	Always ⩾ LLN (n = 1475)	Total (n = 2470)
Total patient-years (patient-years)	311	1581	3634	5397	10,970
Serious infection/100 patient-years	1.6	0.8	1.1	1.0	1.0
Opportunistic infection/100 patient-years	0.3	0	0	0	0.1
Malignancy/100 patient-years	0.6	0.6	0.5	0.4	0.5

ALC, absolute lymphocyte count; LLN, lower limit of normal (0.91×10^9/L).
Patient-year is defined as the last date in study minus the date of first exposure to DMF plus 1, divided by 365.25. Incidence was calculated as the number of patients with specific adverse events divided by the total patient-years of follow-up. Severe prolonged lymphopenia: $<0.5 \times 10^9$/L for ⩾6 months; moderate prolonged lymphopenia: $⩾0.5$ to $<0.8 \times 10^9$/L for ⩾6 months; mild lymphopenia: $<$LLN at any time.
ᵃExcludes $<0.5 \times 10^9$/L for ⩾6 months.
ᵇExcludes $<0.8 \times 10^9$/L for ⩾6 months.
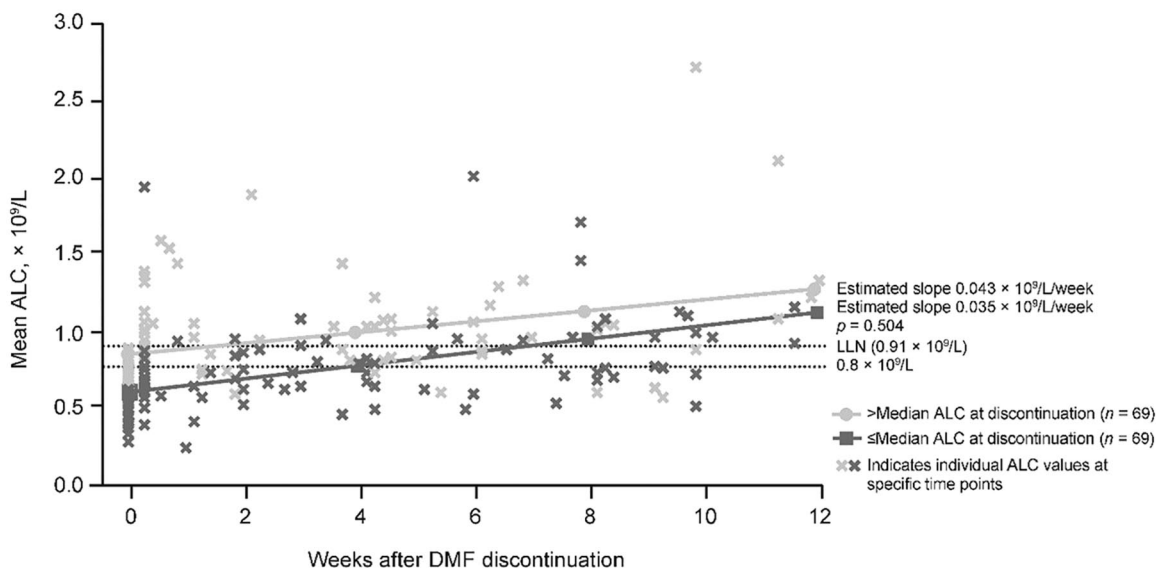
Figure 2. Linear mixed-effect model of lymphocyte reconstitution after DMF discontinuation in patients with mild to moderate lymphopenia.
ALC, absolute lymphocyte count; DMF, delayed-release dimethyl fumarate; LLN, lower limit of normal.

majority of patients in the DMF/DMF and PBO/DMF groups had EDSS scores ⩽3.5 at year 2 [413/479 (86%) and 179/217 (82%), respectively] and year 9 [166/203 (82%) and 66/82 (80%), respectively]. Estimated 24-week CDP to >3.5 at year 8 was 10% (95% CI 7–14%) for the DMF/DMF group and 13% (95% CI 8–21%) for the PBO/DMF group (Figure 3c); sample size prevented the analysis to year 9. Overall, 73% and 74% of DMF/DMF and PBO/DMF patients, respectively, had no 24-week CDP, and 43% and

40%, respectively, were free from clinical disease activity.

Newly diagnosed patients. Relapse rates in newly diagnosed patients were consistent with the overall patient population; for newly diagnosed patients continuously treated with DMF BID (DMF/DMF), the adjusted ARR was 0.24 (95% CI 0.16–0.34) in the first year compared with 0.10 (0.05–0.23) at years 8–9 of DMF treatment (Figure 4a). In the PBO/DMF group, adjusted

(a)

(b)

(c)
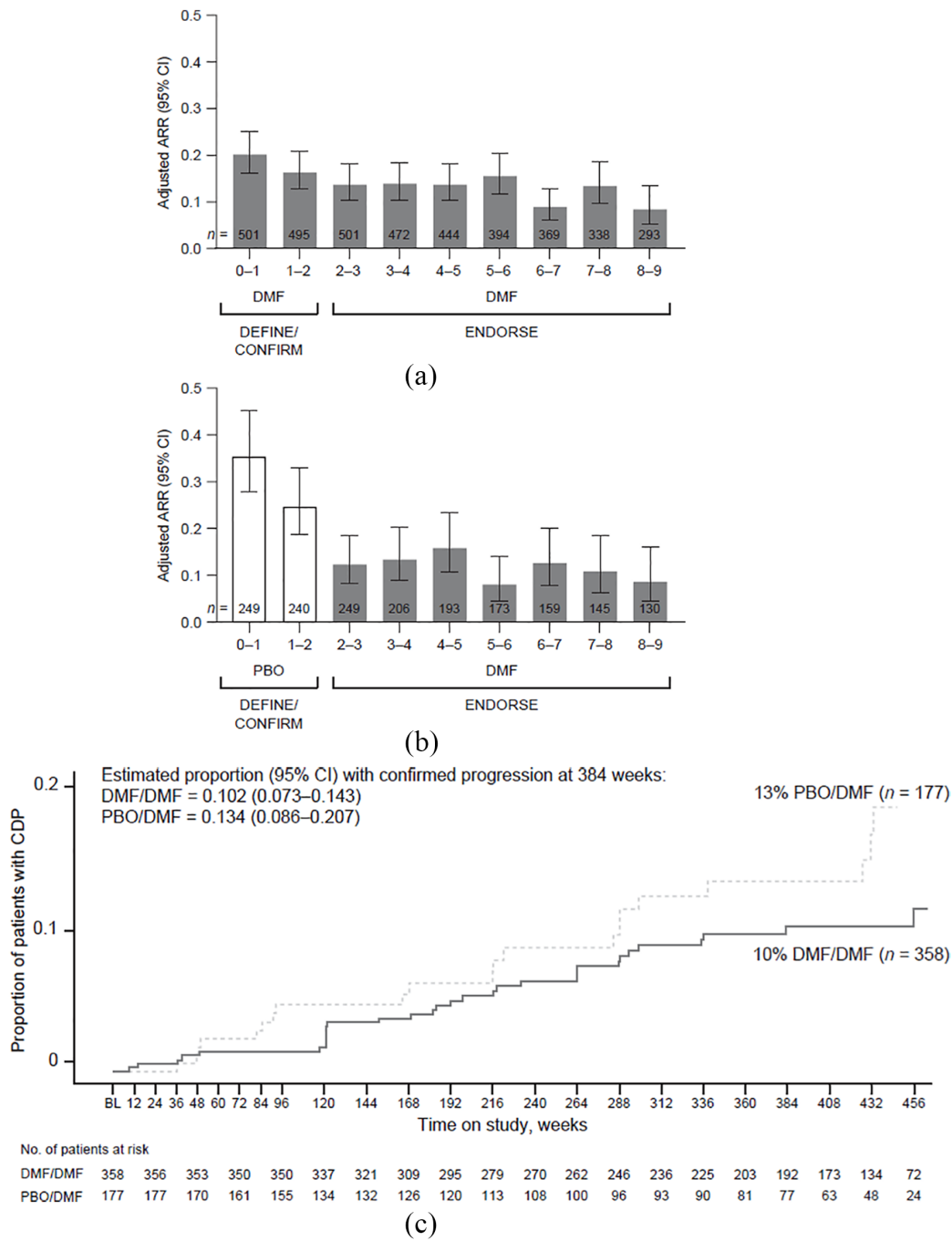
Figure 3. (a) Adjusted ARR by yearly interval for the DMF/DMF and PBO/DMF groups in the overall ENDORSE population over 9 years (ENDORSE 7 years). Adjusted ARR is shown for all patients treated with DMF continuously (DMF/DMF), and for patients treated with PBO in years 0–2 in DEFINE/CONFIRM followed by DMF in years 3–9 in ENDORSE (PBO/DMF). Based on negative binomial regression, except for years 4–5, 5–6, 6–7, 7–8, and 8–9, which are based on Poisson regression, adjusted for baseline EDSS score ($\leqslant 2$, $\geqslant 2.0$), baseline age (< 40, $\geqslant 40$ years), region, and number of relapses in the year before DEFINE/CONFIRM study entry. (b) Adjusted ARR by yearly interval during treatment with PBO (years 0–2 in DEFINE/CONFIRM) and DMF (years 3–9 in ENDORSE) in the overall ENDORSE population. ARR was defined as the total number of relapses divided by the number of patient-years in the study, using a negative binomial regression model, except for years 4–5, 5–6, 6–7, 7–8, and 8–9, which are based on Poisson regression, adjusted for age, number of relapses in the year prior to study entry, baseline EDSS score and region. (c) Proportion of patients in the overall ENDORSE population with baseline EDSS score $\leqslant 3$ and 24-week confirmed progression to EDSS score $\geqslant 4$ over 384 weeks. CDP was defined as $\geqslant 1$-point worsening if baseline score was $\geqslant 1$; thus, only patients with EDSS score $\leqslant 3$ were included. Kaplan-Meier estimate.
ARR, annualized relapse rate; BL, baseline; CDP, confirmed disability progression; CI, confidence interval; DMF, delayed-release dimethyl fumarate; EDSS, Expanded Disability Status Scale; PBO, placebo.
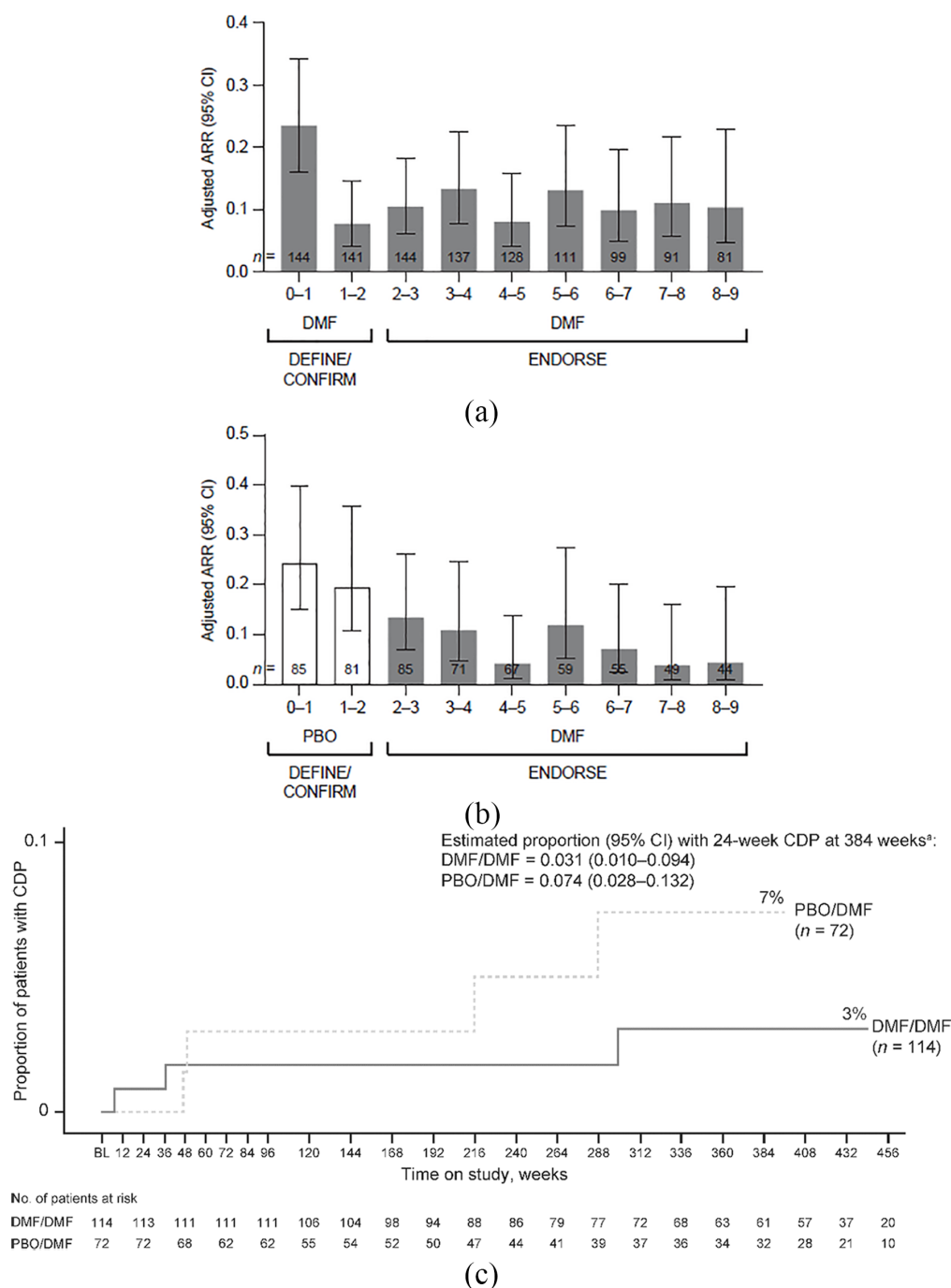
Figure 4. (a) Adjusted ARR by yearly interval for the DMF/DMF and PBO/DMF groups of newly diagnosed patients over 9 years (ENDORSE 7 years). Adjusted ARR is shown for newly diagnosed patients treated with DMF continuously (DMF/DMF), and for newly diagnosed patients treated with PBO in years 0–2 in DEFINE/CONFIRM followed by DMF in years 3–9 in ENDORSE (PBO/DMF). Based on negative binomial regression, except for years 4–5, 5–6, 6–7, 7–8, and 8–9, which are based on Poisson regression, adjusted for baseline EDSS score ($\leqslant 2$, $\geqslant 2.0$), baseline age (< 40, $\geqslant 40$ years), region, and number of relapses in the year before DEFINE/CONFIRM study entry. (b) Adjusted ARR during treatment with PBO (years 0–2 in DEFINE/CONFIRM) and DMF (years 3–9 in ENDORSE) in newly diagnosed patients. ARR was defined as the total number of relapses divided by the number of patient-years in the study, using a negative binomial regression model, except for years 4–5, 5–6, 6–7, 7–8, and 8–9, which are based on Poisson regression, adjusted for age, number of relapses in the year prior to study entry, baseline EDSS score and region. (c) Proportion of newly diagnosed patients with baseline EDSS score $\leqslant 3$ and 24-week confirmed progression to EDSS score $\geqslant 4$ over 384 weeks. CDP was defined as $\geqslant$ 1-point worsening if baseline score was $\geqslant 1$; thus, only patients with EDSS score $\leqslant 3$ were included. Kaplan-Meier estimate.
ARR, annualized relapse rate; BL, baseline; CDP, confirmed disability progression; CI, confidence interval; DMF, delayed-release dimethyl fumarate; EDSS, Expanded Disability Status Scale; PBO, placebo.
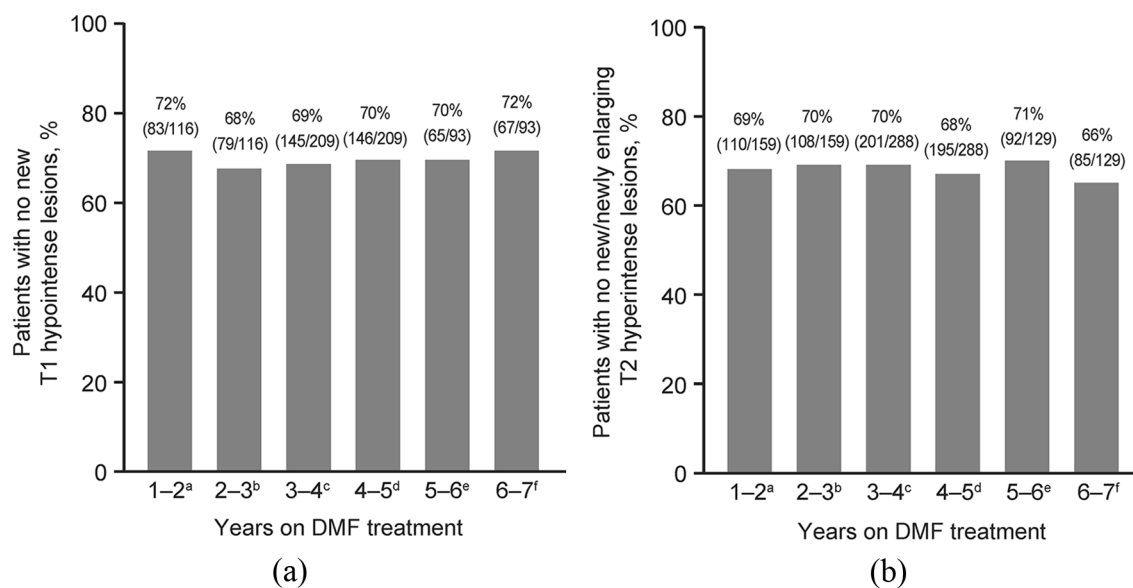
Figure 5. Patients with (a) no new T1 hypointense or (b) no new/newly enlarging T2 hyperintense lesions, calculated by comparing with previous visit with visit for patients who had non-missing data from weeks 48–240 in the ENDORSE magnetic resonance imaging cohort for patients with five consecutive scans. Data after patients switched to alternative multiple sclerosis medications were excluded.
[a]Includes patients from the PBO/DMF and GA/DMF groups in years 1–2 of ENDORSE. [b]Includes patients from the PBO/DMF and GA/DMF groups in years 2–3 of ENDORSE. [c]Includes patients from the PBO/DMF and GA/DMF groups in years 3–4 of ENDORSE and patients in the DMF/DMF group in years 1–2 of ENDORSE. [d]Includes patients from the PBO/DMF and GA/DMF groups in years 4–5 of ENDORSE and patients in the DMF/DMF group in years 2–3 of ENDORSE. [e]Includes patients from the PBO/DMF and GA/DMF groups in years 5–6 of ENDORSE and patients in the DMF/DMF group in years 3–4 of ENDORSE. [f]Includes patients from the PBO/DMF and GA/DMF groups in years 6–7 of ENDORSE and patients in the DMF/DMF group in years 4–5 of ENDORSE.
DMF, delayed-release dimethyl fumarate; GA, glatiramer acetate; PBO, placebo.

ARR (95% CI) was 0.25 (0.18–0.37) during the PBO treatment period (years 0–2 [DEFINE/CONFIRM]) and decreased to less than 0.14 during the DMF treatment period (years 3–9 [ENDORSE]); Figure 4b). This decreased ARR was apparent as early as year 3–4, and was maintained year-over-year throughout the treatment period. By years 8–9, after 7 years of DMF treatment, unadjusted ARR (95% CI) was 0.04 (0.01, 0.20). Over ~9 years, 56% of DMF/DMF and 55% of PBO/DMF patients remained free from relapses; the majority (88%) of patients had two or fewer relapses during this period.

In the newly diagnosed population, mean (SD) EDSS scores were slightly lower than the overall population at the start of ENDORSE (year 2): 1.9 (1.2) for the DMF/DMF group and 2.1 (1.1) for the PBO/DMF group. After ~7 years of DMF treatment in ENDORSE (year 9), mean (SD) EDSS scores remained stable, and were 1.7 (1.3) for the DMF/DMF group and 2.0 (1.1) for the PBO/DMF group. The majority of patients had EDSS scores ≤3.5 at year 2 [129/139 (93%) and 65/72 (90%)] and year 9 [50/54 (93%) and 26/28 (93%)] for the DMF/DMF and PBO/DMF groups, respectively. Importantly, for patients with an EDSS score ≤3.5 at baseline, the majority were estimated not to have progressed to a score of >3.5 during treatment: estimated 24-week CDP to >3.5 at year 8 was 3% (95% CI 1–9%) for the DMF/DMF group and 7% (95% CI 3–19%) for the PBO/DMF group (Figure 4c); sample size prevented the analysis to year 9. Most patients (83% and 77% of DMF/DMF and PBO/DMF patients, respectively), had no 24-week CDP, and 49% and 47%, respectively, were free from clinical disease activity.

MRI end points. Approximately 70% of patients annually had no new T1 or new/newly enlarging T2 lesions after 7 years, treatment with DMF (Figure 5) compared with previous MRI scans, a maintenance of findings observed after 2 years of treatment in the parent studies.
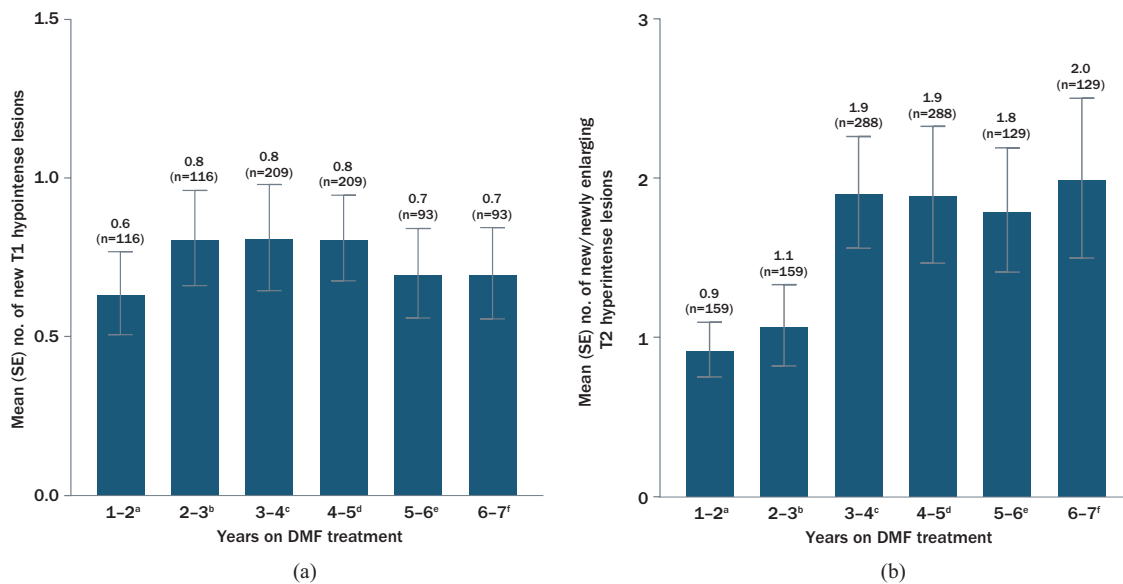
Figure 6. Number of (a) new T1 hypointense and (b) new/newly enlarging T2 hyperintense lesions, comparing with previous visit with visit for patients who had non-missing data from weeks 48–240 in the ENDORSE magnetic resonance imaging cohort for patients with five consecutive scans. Data after patients switched to alternative multiple sclerosis medications were excluded. Number of patients reporting lesions is shown for each time point.
[a]Includes patients from the PBO/DMF and GA/DMF groups in years 1–2 of ENDORSE. [b]Includes patients from the PBO/DMF and GA/DMF groups in years 2–3 of ENDORSE. [c]Includes patients from the PBO/DMF and GA/DMF groups in years 3–4 of ENDORSE and patients in the DMF/DMF group in years 1–2 of ENDORSE. [d]Includes patients from the PBO/DMF and GA/DMF groups in years 4–5 of ENDORSE and patients in the DMF/DMF group in years 2–3 of ENDORSE. [e]Includes patients from the PBO/DMF and GA/DMF groups in years 5–6 of ENDORSE and patients in the DMF/DMF group in years 3–4 of ENDORSE. [f]Includes patients from the PBO/DMF and GA/DMF groups in years 6–7 of ENDORSE and patients in the DMF/DMF group in years 4–5 of ENDORSE. For reference, the annual mean (SD) number of new T1 hypointense lesions for DMF-treated patients in DEFINE/CONFIRM at 2 years was 0.9 (2.8) compared with 3.1 (4.9) for PBO-treated patients; mean (SD) number of new/newly enlarging T2 hyperintense lesions for DMF-treated patients in DEFINE/CONFIRM at 2 years was 1.7 (4.4) compared with 8.2 (11.9) for PBO-treated patients.
DMF, delayed-release dimethyl fumarate; GA, glatiramer acetate; PBO, placebo; SD, standard deviation; SE, standard error.

These findings are consistent with the treatment effects observed by year 2 in DEFINE/CONFIRM: 70% of patients had no new T1 lesions (vs. 40% for PBO); 61% of patients had no new/newly enlarging T2 lesions (vs. 29% for PBO). Similarly, over 7 years' treatment with DMF, the annual number of new T1 hypointense lesions (0.6–0.8) and the number of new/newly enlarging T2 hyperintense lesions (0.9–2.0) were consistent with the mean (SD) observation for DMF-treated patients in DEFINE/CONFIRM at 2 years (Figure 6).

For the PBVC analysis, the adjusted mean PBVC from ENDORSE baseline (6 years of DMF treatment in ENDORSE was –1.32% (range –1.60% to –1.05%). For patients in the PBO/DMF cohort (*n* = 69) adjusted mean yearly PBVC after 6 years' DMF treatment in ENDORSE was –1.36% (–1.68% to –1.04%). The mean of adjusted PBVC compared with previous year ranged from –0.37%

to –0.19% over 6 years of DMF treatment in ENDORSE (Figure 7). For reference, mean PBVC from baseline to year 1 for untreated (PBO) MS patients in DEFINE/CONFIRM was –0.43% (*n* = 307). PBVC in healthy adults ranges from –0.1% to 0.3% annually.[14]

Discussion

These results demonstrate that, similar to what was observed in the pivotal DEFINE and CONFIRM trials,[3,4] after up to 11 years of DMF treatment in ENDORSE, long-term DMF exposure has not resulted in any new or unexpected safety findings. In the overall safety population, the incidence of serious infections, potential hepatic disorders, and malignancies remained low in all treatment groups. The clinical benefits of DMF on relapse activity and disability progression were shown to be maintained over 9 years.
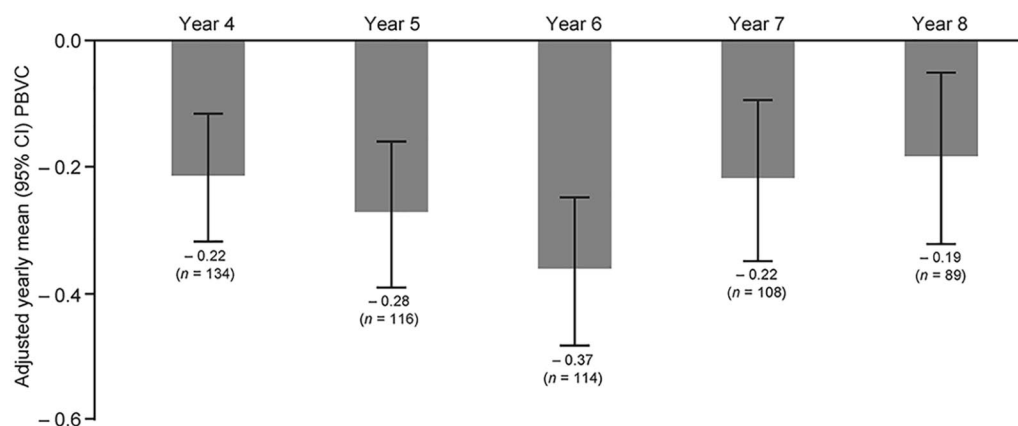
Figure 7. PBVC by year of DMF treatment. Adjusted yearly PBVC change from previous year compared with the annual summary from the DMF/DMF group in the ENDORSE MRI cohort. All patients treated with DMF BID continuously from DEFINE/CONFIRM and ENDORSE were included due to sample size restrictions. Data after patients switched to alternative multiple sclerosis medications were excluded. Adjusted mean, standard error, treatment group difference and 95% CI from an analysis of covariance model adjusted for region and baseline T2 lesion volume. Number of patients with an MRI is shown for each time point.
BID, twice daily; CI, confidence interval; DMF, delayed-release dimethyl fumarate; MRI, magnetic resonance imaging; PBVC, percentage brain volume change.

In patients treated continuously with DMF, it is noteworthy that ARR remained low over 9 years, and, if patients did experience a relapse, the majority did not have more than one. Importantly, patients with a delayed start in treatment with DMF (PBO/DMF) saw a decrease in ARR after initiating DMF, though ARR over the 2-year PBO treatment time remained statistically worse compared with the cumulative 7 years of treatment in the extension study. Disability scores, as measured by EDSS, remained stable over 9 years; and the majority of patients were walking without impairment or assistance after 9 years. Newly diagnosed patients treated with DMF responded to therapy in a similar way to that of the ENDORSE overall population, highlighting the effectiveness of DMF in this specific population.

Although this study provides the unique perspective of a single study following patients continuously for up to 11 years, potential biases inherent in long-term extension studies should be considered. In this analysis, not all patients randomized in the parent study were enrolled and dosed in ENDORSE, and patients who discontinued treatment throughout the study duration did not remain on study for continued follow-up. Therefore, these observations demonstrate the effectiveness of DMF over time but the observations are only relevant for the population who remained on the study, which represents a small proportion of the initial trial enrollment, and does not necessarily apply to the entire population in DEFINE/CONFIRM. That said, the majority of patients discontinued not for efficacy reasons but for safety or patient preference, such as pregnancy and/or commercial availability of DMF requiring less frequent clinic visits. In addition, without a control group, the relative impact of changes in the natural course of MS in ENDORSE cannot be assessed.

Because a bias may have been introduced to this analysis as a function of the study design, statistical modeling restricted to patients with an EDSS ⩽ 3.5 at baseline was performed as a sensitivity measure. The model estimated a maintenance of walking abilities consistent with the observed data (97% for patients treated with DMF continuously; 93% for patients who received PBO prior to DMF). Taken together, these findings suggest that long-term treatment with DMF allows patients to maintain a relatively low rate of relapse and maintenance of walking abilities.

MRI is valuable for diagnosis, prognosis, and assessment of response to disease-modifying therapy in patients with MS.[15] The radiological data reported herein suggest that long-term DMF treatment translates into meaningful benefits of brain tissue protection on MRI, including a low frequency of

new T1 hypointense lesions (suggesting axonal preservation) and new/newly enlarging T2 lesions (consistent with maintained anti-inflammatory effects) over 9 years. The mode of action of DMF is thought to involve both nuclear factor erythroid-derived 2-related factor-dependent and -independent pathways, which lead to an anti-inflammatory immune response and neuroprotection. Loss of brain tissue in patients with MS occurs considerably faster than in healthy individuals,[14,16] and this accelerated brain volume loss in MS correlates with cognitive impairment, worse EDSS, and reduced quality of life.[17–19] Annual changes in brain volume were low, and approached that of loss in healthy individuals (range from –0.1% to 0.3% annually) after 7 years of treatment,[20] suggesting a continuing beneficial effect of DMF on the rate of brain atrophy.

In the integrated analysis of phase II and phase III studies, there was no increased incidence of serious infection in DMF-treated patients with lymphopenia, aside from one case of PML, which occurred in a patient with prolonged, severe lymphopenia. PML has been rarely reported in the post-marketing setting; the rare PML cases in DMF-treated patients were associated primarily with moderate to prolonged lymphopenia. While only a small minority of patients in clinical trials developed severe, prolonged lymphopenia (~2%), most patients in this category do so within the first 3 years (83%),[21] but onset can occur later in rare cases. Therefore, prescribing guidelines recommend intermittent monitoring of ALC throughout treatment in order to facilitate an assessment of the benefit–risk of ongoing treatment. Of patients with lymphopenia who discontinued DMF and remained on study for follow-up, the majority experienced reconstitution of ALCs to normal levels (0.91×10^9/L) within approximately 3 months of discontinuation. These findings are consistent with data collected from a real-world population, in which most patients who discontinued DMF due to lymphopenia experienced a meaningful reconstitution of ALC within 2–4 months following DMF discontinuation.[7] The rate of reconstitution after DMF discontinuation was similar for all patients in this analysis, regardless of ALC at the time of discontinuation. This suggests that, while the rate of reconstitution is not different for patients with lower ALC at time of discontinuation, the time to reconstitute may be longer than those with higher ALCs at the time of discontinuation.

The safety and efficacy profile observed in this analysis for up to 11 years further supports DMF as a valuable long-term treatment option for patients with RRMS, including those newly diagnosed with MS.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Compliance with Ethics Guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Supplemental material

Supplemental material for this article is available online.

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