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An updated systematic review and meta-analysis exploring the efficacy and safety of dimethyl fumarate (DMF) for patients with multiple sclerosis (MS)

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ABSTRACT

Background Dimethyl fumarate (DMF) is increasingly used in treating multiple sclerosis (MS) with controversial results of the safety and efficacy of different DMF doses. We aimed to systematically review the literature to examine the safety and efficacy of DMF for MS patients.

Methods We searched PubMed Medline, Cochrane, Web of Science, Scopus databases and clinicaltrials.gov up to June 2023 for the published trials evaluating the use of DMF for MS in adults. All included studies were screened and abstracted independently by two authors. Efficacy and safety outcome measures were extracted. The meta-analysis was conducted using Review Manager 5.4.

Results 10 studies including eight randomised controlled trials, one open-label and one single-arm before-after study with a total population size of 4278 patients were included. DMF group showed a statistically significant reduction in the proportion of relapses compared with the control group, (OR: 0.47, 95% CI: [0.41, 0.55], p<0.00001) with no statistical differences between 240 mg two times per day and three times a day doses. Furthermore, the DMF group had a significant reduction in Gd-enhanced lesions compared with control (MD=−1.53, 95% CI: [−1.91 to −1.41], p<0.00001). Our results showed a non-significant difference in adverse events that led to discontinuation of the study with an OR of 1.29 (95% CI: [0.98, 1.71], p value=0.07).

Discussion DMF had significant efficacy and safety compared with the control, with no difference between the DMF doses. More studies with large sample sizes and longer follow-ups are needed to detect long-term safety and efficacy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Multiple sclerosis (MS) is the most common demyelinating disease. Disease-modifying therapies aim to modify the underlying disease process, reduce relapse rates, slow down disease progression and reduce disability over time. Dimethyl fumarate (DMF) is a promising treatment option for MS. Several reviews attempted to gather the data on DMF in patients with MS since the largest two clinical trials, DEFINE and CONFIRM studies.

WHAT THIS STUDY ADDS

⇒ This updated review including 10 clinical trials that evaluated DMF shows beneficial effects on clinical relapses and MRI lesions with tolerable safety profile without differences between 240 mg two times per day and three times a day doses.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ DMF can resemble an effective medication to improve both the clinical and imaging profiles of MS patients. Further long-term and real-world studies are needed to validate these results on the longer term and with respect to the clinical real practice.

INTRODUCTION

Multiple sclerosis (MS) is the most common demyelinating disease that affects the central nervous system and predominately affects young people. It affects around 2.8 million worldwide with females being more affected and its prevalence has been increasing in recent years.[1 2] The underlying pathophysiology is not fully understood although autoimmune attacks against myelin and neurons seem to be the most accepted theory which is eventually characterised by inflammation, demyelination and neurodegeneration.[3 4] A variety of symptoms can occur with MS cases, including vision problems, fatigue, numbness and weakness, difficulty with coordination and balance, and cognitive impairment. Many clinical subtypes of MS exist, the most common subtype is relapsing-remitting MS (RRMS). It affects around 80% of cases at onset and is characterised by periods of relapse followed by periods of remission.[2 3]

In recent years, there has been significant progress in the development of treatments for

MS. However, there is still no cure for MS, and the available treatments can only manage the symptoms and slow the progression of the disease.[2 5 6] Disease-modifying therapies (DMTs) are a special category of medications used to treat MS, which aim to modify the underlying disease process, reduce relapse rates, slow down disease progression and reduce disability over time. Some commonly used DMTs are interferon beta, glatiramer acetate, fingolimod, teriflunomide, natalizumab, ocrelizumab, alemtuzumab and dimethyl fumarate (DMF).[2 7]

DMF is an oral medication that has been effective in reducing relapse rates, delaying disability progression and improving quality of life in patients with MS.[8 9] DMF exhibits a variety of mechanisms including anti-inflammatory, antioxidant and immunomodulatory actions. It is thought that DMF helps protect myelin and nerve cells from damage by reducing inflammation and suppressing the activity of overactive immune cells.[10] Many trials and observational studies have assessed the efficacy and safety of DMF on MS patients, each with variable characteristics of the patients, specific type of MS, different doses of DMF, head-to-head comparison and outcome measures.[11–19]

Since the largest two randomised clinical trials (RCTs), DEFINE and CONFIRM studies, several reviews attempted to gather the data on DMF in patients with MS.[11 12] Burness *et al* conducted an early narrative review of DMF properties and use in only RRMS based on preclinical studies and DEFINE and CONFIRM trials.[10] A more recent review addressed only safety of DMF in published studies until 2019[20] . A recent Cochrane review including only RCTs until 2022, DEFINE and CONFIRM studies,[11 12] evaluated the role of immunomodulators including DMF in RRMS in a network meta-analysis.[21] On the other hand, a recent review explored the real-world data on DMF compared with teriflunomide in studies until 2021.[22] Notably, all reviews showed promising results despite their limitations. However, the recent reviews included the two RCTs only on patients with RRMS or addressed safety outcomes in all published studies. No review explored the published trials on DMF with the different used doses, MS types, and efficacy and safety outcomes. A meta-analysis can leverage the evidence collectively from all the trials and thus contribute to the published collective evidence on using DMF for MS.

This systemic review and meta-analysis aim to comprehensively review the available trials on the efficacy and safety of DMF for MS patients. In addition, we will provide an overall estimate of the medication effects on clinical and imaging parameters, as well as adverse effects. The review will also discuss the limitations and challenges of the available trials and future directions of DMF research.

METHODS

Protocol and registration

We conducted the present systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[23] The protocol was registered on the Prospero website (CRD42023439079), the international prospective register of systematic reviews, available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=439079.

Literature search

We carried out a systematic literature review using PubMed Medline, Cochrane, Web of Science and Scopus databases to identify eligible published studies up to June 2023 restricted to the English language. We constructed a thorough search string using relevant keywords (online supplemental appendix 1). The published reviews and reference lists of selected papers were also searched. Additionally, we searched through the ClinicalTrials.gov website up to 30 June 2023.

Eligibility criteria: types of studies, participants, and intervention

We selected eligible studies based on pre-identified criteria. Restriction to study design was applied including only clinical trials. We included studies comparing DMF to any other therapy (or no therapy) and addressing efficacy and/or safety outcomes. Only studies with MS patients were considered regardless of their clinical course or time since diagnosis. The inclusion and exclusion criteria are detailed in online supplemental appendix 2.

Screening of the studies

Two review authors independently screened titles and abstracts of the citations retrieved by the literature search against the inclusion and exclusion criteria. In addition, we removed duplicates of records. We retrieved the full text of the potentially eligible records. Two different independent reviewers screened the full-text papers against the inclusion criteria, with the reconciliation of any differences conducted by a third independent reviewer.

Data extraction and outcome measures

Finally included studies underwent data extraction using specifically designed extraction forms. Two independent reviewers extracted data; a third independent reviewer resolved any differences. Extracted data included but was not limited to study methodology and design, participants' characteristics, and outcome measures. Efficacy outcome measures included change in both clinical (Expanded Disability Status Scale (EDSS), relapses, annualised relapse rate and disease progression) and MRI parameters (T-1, T-2 weighted and Gd-enhanced lesions). For safety outcome measures, adverse effects that led to study discontinuation, serious adverse effects and most common adverse effects were extracted.

Assessment of risk of bias

We have used the Cochrane risk-of-bias 2 tool (ROB2)[24] for randomised trials; whereas, for non-randomised studies of interventions, we have used the ROBINS-I Cochrane risk-of-bias tool.[25] For each study, two authors

independently assessed the risk of bias, and a third author resolved any differences.

Data analysis

We used Review Manager (RevMan) software (V.5.4) for data analysis. Dichotomous outcomes were presented using ORs with a 95% CI, and continuous outcomes were presented as mean differences with a 95% CI. A p value of ≤0.05 was deemed statistically significant. The heterogeneity in the data was examined through x^2 and I^2 tests. If the x^2 and p value were <0.1 and I^2 was above 50%, the data were deemed as heterogenous. Depending on the data's heterogeneity, two models were used for pooling data: a random effects model for heterogeneous data and a fixed-effect model for homogeneous data. If heterogeneity was unresolvable, the Cochrane leave-one-out method was applied, excluding one study from the analysis.[26]

RESULTS

Search results

Our search strategy resulted in a total of 5763 records from literature databases. After removing 2024 duplicate records, we screened the title and abstract of 3739 references. After excluding irrelevant 3668 records (titles/abstracts), we retrieved 71 articles for full-text review. One report could not be retrieved. Of the 70 reports assessed for eligibility, 44 were of ineligible study design and 16 had ineligible PICO elements. 10 references met our inclusion criteria and were finally included in our review (figure 1).

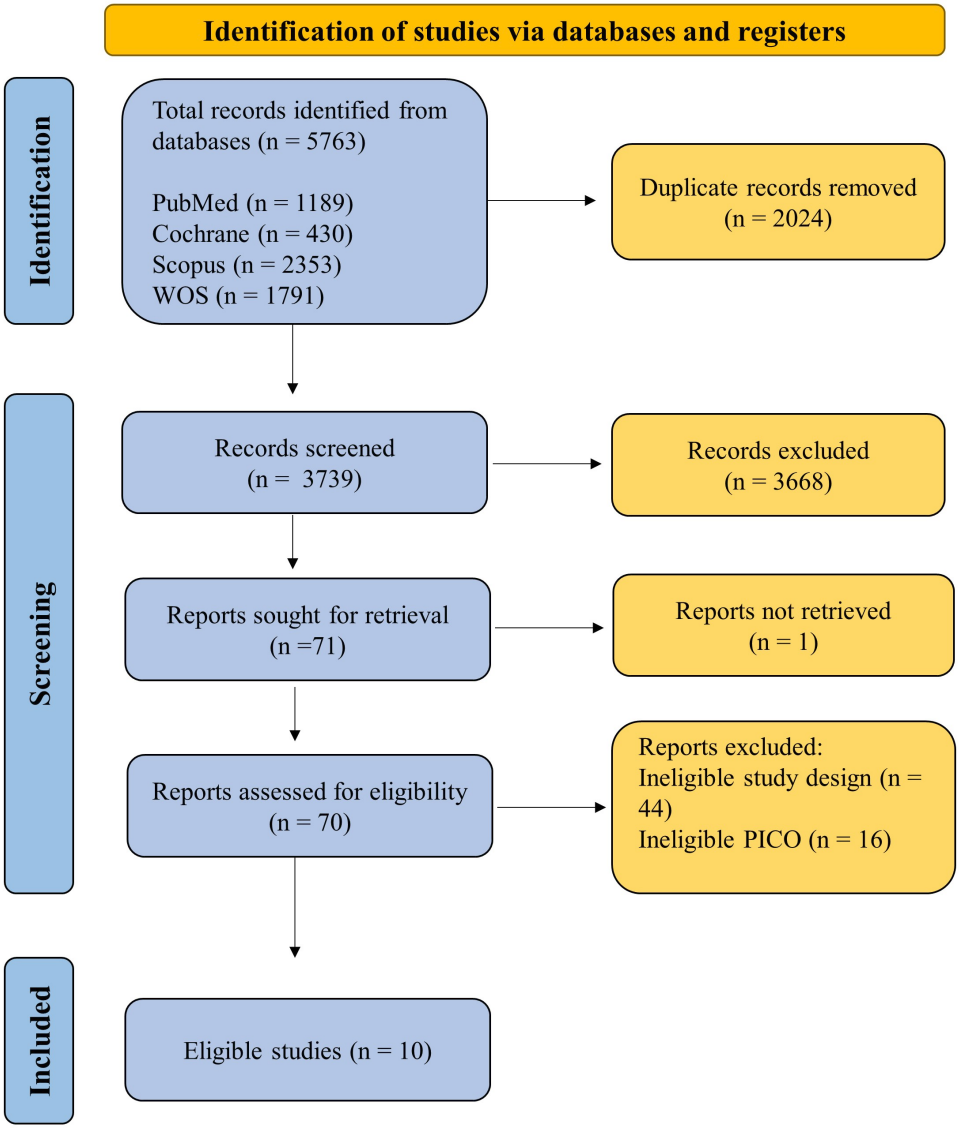

Figure 1 PRISMA flow diagram of the systematic review process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Characteristics of the included studies and patients

Of the 10 included trials, eight were RCTs,[11–18] one single-arm before-after trial[27] and an open-label clinical trial[28] with a total population size of 4278 patients. All studies included adult patients with variable sample sizes from 50 to 1234 participants. The study duration varied from 5 weeks to 2 years. The summary of study characteristics is shown in tables 1 and 2. The majority of participants were females with mean age ranging from 34.8±10.2 to 55.7±5.5 years. Online supplemental appendix 3 contains the baseline characteristics of the participants.

Risk of bias

All the included studies were deemed to be of low risk except Fourghipour 2019[27] and PROCLAIM[28] which were both found to have a serious risk of bias and Montalban 2019[15] which was found to have some concerns. The details of the risk of bias results of all studies are shown in online supplemental appendix 4 and 5.

Meta-analysis

Efficacy of DMF

Proportion of patients with relapses

Our results, based on a subgroup analysis evaluating the dosage of DMF, demonstrated a significant reduction in the proportion of patients with relapses in the DMF 240 mg two times per day group compared with the control. Data from four studies were pooled (OR: 0.52, 95% CI: [0.42, 0.63], p<0.00001). Likewise, the DMF 240 mg three times a day group, with data from two studies, also showed a significant reduction compared with the control (OR: 0.43, 95% CI: [0.35, 0.53], p<0.00001). No heterogeneity was found in both results (I^2=0%, p values of 0.42 and 0.64, respectively). Furthermore, there was no statistically significant difference between the effects of the two dosage groups (x^2 = 1.46, df=1, p=0.23), suggesting that the dosage variations did not lead to significant differences in the proportion of patients with relapse (figure 2A).

Annualized relapse rate (ARR)

Based on the subgroup analysis focusing on different dosages of DMF, a similar significant reduction in the annualised relapse rate (ARR) was found in both DMF groups compared with the control group. Data from three studies were pooled for each subgroup. For the DMF 240 mg two times per day group, the mean difference (MD) was −0.19 (95% CI: [−0.24, −0.13], Z=6.14, p<0.00001), and for the DMF 240 mg three times a day group, the MD was −0.18 (95% CI: [−0.24, −0.12], Z=6.00, p<0.00001). In total, the analysis included 1647 and 1660 participants in the two groups, respectively. No evidence of heterogeneity was detected in either group (I^2=0%, p value=0.98 for two times per day; I^2=0%, p value=0.88 for three times a day). Additionally, there was no significant subgroup difference detected (x^2 = 0.00, df=1, p=0.97) (figure 2B).

Participants with confirmed disease progression

Based on a subgroup analysis evaluating the dosage of DMF, our results demonstrated a significant reduction in the number of participants with confirmed disease progression in both the DMF 240 mg two times per day and three times a day groups compared with the control. For the DMF 240 mg two times per day group, data from two studies were pooled, yielding an OR of 0.59 (95% CI: [0.46, 0.77], Z=3.90, p<0.0001). For the DMF 240 mg three times a day group, data from two studies were pooled as well, resulting in an OR of 0.65 (95% CI: [0.50, 0.84], Z=3.26, p=0.001).

The pooled analysis encompassed 232 events from 1529 participants across both dosage groups. Notable heterogeneity was observed in the two times per day group (I^2=41%), while no significant heterogeneity was detected in the three times a day group (I^2=0%). Moreover, there were no significant subgroup differences identified (x^2 = 0.23, df=1, p=0.63), indicating that the variations in dosage did not lead to substantial differences in the prevention of disease progression (figure 2C).

EDSS change from baseline

The results showed no significant change in EDSS from baseline between DMF 240 mg two times per day and control groups for which data from two studies were pooled (95% CI: [−0.08, 0.15], Z=0.60, p=0.55) with a mean difference of 0.03. Moderate heterogeneity was observed (I^2=42%) (figure 2D).

New or enlarging GD-enhanced lesions

Based on the subgroup analysis focusing on different dosages of DMF, there was a significant reduction in the number of new or enlarging GD-E lesions in both the DMF 240 mg two times per day and three times a day groups compared with the control. Data from two studies were pooled for each dosage group. For the DMF 240 mg two times per day group, the MD was −1.64 (95% CI: [−2.17, −1.11], Z=6.03, p<0.00001), and for the DMF 240 mg three times a day group, the MD was −1.41 (95% CI: [−1.96, −0.85], Z=4.96, p<0.00001). In total, the analysis included 598 participants across both dosages. No evidence of heterogeneity was detected in either subgroup (I^2=0%, p value=0.73 for two times per day; I^2=0%, p value=0.61 for three times a day). Additionally, there was no significant subgroup difference detected (x^2 = 0.35, df=1, p=0.55) (figure 3A).

New T1-weighted Hypointense lesions

A non-significant reduction was detected in the number of new T1-weighted hypointense lesions between DMF 240 mg two times per day and control groups for which data from two studies were pooled (95% CI: [−7.47, 1.34], Z=1.36, p=0.17) with mean difference −3.06, significant heterogeneity was detected (I^2=94%) (figure 3B).

New or enlarging T2-weighted hyperintense lesions

Based on the subgroup analysis focusing on different dosages of DMF, there was a varied effect on the number of new or enlarging T2-hyperintense lesions in both DMF groups compared with the control group. Data from three studies were pooled for each dosage. For the DMF 240 mg two times per day group, the MD was −9.03, and it was not statistically significant (95% CI: [−19.44, 1.38], Z=1.70, p=0.09). In contrast, the DMF 240 mg three times a day group showed a significant reduction,

Table 1 Summary of characteristics of the included studies

Reference/study	Study design/phase	Country/region	Study duration	Type of MS	Total sample size	Population	Intervention	Control (with dose, frequency, duration …etc) (N=??)
DEFINE study	RCT/phase 3	Multicentre, 28 countries	2 years	Relapsing-remitting	1234	▶ Age of 18–55 years old ▶ Baseline EDSS score from 0 to 5 ▶ Disease activity (at least one clinically documented relapse within 12 months OR MRI with at least one Gd-enhanced lesion obtained 6 weeks before randomisation	▶ BG-12 240 mg two times per day (n=420) ▶ BG-12 240 mg three times a day (n=416)	Placebo (n=408)
CONFIRM study	RCT/phase 3	Multicentre, 200 sites in 28 countries	2 years	Relapsing-remitting	1417	▶ Age of 18 to 55 years ▶ Baseline EDSS score from 0 to 5 ▶ Disease activity (at least one clinically documented relapse within 12 months OR MRI with at least one Gd-enhanced lesion obtained 6 weeks before randomisation	▶ BG-12: 240 mg two times per day (n=359) ▶ BG-12: 240 mg three times a day (n=345) ▶ Glatiramer acetate: included as a reference comparator (n=350)	Placebo (n=363)
FUMAPMS study	RCT/phase 2	Copenhagen University Hospital, Rigs Hospitalet, Denmark	48 weeks	Primary progressive	54	▶ Age of 18 to 65 years ▶ Disease duration of at least 1 year ▶ EDSS ≤6.5 ▶ CSF NFL levels above 380 ng/L	▶ BG-12 240 mg two times per day (n=27)	Placebo (n=27)
Foroughipour 2019	Single-arm before-after clinical trial	The Mashhad University of Medical Sciences, Iran	12 months	Relapsing-remitting	50	▶ Age of 15–50 years	▶ BG-12 240 mg two times per day (n=50)	–
Kappos 2008	RCT/phase 2b	Multicentre, 43 centres in 10 countries	48 weeks	Relapsing-remitting	256	▶ Age of 18–55 years ▶ EDSS between 0 and 5 ▶ Either at least one relapse within 12 months of randomisation and a previous cranial MRI scan showing lesions consistent with multiple sclerosis, or Gd-enhanced lesions on MRI scans done within 6 weeks of randomisation	▶ BG-12 120 mg once a day (n=64) ▶ BG-12 120 mg three times a day (n=64) ▶ BG-12 240 mg three times a day (n=63)	Placebo (n=65)
PROCLAIM study	Open-label phase 3 study	Multicentre in six countries	2 years	Relapsing-remitting	218	▶ Age of 18–65 years	▶ BG-12 240 mg two times per day (n=218)	–
Masjedi 2021	RCT	Isfahan University, Iran.	2 years	–	60	▶ Age of 18–55 years ▶ Not received any immunomodulatory therapy except for corticosteroids	▶ BG-12 240 mg two times per day (n=30)	Fingolimod 0.5 mg daily (n=30)

Continued

Table 1 Continued

Reference/study	Study design/phase	Country/region	Study duration	Type of MS	Total sample size	Population	Intervention	Control (with dose, frequency, duration …etc) (N=??)
EVOLVE-MS-2 study	RCT/phase 3	Multicentre in 70 sites in the USA and Europe.	5 weeks	Relapsing-remitting	504	▶ Age of 18–65 years ▶ Neurologically stable with no evidence of relapse in the 30 days before screening. ▶ Not received fumarate treatment before.	▶ BG-12 120 mg two times per day for week 1 ▶ BG-12 240 mg two times per day for weeks 2–5	▶ DRF 231 mg two times per day for week 1 ▶ DRF 462 mg two times per day for weeks 2–5
APEX 1 study	RCT/phase 3	Multicentre in five countries	24 weeks	Relapsing-remitting	224	▶ Age of 18–55 years ▶ EDSS score of 0–5.0 ▶ Disease activity as evidenced by ≥1 relapse within the 12 months before randomisation or the presence of Gd-enhanced lesions on brain MRI scans within 6 weeks before randomisation	▶ BG-12 240 mg two times per day (n=111)	Placebo (n=113)
Montalban 2019	RCT/phase 2	Multicentre in 56 centres	24 weeks	Relapsing-remitting OR secondary progressive with superimposed relapses	261	▶ Age of 18–65 years ▶ EDSS no more than 6	▶ Evobrutinib 25 mg once a day (n=50) ▶ Evobrutinib 75 mg once a day (n=51) ▶ Evobrutinib 75 mg two times per day (n=53)	▶ BG-12 240 mg two times per day (n=54) ▶ Placebo (n=53)

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RCT, randomised clinical trial.

Table 2 Endpoints and outcomes of the included studies

Reference/study	Study endpoints			Data collection time points	Outcome findings
	Primary endpoints	Secondary endpoints	Tertiary endpoints		
DEFINE study	► Proportion relapsed at 2 years	► Annualised relapse rate ► Number of Gd-enhanced lesions ► New or enlarging T-2 hyperintense lesions ► Time to progression of disability	► Quality of life of patients	► Baseline ► 2 years	Both BG-12 regimens significantly reduced the proportion of patients who had a relapse, annualised relapse rate, disability progression rate and the number of lesions on MRI compared with placebo
CONFIRM study	► Annualised relapse rate at 2 years	► Number of new or enlarging hyperintense lesions on T2-weighted images ► Number of new hypointense lesions on T1-weighted images ► Proportion of patients with a relapse at 2 years ► Time to disability progression at 2 years	► Comparison of the relative benefits and risks of BG-12 or glatiramer acetate vs placebo at 2 years ► Number of Gd-enhanced lesions at 2 years ► Quality of life of patients	► Baseline ► 2 years	BG-12 at a dose of 240 mg two or three times daily, as compared with a placebo, significantly reduced the rate of relapse, the proportion of patients with a relapse and disease activity as measured by various MRI endpoints
FUMAPMS study	► Difference in change in the CSF concentration of NFL from screening to week 48	► CSF endpoints: concentrations of MBP, sCD27, sBCMA, CHI3L1, and sCD14, IgG-index, and CSF-serum albumin quotient	► MRI endpoints: number of new or enlarged T2 lesions, FA in NAWM, lesion volume, (MTR) in lesions, thalamic volume, PBVC ► Clinical endpoints: EDSS, T25FW, 9HPT, BICAMS, SDMT	► Baseline ► 48 weeks	Dimethyl fumarate treatment for 48 weeks did not affect any of the investigated efficacy measures in patients with PPMS
Foroughipour 2019	► EDSS score ► Change in Gd-enhanced lesions ► Number of relapses	► Patient satisfaction ► Treatment complications	--	► Baseline ► 12 months	The drug reduced disability, relapses and MRI lesions and provided satisfaction after 1 year of treatment
Kappos 2008	► New Gd-enhanced lesions over four scans at weeks 12, 16, 20 and 24 (calculated as the sum of the scans)	► The cumulative number of new Gd-enhanced lesions from weeks 4 to 24 ► New or enlarging T2-hyperintense lesions at week 24 ► New T1-hypointense lesions at week 24	► All adverse events	► Baseline ► 4, 12, 24 weeks	BG-12 240 mg three times a day reduced the mean total number of new Gd-enhanced, new or enlarging T2-hyperintense and new T1-hypointense lesions compared with placebo. Adverse events more common in patients given BG-12 than in those given placebo included abdominal pain, flushing and hot flush. Dose-related adverse events in patients on BG-12 were headache, fatigue and feeling hot.

Continued

Table 2 Continued

Reference/study	Study endpoints			Data collection time points	Outcome findings
	Primary endpoints	Secondary endpoints	Tertiary endpoints		
PROCLAIM study	▶ Lymphocyte subset counts	▶ The pharmacodynamic effect of DMF on ALCs and Ig isotypes	▶ Safety and tolerability in 96 weeks ▶ Lymphocyte subset count in 96 weeks ▶ The relationship between changes in ALC and lymphocyte subsets and MS disease activity	▶ Baseline ▶ Every 12 weeks, from 12 to 96 weeks	Lymphocyte decrease with DMF was maintained over treatment, yet immunoglobulins remained stable. No increase in infection incidence was observed in patients with or without lymphopenia.
Masjedi 2021	▶ EDSS ▶ MRI lesions	▶ Relapses re-experience ▶ Adverse effects	–	▶ 6 weeks ▶ 12 months ▶ 24 months	DMF was neither superior nor inferior to FTY comparing MRI lesions, EDSS scores and adverse effects within 2 years. However, further evaluations with larger sample sizes are recommended
EVOLVE-MS-2 study	▶ Gastrointestinal tolerability ▶ Safety	–	–	▶ Baseline ▶ Weekly, from 1 to 5 weeks	DRF has an improved GI tolerability profile compared with DMF, which may lead to better long-term adherence and persistence to therapy.
APEX 1 study	▶ New Gd+lesions on brain MRI scans from weeks 12–24	▶ New Gd+lesions from baseline to week 24 ▶ New/newly enlarging T2 hyperintense lesions at week 24 from baseline	▶ Safet; adverse effects ▶ Annualised relapse rate at 24 weeks ▶ Proportion of patients with a relapse at 24 weeks	▶ Baseline ▶ 12 weeks ▶ 24 weeks	The study shows a strong efficacy and favourable benefit-risk profile of DMF
Montalban 2019	▶ Gd-enhancing lesions identified on T1-weighted MRI	▶ ARR ▶ Change in EDSS from baseline ▶ Safety	–	▶ Baseline ▶ 24 weeks	Patients with relapsing multiple sclerosis who received 75 mg of evobrutinib once daily had significantly fewer enhancing lesions during weeks 12 through 24 than those who received a placebo

ARR, annualised relapse rate; DMF, dimethyl fumarate; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

with an MD of −9.30 (95% CI: [−17.82, −0.78], Z=2.14, p=0.03).

In total, the analysis included 664 participants across both dosage groups. Significant heterogeneity was observed in both dosage groups (I^2=97% for two times per day; I^2=95% for three times a day), indicating substantial variability in the outcomes across the studies. Furthermore, there were no significant subgroup differences found ($x^2 = 0.00$, df=1, p=0.97), suggesting that the dosage variations did not significantly impact the number of new or enlarging T2-hyperintense lesions (figure 3C).

After applying the leave-one-out technique, we managed to eliminate the heterogeneity by excluding FUMAPMS 2021 from the 240 mg two times per day analysis and Kappos 2008 from the 240 mg three times a day analysis. Consequently, we observed significant findings in favour of DMF 240 mg two times per day patients over the control, with a mean difference of −13.66, 95% CI: [−16.58 to −10.75], and a p value of less than 0.00001. For DMF 240 mg three times a day, the mean difference was −13.07 with 95% CI: [−16.19 to −9.94], and a p value of less than 0.00001 (figure 4).

Safety of DMF

Patients with adverse effects that led to study discontinuation

Overall, 284 (11.9%) of 2382 patients taking DMF had adverse events that led to study discontinuation (online supplemental appendix 6). Based on a subgroup analysis evaluating the dosage of DMF, our results did not show a significant difference in the number of patients who

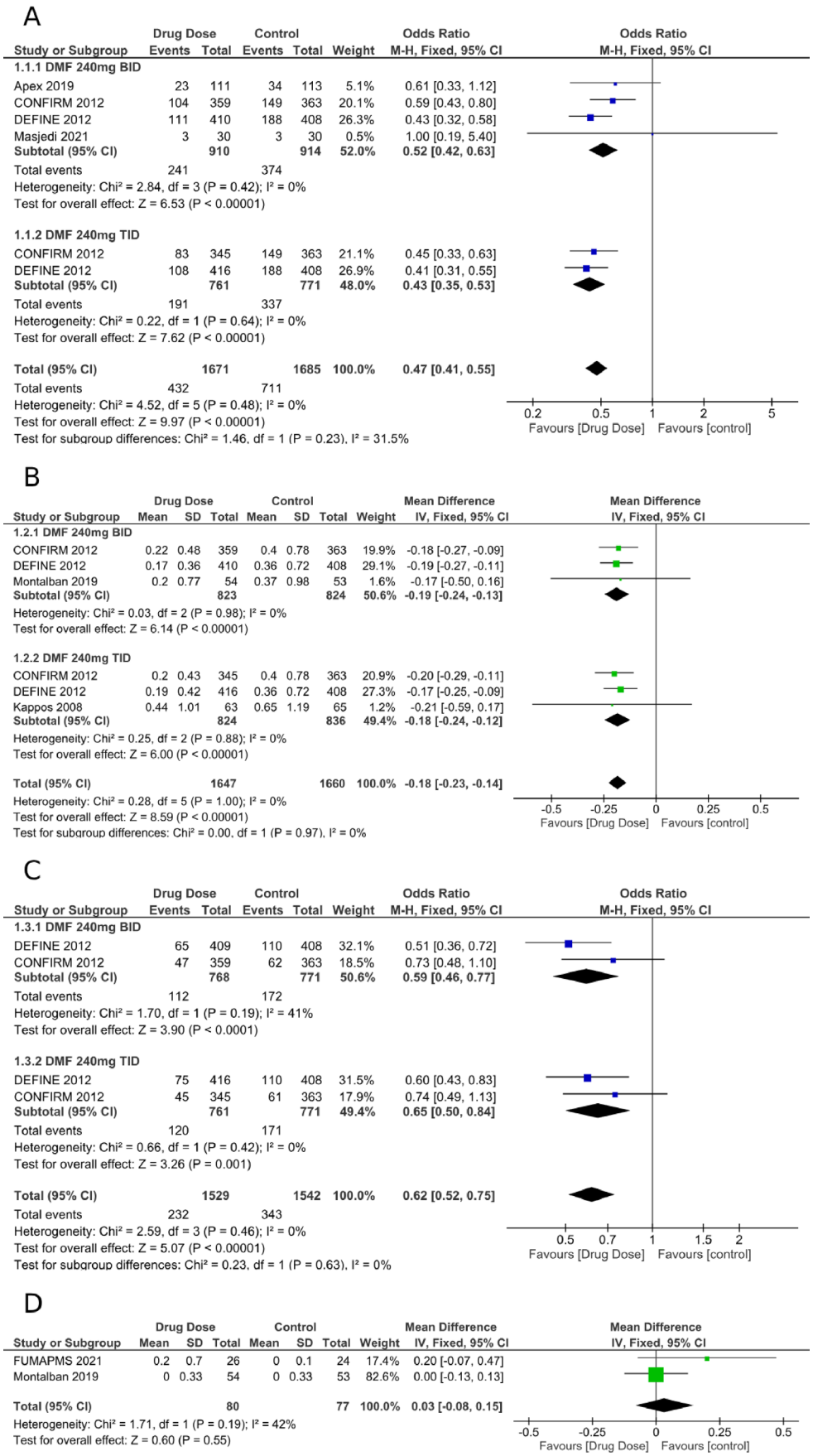

Figure 2 Efficacy clinical outcomes. (A) Proportion of patients with relapses. (B) Annualised relapse rate (ARR). (C) Participants with confirmed disease progression. (D) EDSS change from baseline. EDSS, Expanded Disability Status Scale.

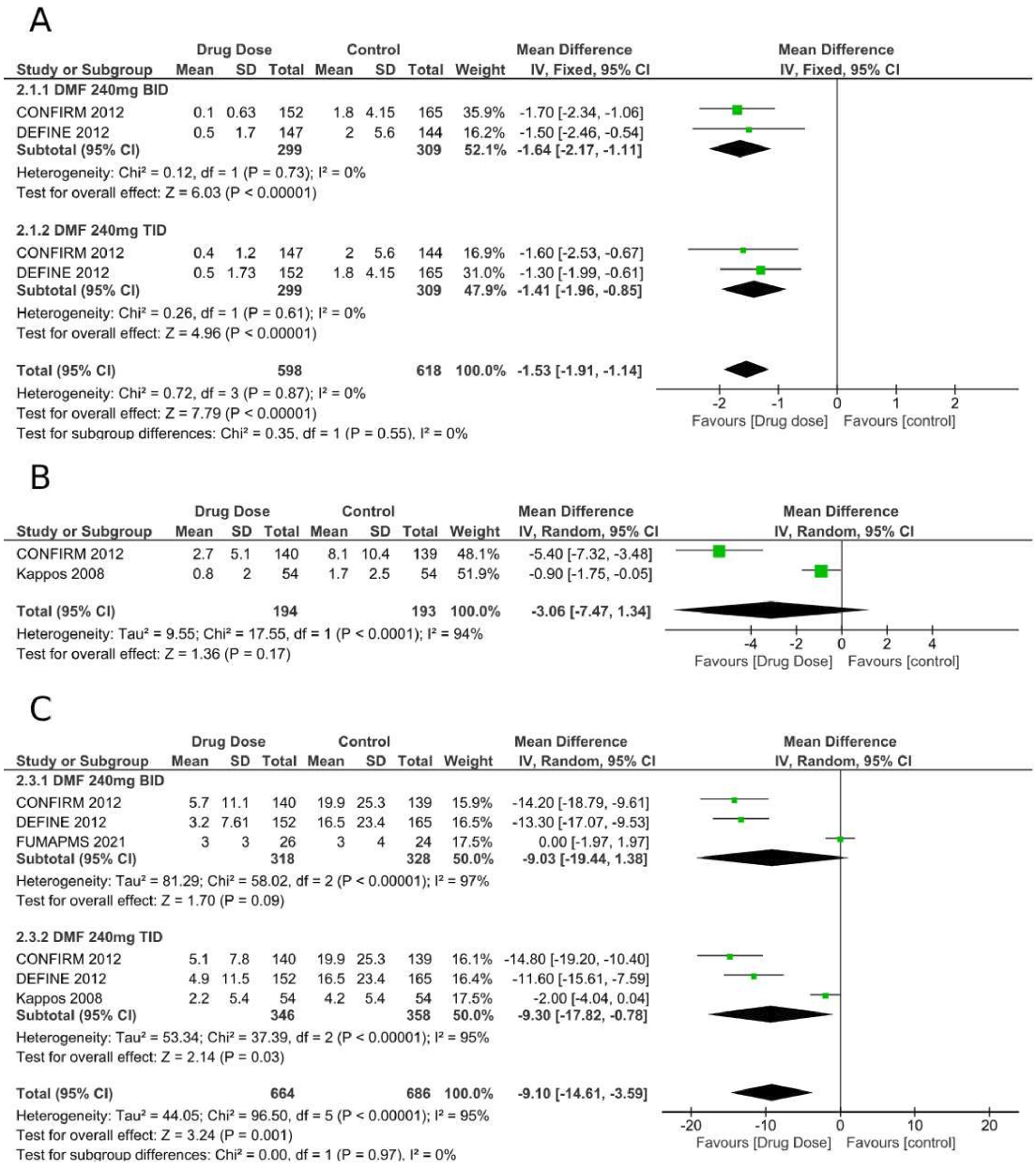

Figure 3 Efficacy MRI outcomes. (A) New or enlarging Gd-enhanced lesions. (B) New T1-weighted hypointense lesions. (C) New or enlarging T2-weighted hyperintense lesions.

discontinued the study due to adverse effects between the DMF groups and the control. In the DMF 240 mg two times per day group, data from five studies were pooled, resulting in an OR of 1.29 (95% CI: [0.98, 1.71], p value=0.07). Similarly, in the DMF 240 mg three times a day group, data from two studies were pooled, resulting in an OR of 1.21 (95% CI: [0.90, 1.63], p value=0.20).

The combined analysis included 1919 participants across both dosages. Heterogeneity was observed in the two times per day group (I^2=25%, p value=0.25) but was not significant in the three times a day group (I^2 = 0%, p value=0.80). Furthermore, no significant subgroup differences were found (x^2 = 0.09, df=1, p=0.77), suggesting that dosage variations did not substantially impact the number of patients discontinuing the study due to adverse effects (figure 5A).

Patients with any adverse effects

Our results, based on a subgroup analysis evaluating the dosage of DMF, demonstrated a significant increase in the number of patients with adverse effects in the DMF 240 mg two times per day group compared with the control. Data from five studies were pooled (OR: 1.79, 95% CI: [1.28, 2.51], p=0.0008). Conversely, the DMF 240 mg three times a day group, with data from three studies, did not show a significant difference compared with the control (OR: 1.18, 95% CI: [0.82, 1.72], p=0.37).

The pooled analysis included a total of 1760 participants across both dosages, involving 1637 events. Heterogeneity was minor in both results (I^2 = 0% for two times per day with a p value of 0.43; I^2 = 10% for three times a day with a p value of 0.33). Furthermore, there was no statistically significant difference between the effects of the two

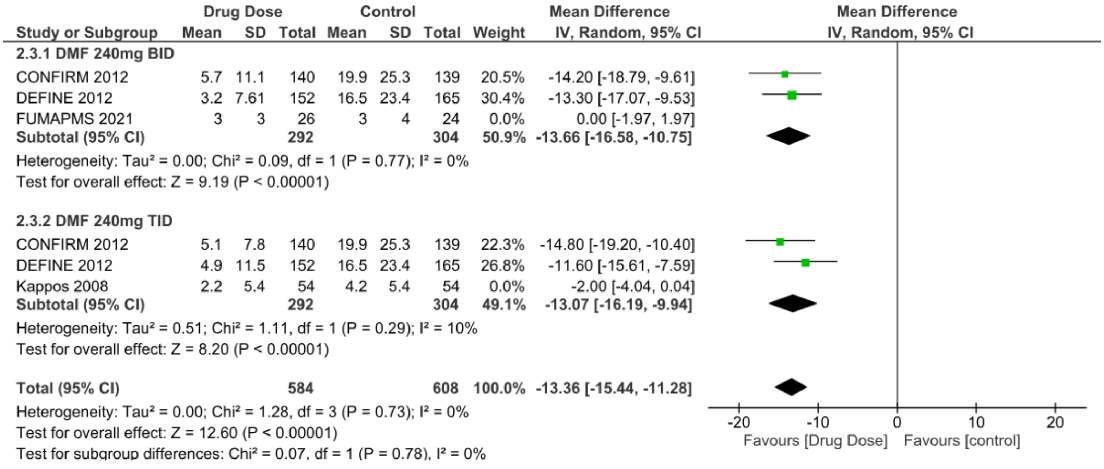

Figure 4 Efficacy MRI outcomes: new or enlarging T2-weighted hyperintense lesions after applying the leave-one-out technique to eliminate the heterogeneity.

dosage groups (x^2 = 2.58, df=1, p=0.11), suggesting that the dosage variations did not lead to significant differences in the number of patients experiencing adverse effects (figure 5B).

Overall, 2182 (7.48%) of 2434 patients taking DMF had any adverse events during the study duration (online supplementalAppendix 6). In total, the most commonly reported adverse effect was flushing (831/2431; 34.18) followed by diarrhoea (360/2431; 14.81%) and nausea (324/2431; 13.33%). Death was reported in only three cases (3/2190; 0.14%) while serious infections and severe lymphopenia were reported in (79/1300; 6.07%) and (79/1989; 3.97%) respectively (online supplemental Appendix 7).

Patients with any serious adverse effects

In total, 300 (13.87%) of 2163 patients taking DMF experienced any serious adverse events during the study duration (online supplementalAppendix 6). Our results, based on a subgroup analysis evaluating the dosage of DMF, demonstrated varied effects on the number of patients with serious adverse effects. For the DMF 240 mg two times per day group, data from four studies were pooled, showing no significant difference compared with the control (OR: 0.80, 95% CI: [0.63, 1.02], p=0.07). Conversely, the DMF 240 mg three times a day group, with data from two studies, showed a significant reduction compared with the control (OR: 0.68, 95% CI: [0.53, 0.89], p=0.004).

The pooled analysis encompassed 272 events from 1667 participants across both dosages. No evidence of heterogeneity was detected in either result (I^2 = 0%, p values of 0.92 for two times per day and 0.90 for three times a day, respectively). Furthermore, there was no statistically significant difference between the effects of the two dosage groups (x^2 = 0.79, df=1, p=0.37), suggesting that the dosage variations did not lead to significant differences in the occurrence of serious adverse effects (figure 5C).

DISCUSSION

To the authors' knowledge, this is the first study to extensively investigate the existing trials regarding the efficacy and safety of DMF for MS patients. Our meta-analysis pointed out that dimethyl fumarate can be an effective and safe treatment for multiple sclerosis especially RRMS.

DMF is an approved medication for the treatment of MS patients by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in early 2013.[8] In vitro and in vivo studies have revealed that DMF has a multitude of biological actions including immunomodulatory anti-inflammatory effects through the promotion of Th2 profile as well as the positive impact on natural anti-oxidation mechanisms.[8 10] This meta-analysis suggests that DMF, at both tested doses of 240 mg two times per day and three times a day, is efficacious in reducing the clinical relapse rate and disease progression. Such results are in accordance with most individual trials[12–14 17] revealing a significant reduction in clinical relapses and disease progression except one study (CONFIRM study)[11] that showed a non-significant reduction (17%). Compared with the DEFINE study, the CONFIRM trial included smaller sample with lower proportion of patients having used DMT prior to the study (29% vs 40%). Another potential contributor to this difference is the lower proportion of patients with disability progression in placebo group (17%) in the CONFIRM study[11] than those in the DEFINE study (27%).[12]

The primary aim of DMTs has always been to control the disease progression and clinical relapses which further contribute to the clinical disability status.[10] EDSS is the most commonly used disability scale for MS patients.[29] Our analysis showed no significant change at the EDSS among patients on DMF 240 mg two times per day. Notably, only two studies with different clinical subtypes were included: primary progressive in FUMAPMS study[18] both relapsing-remitting, and secondary progressive in Montalban *et al*[15] which could have been the cause of

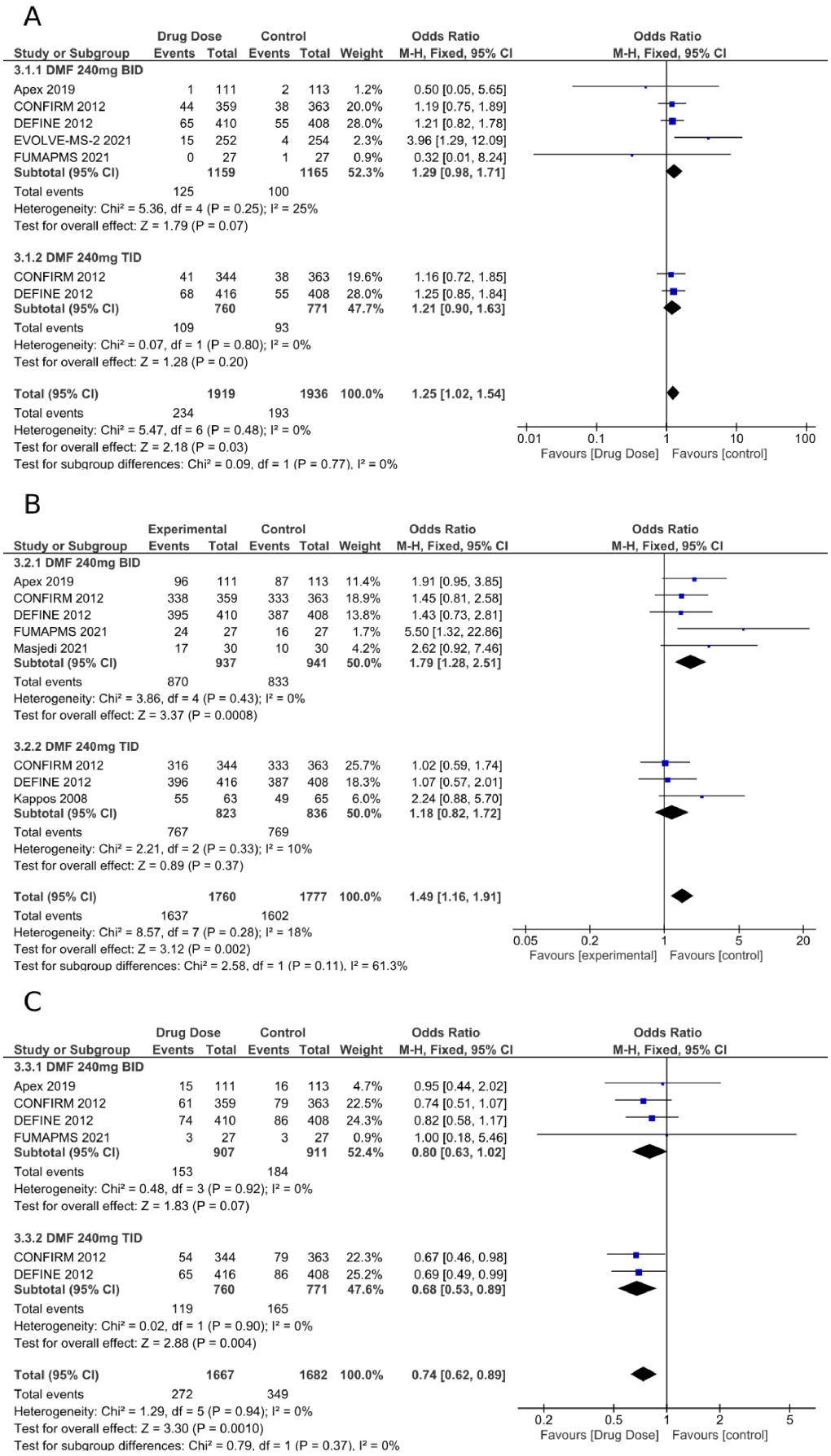

Figure 5 Safety outcomes. (A) Patients with adverse effects that led to study discontinuation. (B) Patients with any adverse effects. (C) Patients with any serious adverse effects.

moderate heterogeneity. Notably, the FUMAPMS trial failed to show beneficial effects of DMF over placebo.[18] Similarly, the RCT by Masjedi *et al* showed no difference between DMF and fingolimod in improving clinical or imaging parameters.[14] Differences in participants' baseline characteristics are potential sources of heterogeneity. Both CONFIRM and DEFINE studies did not assess EDSS as distinct endpoint.[11 12] An observational study on progressive MS revealed no change in EDSS between DMF and glatiramer (GA) despite a trend reduction in T2 lesions.[30] A single-arm trial on Iranian patients revealed significant reduction of both relapses and EDSS after 12 months on DMF 240 mg two times per day.[27]

This review exhibits discrepancy between improvement in relapse rates and confirmed progression compared with change in disability scale (EDSS). It noteworthy to acknowledge the differences in comparators in studies of both outcomes. The influence of reduced relapses on preventing disability in an individual patient remains unclear.[7] A recent pooled analysis of around 200 000 EDSS transitions from more than 27 000 patients with less than 15 years follow-up investigated the contribution of relapse-associated worsening (RAW) and progression independent of relapse activity (PIRA) to disability worsening.[31] While relapses contribute to worsening of disability, PIRA starts early in disease and becomes the dominant driver for disability. It takes years for increased limitation with subsequent change in EDSS.[31] The high rates of inter-rater variability in EDSS should be acknowledged.[7] Improvement of the disability level should be specifically an aim of further trials and real-world studies with longer follow-up durations.

It has been argued that MRI-based parameters may correlate with the extent of disability.[32 33] MRI-based markers of neuroinflammation and neurodegeneration have been crucial in the diagnosis and follow-up of MS patients.[32 33] Our analysis showed that patients on DMF 240 mg two times per day had statistically insignificant fewer T1-weighted hypointense lesions. Notably, only two studies[11 13] were included for two times per day dose with significant heterogeneity while there were not sufficient data for three times a day dose. It is noteworthy that each of both studies showed a significant reduction in T1 lesions.[11 13] T1 hypointense lesions are usually referred to as black holes which are likely to be the most destructive lesions with underlying severe demyelination and axonal loss.[34] Although T1 lesions provide high clinical significance, they are usually assessed manually because they are difficult to segment.[35] On the other hand, for Gd-enhanced lesions, both doses were efficacious in reducing the number of new or enlarging lesions.

The classical MRI findings of MS patients include hyperintense T2 lesions with variable size and shape that are historically considered more specific and correlating to the periventricular pathology (Dawson's fingers).[36] Additionally, most automatic segmentation methods detect and delineate T2 lesions.[35] The pooling of three studies per dose of DMF in our analysis resulted in a significant reduction in new or enlarging T2 lesions for three times a day dose only while both data of both subgroups showed significant heterogeneity. Such heterogeneity could be due to variations in the patients' age, gender proportion, MS subtype and/or baseline disease parameters (eg, EDSS, MRI lesions) and/or study duration. Consequently, after resolving the heterogeneity, both doses showed a significant reduction in T2 lesions with only two studies per each subgroup analysis.[11 12] Notably, these two trials are the largest clinical trials investigating DMF for MS patients so far and both showed significant reduction in T2 lesions.[11 12]

MS is a chronic disease that requires medication persistence among patients. This study suggests that DMF in both doses is a safe and well-tolerated medication. Although nearly 90% of the DMF population had an adverse event, only 11% of the population discontinued the medication due to an adverse event. Additionally, there was no significant difference in the incidence of events that led to discontinuation between each DMF group and placebo. The single-arm study by Foroughipour *et al* showed that 86% of patients were satisfied with their treatment after 1 year.[27]

It is noteworthy that only the DMF two times per day group had significantly higher odds of experiencing any adverse events; whereas, only the three times a day group had interestingly lower odds of having serious adverse events. Nevertheless, after combining both doses' subgroups, the DMF group had higher odds of developing any adverse events and to a lesser extent, discontinuing the study due to adverse events. On the other hand, the DMF group had lower odds of developing serious adverse events. A previous systematic review revealed a comparable result regarding the risk of developing any adverse events but no difference in serious adverse events.[20] Such discrepancy in total and subgroup analysis of DMF in safety profile can urge for research for the ideal DMF dosage since they are highly comparable in clinical and imaging outcomes.

Notably, serious infections occurred only in 6% of patients taking DMF while severe lymphopenia occurred in around 4%. The previous review by Liang *et al* assessing safety of DMF in trials and observational studies revealed a comparable rate of severe lymphopenia (4.1%) while lower rates of serious infections (3%).[20] It is noteworthy that the included studies in this review were all of short duration with a maximum of 2-year duration. Results of long-term trials have shown sustained efficacy and safety profile of DMF for 11 and 13 years, supporting DMF as a long-term treatment option that has a positive benefit/risk ratio, especially for RRMS.[9 37] Furthermore, real-world data and practice observations revealed sustained efficacy and safety results with low rates of drug discontinuation and high medication persistence.[19 38–40]

Limitations

Although this systematic review is the first to comprehensively assess the efficacy and safety of DMF in the

treatment of MS in clinical trials, it has several limitations. Concerning the review design, although it included all published trials, interpretation should be cautious and along with real-world data and observational studies. The review included studies with different comparator arms. Furthermore, certain outcomes showed marked heterogeneity despite the sensitivity analysis. Additionally, it is possible that studies with positive results were more likely to be published than studies with negative results, potentially leading to an overestimation of DMF's benefits. Publication bias is a common limitation of all systematic reviews, and it is difficult to quantify its impact on the results of this review.[26]

Most of the studies on DMF included in this review were relatively short-term, with follow-up periods of less than 3 years. The variation in baseline characteristics and comparators (clinical diversity) could have contributed to the heterogeneity in some subgroups.[26] For instance, studies have variable patients' age. It is noteworthy that most of the studies included the RRMS subtype. Some of the clinical and MRI outcomes that were measured in the studies included in this review have limitations. For example, the proportion of patients with relapses may be underestimated if patients do not report all of their relapses to their physician. The EDSS score, although commonly used, has issues with inter-rater reliability and functions as cognition, upper limb and vision are underestimated and their change may not affect the global EDSS score.[29] Additionally, the number of Gd-enhancing lesions, T1-hypointense lesions and T2-hyperintense lesions on MRI does not necessarily correlate with the severity of disease progression or the patient's symptoms.

Implications

Despite these limitations, this systematic review provides a comprehensive and updated evaluation of the existing trials on the safety and efficacy outcomes of DMF in the treatment of MS. This review establishes the short-term efficacy and tolerability of DMF, in consistency with previous trials, without significant differences between both doses. We also highlight the need for more long-term studies and studies that use more objective measures of clinical and MRI outcomes. We believe DMF can resemble an effective medication to improve both the clinical and imaging profiles of MS patients. In addition, safety results are promising as the drug was shown to be safe and well-tolerated. Yet, our findings should be interpreted cautiously due to marked heterogeneity in certain outcomes along with the clinical diversity among studies. Thus, more extensive studies can help support such evidence for clinical practice. Future research should include patients with balanced characteristics and clinical subtypes. Specific comparison should be designed to entail the superiority of treatment of options including DMF. Long-term trials and real-world data should be implemented to address the long-term effect of DMF.

CONCLUSION

The meta-analysis provides evidence supporting the efficacy of dimethyl fumarate in reducing relapses, disease progression and inflammatory activity, as well as improving MRI outcomes in patients with multiple sclerosis. The study also shows a generally favourable safety profile of dimethyl fumarate, although we recommend close monitoring of adverse effects. Further research is needed to validate and explain these findings, especially regarding long-term safety and optimal dosing strategies and scheduling.

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