

Dimethyl fumarate in the management of multiple sclerosis: appropriate patient selection and special considerations

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Abstract: Delayed-release dimethyl fumarate (DMF), also known as gastroresistant DMF, is the most recently approved oral disease-modifying treatment (DMT) for relapsing multiple sclerosis. Two randomized clinical trials (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing–Remitting MS [DEFINE] and Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis [CONFIRM]) demonstrated significant efficacy in reducing relapse rate and radiological signs of disease activity, as seen on magnetic resonance imaging. The DEFINE study also indicated a significant effect of DMF on disability worsening, while the low incidence of confirmed disability worsening in the CONFIRM trial rendered an insignificant reduction among the DMF-treated groups when compared to placebo. DMF also demonstrated a good safety profile and acceptable tolerability, since the most common side effects (gastrointestinal events and flushing reactions) are usually transient and mild to moderate in severity. Here, we discuss the place in therapy of DMF for individuals with relapsing multiple sclerosis, providing a tentative therapeutic algorithm to manage newly diagnosed patients and those who do not adequately respond to self-injectable DMTs. Literature data supporting the potential role of DMF as a first-line therapy are presented. The possibility of using DMF as switching treatment or even as an add-on strategy in patients with breakthrough disease despite self-injectable DMTs will also be discussed. Lastly, we argue about the role of DMF as an exit strategy from natalizumab-treated patients who are considered at risk for developing multifocal progressive leukoencephalopathy.

Keywords: multiple sclerosis, dimethyl fumarate, oral drugs, therapeutic algorithm

Introduction

Multiple sclerosis (MS) is a chronic immunomediated inflammatory disease of the central nervous system (CNS) that typically affects young adults.¹ The risk of MS is greater in women than in men; female:male ratios are between 1.5:1 and 3.5:1 in most populations, with a trend toward greater values in the most recent studies.²

The etiology of MS is still not completely known, but presumably involves interaction among genetic, environmental, and other factors triggering an aberrant autoimmune attack, resulting in damage to myelin and axons.³ The pathogenesis of MS involves immune attack against CNS antigens mediated through activated CD4⁺ myelin-reactive T cells, with contribution by B cells.⁴ Therefore, MS is believed to be an autoimmune disorder, but the antigen specificity of the immune response is still unknown.⁴ Pathologically, MS is characterized by perivascular infiltrates of mononuclear cells, demyelination, remyelination, oligodendrocyte depletion, astrocytosis, axonal loss, and neuronal degeneration that result in the formation of MS plaques in the brain and spinal cord.⁵

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The clinical course of MS may be considered the expression of two clinical phenomena: relapses of acute neurological symptoms, which end with a partial or complete remission, and progression, which refers to the steady and irreversible worsening of symptoms.⁶ This analysis brings into the equation the interplay between two biological activities: inflammation and degeneration.⁷

Historically, four clinical MS phenotypes were defined: relapsing remitting, secondary progressive, primary progressive, and progressive relapsing.⁸ However, more recently there was a reexamination of MS disease phenotypes that included a consideration of inflammatory activity (based on the clinical relapse rate and imaging findings), disability worsening (as a consequence of relapses), and disease progression.⁹ Accordingly, “progressive relapsing” was merged with the primary-progressive phenotype.⁹

Moreover, the therapy landscape in MS over the last few years has dramatically broadened, thus increasing the complexity of treatment decisions.¹⁰ Therefore, the new classification has provided a framework not only for communication, prognostication, and clinical trial design but also to guide treatment decision-making in daily clinical setting.⁹

Currently available disease-modifying treatments for relapsing–remitting multiple sclerosis

At the time of writing, 12 disease-modifying treatments (DMTs) are available for the treatment of relapsing MS (R-MS; Table 1): self-injectable drugs, including four IFN β

formulations and two glatiramer acetate (GA) formulations; an immunosuppressive agent (mitoxantrone); two humanized monoclonal antibodies (natalizumab and alemtuzumab); and three oral compounds (fingolimod, teriflunomide, and dimethyl fumarate [DMF]).^{11–29}

Historically, self-injectable DMTs have been the mainstay of MS therapy, and are still widely used in patients with R-MS. Based on data from the head-to-head randomized controlled trials (RCTs) INCOMIN and EVIDENCE, high-dose, high-frequency IFN β formulations are considered more efficacious than low-dose subcutaneous (SC) IFN β_{1a} , especially in the short term.^{30,31} However, a Danish RCT and some postmarketing studies did not fully support this observation, providing conflicting results.^{32–37} According to findings from three head-to-head RCTs (BECOME, REGARD, and BEYOND), the efficacy of GA is comparable to that of IFN β_{1a} and IFN β_{1b} ,^{38–40} even though IFN β appeared better than GA in controlling radiological disease activity, as seen on brain magnetic resonance imaging (MRI).^{41,42} By contrast, the CombiRx study found GA significantly better than IFN β in reducing the risk of relapse; however, this RCT was not specifically designed to compare IFN β and GA.⁴³ More recently, a large multicenter real-world study showed slightly lower relapse incidence among patients treated with GA or SC IFN β_{1a} relative to intramuscular IFN β_{1a} and SC IFN β_{1b} , without any difference in terms of disability worsening.⁴⁴

Despite their excellent safety profile, IFN β and GA may be poorly tolerated, due to systemic or injection-related adverse events, leading to discontinuation or lack of

Table 1 Currently available disease-modifying treatments for relapsing multiple sclerosis

Molecule	Route	Dosage	Schedule	Brand name	Company
IFN β_{1b}	SC	250 μ g	EOD	Betaseron	Bayer
				Betaferon	Bayer
				Extavia	Novartis
IFN β_{1a}	IM	30 μ g	OW	Avonex	Biogen
				Rebif	Merck Serono
PEGylated IFN β_{1a}	SC	125 μ g	E2W	Plegridy	Biogen
Glatiramer acetate	SC	20 mg	OD	Copaxone	Teva
				Copaxone 40	Teva
Mitoxantrone	IV	8–12 mg/mq	E1-3M	Novantrone	Wyeth
Natalizumab	IV	300 mg	E4W	Tysabri	Biogen
Alemtuzumab	IV	12 mg	O5D (1st year)	Lemtrada	Genzyme
			O3D (2nd year)		
Fingolimod	PO	0.5 mg	OD	Gilenya	Novartis
Teriflunomide	PO	14 mg	OD	Aubagio	Genzyme
Dimethyl fumarate	PO	240 mg	BID	Tecfidera	Biogen

Abbreviations: BID, bis in die (twice daily); E1-3M, every 1–3 months; E2W, every 2 weeks; E4W, every 4 weeks; EOD, every other day; IM, intramuscular; IV, intravenous; O3D, over 3 days; O5D: over 5 days; OD, once daily; OW, once weekly; PO, per os (by mouth); SC, subcutaneous; TIW, ter in week (thrice weekly).

adherence in a relevant number of patients.^{45,46} Moreover, self-injectable DMTs are only partially effective in preventing clinical and MRI activity.⁴⁷ Mitoxantrone was approved for rapidly worsening R-MS or secondary-progressive MS, and has proven its efficacy in several trials,^{18,19,48} however, the increased incidence of cardiotoxicity and treatment-related leukemia has discouraged its more widespread use.^{49,50} According to European Medicines Agency criteria, monoclonal antibodies, such as natalizumab and alemtuzumab, are currently used in adult patients with R-MS who do not adequately respond to a self-injectable DMT or in those presenting rapidly evolving disease activity, defined by clinical or imaging features.^{51,52}

There is evidence that alemtuzumab is superior to SC IFN β_{1a} in reducing relapse rate, disability worsening, and MRI activity.^{21–23} Moreover, nonrandomized postmarketing observational studies support the use of natalizumab rather than self-injectable DMTs or fingolimod in nonresponders to a first-line treatment course.^{53–55} Despite the two drugs' impressive efficacy in controlling disease activity, and even in reducing disability (in some cases), there are several safety concerns, due to the increased risk of opportunistic infections and autoimmunomediated conditions in patients treated with natalizumab and alemtuzumab.^{56,57}

Orally administered DMTs (fingolimod, teriflunomide, and DMF) represent a significant therapeutic advance, since the oral administration route represents an attractive opportunity for patients and may potentially promote enhanced therapeutic adherence.⁵⁸ Moreover, data from RCTs has shown that these oral drugs are at least equivalent or even superior to self-injectable DMTs in terms of efficacy.^{25,29,59} Fingolimod demonstrated higher efficacy than intramuscular IFN β_{1a} on both clinical and MRI end points; however, there were no between-group differences in terms of disability outcomes.²⁵ Although CONFIRM was not designed as a head-to-head RCT, its post-hoc analysis showed a significantly greater treatment effect of DMF versus GA in reducing relapse rate and MRI activity, but not disability worsening.²⁹ A similar risk of treatment failure (defined as first occurrence of confirmed relapse or permanent treatment discontinuation for any cause) was reported between teriflunomide 14 mg and SC IFN β_{1a} 44 μ g in the TENERE study.⁵⁹ However, despite these encouraging data, even oral DMTs may have safety and tolerability issues, especially when compared with the good and well-known long-term safety profile of self-injectable platform therapies.⁶⁰ Table 2 shows the main findings in terms of efficacy, safety, and tolerability regarding oral DMTs currently used in R-MS.

Table 2 Main features of the currently approved oral disease-modifying treatments for relapsing multiple sclerosis (only data relative to currently approved dose presented)

Molecule Trials	Efficacy		Safety	Tolerability
	Relapse ^a	Disability ^a		
Fingolimod Fingolimod Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis (FREEDOMS) ²⁴ TRIAL Assessing injectable interferon vs. FTY720 Oral in RRMS (TRANSFORMS) ²⁵	-55%	-26.6% ^b	Herpes virus and other opportunistic infections, ^d bradyarrhythmias, macular edema, skin neoplasms	High burden for first-dose administration
Teriflunomide Teriflunomide Multiple Sclerosis Oral (TEMPO) ²⁶ Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER) ²⁷	-31.5% -36.3%	-25.3% ^c	Liver-enzyme increase, neutropenia, pregnancy issues	Hair thinning, gastrointestinal events
Dimethyl fumarate Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS (DEFINE) ²⁸ Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis (CONFIRM) ²⁹	-41.3% -44.0%	-38% -21% ^c	Leukopenia, lymphopenia ^e	Flushing, gastrointestinal events

Notes: ^aRelative reduction in relapse rate (primary end point) and disability worsening (secondary end point) versus placebo; ^bversus IFN β_{1a} 30 μ g once weekly (12-month follow-up); ^cnot significant; ^dincluding progressive multifocal encephalopathy and cryptococcosis; ^efour patients older than 50 years developed progressive multifocal encephalopathy following a prolonged grade 2 or 3 lymphopenia.

Dimethyl fumarate for relapsing–remitting multiple sclerosis: mechanisms of action

Fumaric acid (FA) and its derivatives have been used for decades as topical and oral long-term treatments for psoriasis, a long-lasting inflammatory skin disease. In 1994, Germany approved an oral compound of FA esters (FAEs) containing DMF and ethyl hydrogen fumarate as mixed salts for psoriasis treatment, but it is also used off-license in many other countries.⁶¹ Evidence shows that FAEs provided long-term safety and effectiveness in patients with psoriasis.^{62,63} Based on prolonged experience, and combined with the positive results obtained in the animal model of MS,⁶⁴ the prospect of utilizing DMF for autoimmune conditions other than psoriasis was envisioned.⁶⁵

In 2003, Biogen purchased licensing rights to develop a second-generation DMF for treating psoriasis and MS,⁶⁶ two conditions sharing an autoimmune T-cell-mediated pathogenetic pathway.⁶⁷ DMF is a lipophilic ester of FA (a key intermediate in the citric acid cycle used by cells to produce energy) that after oral assumption is rapidly metabolized into its active metabolite monomethyl fumarate (MMF) by intestinal esterases.^{68,69} The currently used oral delayed-release DMF formulation allows the compound to bypass the stomach and be released at intestinal level. After administration, the blood concentration of MMF peaks at approximately 2–2.5 hours (T_{max}), but it is delayed with coingestion of a fat-rich meal. This latter phenomenon underpins the observed lower incidence of metabolism-related side effects of DMF when the drug is taken with high-calorie food.^{70,71}

Preclinical studies have demonstrated that DMF has immunomodulating and antioxidant properties, and similarly to other DMTs, such as IFN β , GA, and fingolimod, DMF exerts a pleiotropic effect.⁷² The immunomodulating properties of DMF mainly encompass the induction of a shift from a proinflammatory Th1- to an anti-inflammatory Th2-cytokine pattern.⁷³ Due to its lipophilic nature, the DMF derivative MMF is able to translocate into blood cells, where it interacts with glutathione and promotes glutathione depletion.^{74,75} The rapid decrease of intracellular glutathione leads to a rebound increase in concentration that in turn suppresses the translocation of nuclear NF κ B into the nucleus, thereby preventing the transcription of inflammatory cytokines and adhesion molecules.⁷⁵

The antioxidant potential of DMF appears to be mediated by two different molecular pathways involving the nuclear factor Nrf2⁷⁶ and the high-affinity receptor for nicotinic acid/

niacin and β -hydroxybutyrate HCAR2.^{77,78} Under normal conditions, Nrf2 is sequestered in the cytosol via Keap1; DMF/MMF irreversibly bind to Keap1, leading to translocation of Nrf2 into the nucleus, thus imitating the physiological oxidative stress-response pathway that activates cell-defense mechanisms.^{76,79}

HCAR2 is a G-protein-coupled membrane receptor; its activation results in reduced cAMP levels, which in turn leads to neutrophil apoptosis. After crossing the blood–brain barrier (BBB), MMF binds to HCAR2 and switches microglia and astrocytes to an anti-inflammatory phenotype, thereby indirectly affecting neuronal survival and function, including restoration of synaptic alterations occurring in experimental MS models.^{77,78} The potential for a direct effect on CNS-resident cells is supported by the evidence that upon oral administration, DMF is rapidly metabolized to MMF, which crosses the BBB and achieves detectable levels in the CNS.⁷⁹

This latter pathway is also implicated in the flushing reaction, a well-recognized side effect of DMF due to increased prostaglandin levels; indeed, by binding HCAR2, MMF induces prostanoid-forming enzymes in different epidermal cell types.⁸⁰ Although the proposed mechanism of action does not include effects on lymphocytes, DMF shifts the immunophenotypes of circulating T cells, leading to a reduction of memory cells and a relative expansion of naïve cells, regardless of the absolute lymphocyte count (ALC).⁸¹ In addition, ALC reduction of about a third has been observed in RCTs and in a recent post-marketing experience,^{28,29} with the most relevant reduction for CD8 and CD19 cells (40% and 48%, respectively).^{82,83}

Dimethyl fumarate for relapsing multiple sclerosis: efficacy data

In 2006, an 18-week open-label prospective study in ten patients with R-MS demonstrated that 720 mg FAEs (240 mg thrice weekly) induced significant reduction in number and volume of contrast-enhancing lesions (CELs) compared with baseline ($P<0.05$); this effect was sustained over a further 48-week treatment phase with 360 mg FAEs (120 mg thrice weekly) and even after a 4-week washout period.⁸⁴

A 48-week, Phase IIB, randomized, placebo-controlled, double-blind study of DMF was subsequently conducted on 257 patients with R-MS.⁸⁵ When compared with placebo, patients treated with DMF 240 mg TID (ter in die [thrice daily]) had a 69% reduction in the mean cumulative number of CELs ($P=0.002$), 48% reduction in the mean

number of new or newly enlarging T_2 -hyperintense lesions ($P<0.001$), and 53% reduction in the mean number of new T_1 -hypointense lesions ($P=0.01$). The annualized relapse rate (ARR) also decreased by 32% in the active group versus placebo ($P<0.05$). Subsequent data analysis also showed that the percentage of CELs evolving to T_1 -hypointense lesions (“black holes”) was 34% lower with DMF treatment versus placebo.⁸⁶

Following these seminal studies, two pivotal Phase III randomized double-blind clinical trials were conducted in patients with R-MS and at least one relapse in the previous year or at least one CEL within 6 weeks prior to randomization: DEFINE and CONFIRM.^{28,29}

In the 2-year DEFINE study, the ARR decreased by 53% and 48% in the DMF 240 mg BID (bis in die [twice daily]) and 240 mg TID groups, respectively, when compared with placebo ($P<0.001$). The risk of confirmed disability worsening was also reduced by 38% and 34% in the DMF 240 mg BID and 240 mg TID groups, respectively, when compared with placebo ($P\leq 0.01$). Moreover, both DMF doses significantly reduced the numbers of CELs and new or enlarging T_2 -hyperintense lesions ($P<0.001$).²⁸ A potential cytoprotective and remyelinating effect of DMF was also suggested by a subset analysis of the DEFINE study in patients who underwent unconventional MRI investigation based on magnetization-transfer ratio.⁸⁷

The 2-year CONFIRM trial, which included an active-comparator group of patients treated with GA, demonstrated ARR reductions of 44%, 51%, and 29% in the DMF 240 mg BID, DMF 240 mg TID, and GA groups, respectively, compared to the placebo group ($P\leq 0.01$).²⁹ Reductions in disability worsening versus placebo were not significant either in the DMF groups and in the GA group, probably due to the low proportion of patients with disability worsening in the placebo group. Compared with placebo, DMF 240 mg BID, DMF 240 mg TID, and GA significantly reduced the numbers of CELs, new or enlarging T_2 -hyperintense lesions, and new T_1 -weighted hypointense lesions ($P<0.001$). Although CONFIRM was not specifically designed as a head-to-head study, a post hoc direct evaluation showed a stronger effect of both DMF 240 mg BID and DMF 240 mg TID in reducing the number of new or enlarging T_2 -hyperintense lesions when compared to GA ($P<0.01$). Moreover, DMF 240 mg TID but not DMF 240 mg BID was superior to GA in reducing ARR and new T_1 -hypointense lesions ($P<0.05$). No significant differences were found in proportion of relapsing patients with, or time to, disability worsening.²⁹ A more recent post hoc analysis showed that DMF significantly reduced the risk

of inflammatory disease activity (defined as such an event as relapse, CELs, or new/enlarging T_2 -hyperintense lesions) over 2 years compared with GA; the differential treatment effect was seen by 24 weeks.⁸⁸

A subsequent MRI analysis of CONFIRM also showed that DMF BID and TID produced significant and consistent reductions versus placebo of lesion volumes, but reductions in brain atrophy and magnetization-transfer ratio changes did not reach statistical significance.⁸⁹

An integrated analysis of the two pivotal Phase III trials showed that at 2 years, DMF 240 mg BID and TID significantly reduced the ARR and the risks of relapses, with 12-week and 24-week confirmed disability worsening in respect to placebo.⁹⁰ Although the efficacy of DMF is generally consistent across patient subgroups, the most relevant effect of DMF is observed in younger treatment-naïve individuals with low Expanded Disability Status Scale (EDSS) score.⁹⁰ Moreover, patients treated with both DMF doses improved in some patient-reported outcomes referring to quality of life with respect to placebo.⁹¹

ENDORSE (NCT00835770) is an ongoing 8-year extension phase including patients enrolled in both pivotal trials to evaluate the long-term efficacy and safety of DMF.⁹² An interim analysis of this extension study supports the use of DMF as a long-term treatment option for patients with R-MS, since early treatment with DMF was associated with lower relapse rates and reduced risk of disability worsening over 5 years when compared with patient groups originally randomized to GA or placebo.⁹³

According to a recent Cochrane review, there is moderate-quality evidence to support the use of DMF for reducing both the proportion of relapsing patients and the ARR, while there is no evidence to support the benefit on disability outcome, and the quality of available data is too low to evaluate the benefit on MRI outcomes.⁹⁴

Dimethyl fumarate for relapsing multiple sclerosis: safety and tolerability data

Overall, the short-term safety profile for DMF in patients with R-MS is highly favorable,^{28,29} and long-term safety analysis from ENDORSE study sustains a good benefit:risk ratio for this oral compound.⁹⁵

The commonest adverse events observed in patients receiving DMF include flushing, gastrointestinal (GI) events (eg, diarrhea, nausea, abdominal pain, and vomiting), proteinuria, and pruritus.^{28,29} Flushing and GI events are usually highest in the first few weeks of treatment and decrease

thereafter.⁷¹ Flushing is a prostaglandin-mediated phenomenon that may be mitigated by pretreatment with aspirin,⁹⁶ but the appropriate dose and schedule of administration of aspirin is not yet established for this purpose. While the exact mechanisms leading to GI events are not well known, the observation of transient eosinophilia in the gastric mucosa of patients treated with DMF suggested that the leukotriene-receptor antagonist montelukast may help to control some GI symptoms.⁹⁷ Moreover, it has been observed that consuming a high-fat and -protein meal just before DMF administration may reduce GI and flushing side effects by effectively delaying intestinal absorption.⁹⁸ In the daily clinical setting, dose titration with DMF 120 mg BID for 7 days, and then increased to 240 mg BID, is recommended to reduce the incidence of flushing and GI events. In some patients, a slower increase may be tried to enhance tolerability, based on weekly increases by 120 mg, as follows: first week, 120 mg OD; second week, 120 mg BID; third week, 120 mg and 240 mg daily; fourth week, 240 mg BID.⁹⁹

According to Phase III trials, the incidences of flushing and GI events range from 28% to 35% and 10% to 17%, respectively, and are of mild or moderate severity.^{28,29} Although the overall incidence of adverse events leading to treatment discontinuation was similar across the study groups (DEFINE, 13% in the placebo group and 16% in each of the DMF groups; CONFIRM, 10% in the placebo group, 12% in each of the DMF groups, and 10% in the GA group), discontinuations due to flushing and GI events occurred more frequently in patients who received DMF than in those randomized to placebo. Discontinuations due to flushing and GI events were 2%–4% and 2%–6%, respectively, in patients treated with DMF versus $\leq 1\%$ in placebo group.^{28,29}

According to Phase III RCTs, at 1 year, white-cell and lymphocyte counts decrease by approximately 10%–12% and 28%–32%, respectively, in respect to baseline values. The incidences of grade 2 leukopenia ($<3 \times 10^9/L$) and grade 3 lymphopenia ($<0.5 \times 10^9/L$) were 4%–10% and 4%–7% in the DMF groups, respectively, versus $\leq 1\%$ in the placebo groups.^{28,29} A 35% reduction in ALC has also been reported after 3–6 months of DMF treatment in a real-world retrospective study. In this latter, grade 3 (ALC $<0.8 \times 10^9$) and grade 2 lymphopenia occurred in 24% and 5% of treated patients, respectively.⁸³

A higher risk of lymphopenia has been noted in adults older than 55 years, in those with lower baseline lymphocyte counts, and in those switching from natalizumab.¹⁰⁰ Although incidences of infections and serious infections in RCTs are similar for patients on DMF and placebo, a theoretical increased risk for developing opportunistic John

Cunningham virus (JCV)-mediated progressive multifocal leukoencephalopathy (PML) has been postulated in DMF-treated patients with MS.⁸²

To the best of our knowledge, six cases of PML have been reported so far in patients receiving FAEs for psoriasis.^{101–107} Notably, each of these patients had well-known risk factors for PML, including lymphocytopenia, sarcoidosis, cancer history, and prior efalizumab use.

One recent article assumes that there is no increased incidence of PML in DMF-treated patients with MS, and provides a mathematical model to estimate the risk of PML under immunotherapy assuming a constant incidence rate of three cases per million person-years.¹⁰⁸ However, at the time of that publication, only one case of PML had been reported. To date, four cases of PML (one fatal) have occurred in DMF-treated patients with MS who had not been treated before with other DMTs known to be associated with an increased PML risk. All cases occurred in subjects older than 50 years. Three of four patients had prolonged grade 3 lymphopenia prior to PML development. The remaining case had prolonged ALC 0.6×10^9 (corresponding to a grade 2 lymphopenia) for more than 6 months before PML diagnosis.¹⁰⁹

According to the European Medicines Agency, a baseline brain MRI should be available as a reference, and a complete blood count is recommended prior to initiation of DMF and should be repeated every 3 months during treatment for safety monitoring. Grade 3 lymphopenia should be monitored at even shorter intervals. Many clinicians advocate dosage reduction with grade 3 lymphopenia. DMF should be discontinued in cases of persistent grade 3 lymphopenia for 6 or more months, and ALC monitoring should be provided until lymphopenia resolution. When PML is suspected, treatment should be withdrawn immediately and appropriate diagnostic workup performed.¹⁰⁹

Increased liver enzymes were transiently observed in the first few months of treatment, and in all cases were not accompanied by concurrent increase of bilirubin levels.^{28,29} DMF is not recommended for use in pregnant women (pregnancy category C).¹¹⁰ However, gestational exposure to DMF seems to be not associated with increased risk of fetal abnormalities or adverse pregnancy outcomes, as indicated by both preclinical data from animal reproductive toxicology studies and the outcomes of pregnancies occurring during the clinical development program.¹¹¹

Selection of appropriate drug for individual patients

Before starting any DMT, neurologists must consider the patient's views, requirements, and potential adherence

difficulties. Treatment history (if applicable), psychological aspects potentially affecting treatment adherence, pregnancy desire, and coping strategies (especially in the newly diagnosed) should be carefully evaluated. The oral administration route of DMF is an attractive opportunity for patients, and may potentially provide an enhanced therapeutic adherence compared with self-injectable DMTs.⁵⁸

Despite the efficacy of DMF 240 mg BID and TID being broadly comparable, DMF is authorized at 240 mg BID as first-line therapy for patients with an established diagnosis of R-MS. This “place in therapy” should allow neurologists to prescribe early over the course of the disease, before irreparable damage has occurred and when the chance to obtain a good therapeutic response is highest. This latter notion is supported by post hoc analyses combining data from DEFINE and CONFIRM showing that early treatment with DMF (defined as within 1 year from MS diagnosis or EDSS score ≤ 2) resulted in a stronger effect when compared to the whole intention-to-treat combined cohort.^{112,113} Consistently, subgroup analyses of the two pivotal RCTs showed that the treatment effect of DMF seems to be particularly great in patients who were treatment-naïve and in those with a lower baseline EDSS.^{114,115} However, DMF may be still effective in patients with suboptimal response to prior treatment with IFN β , as suggested by another integrated analysis of DEFINE and CONFIRM.⁹⁰

The possibility of using DMF as an add-on treatment in patients who do not adequately respond to IFN β or GA was investigated in the Phase II open-label EXPLORE study.¹¹⁶ In this study, 108 patients with R-MS who experienced disease activity (defined as either one or more relapses within 12 months or one or more CELs on brain MRI within 6 weeks prior to study enrollment) while under established treatment with IFN β or GA for at least 1 year were submitted to receive a 6-month course of DMF 240 mg TID in addition to their prescribed self-injectable DMT. Although the study was designed to test the safety and tolerability of add-on therapy, MRI activity was also investigated. Though DMF was used at a higher dosage (720 mg daily), the safety profile of its combination with IFN β or GA was consistent with the known safety profile of DMF monotherapy. The exploratory MRI analysis showed a decrease in mean number of CELs and new T_2 -hyperintense lesions. Despite these promising results on the control of MRI activity, the EXPLORE study suffers from several weaknesses, including a very short follow-up and lack of randomization and a control group.¹¹⁶ Therefore, future efforts should investigate the efficacy and longer-term safety profile of combining DMF with injectable DMTs in cases of suboptimal response to GA or IFN β .

Use in JCV-positive patients

The possibility of using DMF as an effective exit strategy from natalizumab is under investigation.¹¹⁷ Other than natalizumab exposure, previous immunosuppression and to a greater extent seropositivity to JCV are the main risk factors for developing PML.¹¹⁸ As a result, the majority of patients at high risk of PML are advised to stop treatment.¹¹⁹ Natalizumab discontinuation may induce the clinical and radiological disease reactivation that in some cases may lead to the accumulation of fixed disability.¹²⁰ Currently, there are no evidence-based data or established guidelines driving specific treatment switching to control following natalizumab disease reactivation.

A recently published case report suggests that DMF may not be able to halt clinical and radiological post-natalizumab disease reactivation in patients with highly active MS.¹²¹ However, preliminary results on 530 patients suggested that initiation of DMF within 90 days of washout after natalizumab withdrawal may represent a valid treatment option with only minor safety concerns.¹¹⁷ In fact, the increased risk for PML in natalizumab is explained by the specific mode of action of this drug, which decreases immunosurveillance of the brain through its effect on the adhesion molecule located at the BBB level. By contrast, the mechanism of action of DMF does not seem to explain an increased risk for PML, unless severe lymphocyte depletion occurs.¹⁰⁰ Another proposed mechanism by which DMF may potentially induce PML encompasses its capacity to reduce binding of peripheral blood mononuclear cells to vascular cell-adhesion molecules.¹²² Potentially, this may not only preclude effective neuroimmunosurveillance for JCV infected cells but also may induce the release of premature B cells from marrow stores, which has been suggested to be implicated in viral expression and transformation.¹²³

However, screening for anti-JCV antibody status is not recommended for DMF treatment. A possible diagnosis of preclinical PML should be ruled out in patients who discontinue natalizumab before starting DMF. In light of the increased risk of DMF-induced lymphopenia in patients previously treated with natalizumab,¹⁰⁰ stringent monitoring of differential blood count and prompt DMF discontinuation in the event of a 6-month sustained grade 3 lymphopenia are recommended to reduce the risk of PML.¹⁰⁹ Special attention should also be paid to older patients changing treatment from natalizumab to DMF.¹⁰⁰

What if treatment fails?

As required for all other first-line DMTs, once the therapy is started, the response to DMF should be carefully assessed

to early identify those patients who experience breakthrough disease.⁴⁷ If relapses and MRI activity occur in the first few months from DMF beginning, the possibility of a delayed treatment effect should be considered and therapy with DMF continued. This suggestion comes from findings from a Phase IIB RCT showing that the effect of DMF on the control of BBB breakdown was delayed up to 8–12 weeks from treatment start (when compared to placebo).⁸⁵ In cases of disease activity 6–12 months after treatment start, a prompt switch to an alternative and more effective drug should be considered to avoid further relapses and the accumulation of disability over time. In this scenario, we recommend not trying all available first-line DMTs, but an escalation to second-line DMTs, such as natalizumab and alemtuzumab, is warranted.^{53,55}

Based on a recent systematic review with mixed-treatment comparisons, DMF seems to have no significant difference in terms of efficacy (ARR) when compared to fingolimod, and even to be superior to teriflunomide.¹²⁴ However, several methodological concerns have been raised for carrying out indirect comparisons of treatment arms across RCTs as done by Hutchinson et al,¹²⁴ and thus further studies based on more advanced statistical approaches (eg, network meta-analysis) are warranted to better compare the efficacy and safety of

different DMTs.¹²⁵ In the absence of head-to-head comparison RCTs, the best way to indirectly assess the benefit of DMTs across different independent studies is absolute risk reduction, which is very similar for DMF, fingolimod, and teriflunomide, ranging from 17% to 22%.

Other aspects should also be taken into consideration. Despite its supposed inferiority in reducing the ARR, teriflunomide is the only oral agent that met the disability-worsening end point in two independent trials.^{26,27} In addition, fingolimod is the only oral agent that demonstrated a significant reduction in brain-volume loss compared to placebo,²⁴ while DMF and teriflunomide did not meet the brain-atrophy end point.^{26,89}

With regard to tolerability, discontinuation due to side effects has been reported to be higher with DMF than fingolimod.¹²⁶ Therefore, we might suggest switching from DMF to fingolimod (or teriflunomide) predominantly in cases of intolerable GI events or other side effects. However, teriflunomide may be associated with teratogenicity, thus contraindicating its use in potentially childbearing women.¹¹⁰

Conclusion

A treatment algorithm based on the efficacy and safety profile of DMF is proposed in Figure 1. For newly-diagnosed

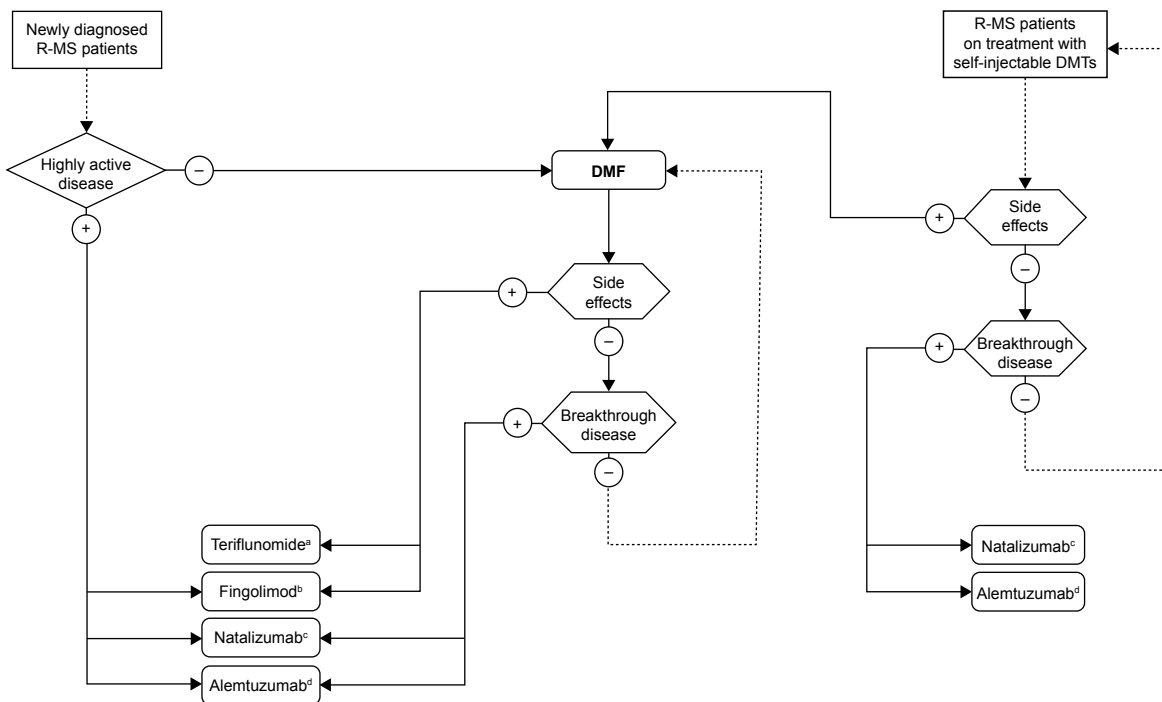


Figure 1 Proposed treatment algorithm for treating R-MS with DMF.

Notes: ^aConsider pregnancy desire; ^bconsider anti-VZV serological status, comorbidities, and concomitant non-MS treatments (eg, cardiac illnesses, antihypertensive drugs); ^cconsider anti-JCV serological status; ^dconsider anti-VZV serological status, latent tuberculosis, and HPV screening. Please note that this algorithm, though based on currently available literature data, represents the authors’ opinion only.

Abbreviations: R-MS, relapsing multiple sclerosis; DMF, dimethyl fumarate; VZV, varicella zoster virus; JCV, John Cunningham virus; HPV, human papillomavirus; DMTs, disease-modifying treatments.

patients with R-MS, we suggest considering first-line treatment with DMF over self-injectable therapies, due to its demonstrated efficacy, simplicity of treatment initiation, and administration route. Phase III RCTs have demonstrated its success as an efficacious oral DMT with a favorable tolerability and safety profile.^{28,29} The early side effects of DMF, such as GI and flushing reactions, tend to decrease with time on therapy and are generally self-limited.⁷¹

Patients experiencing breakthrough disease with self-injectable DMTs may be favorably switched to DMF,¹²⁴ but in cases of relapse with residual disability might be recommended to escalate to high-efficacy monoclonal antibodies (natalizumab, alemtuzumab).^{21–23,53–55} This latter suggestion also comes from subgroup analysis of RCTs showing that the treatment effect of oral drugs seems to be particularly great in patients with a lower EDSS.^{114,115} An escalation strategy, rather than a switch to other oral drugs (fingolimod or teriflunomide), is even suggested in patients who have failed DMF treatment,¹²⁴ while there are still no recommendations or suggestions to manage patients with subclinical disease activity while on DMF.

Based on its putative antioxidative cytoprotective effect, DMF may also be considered as a therapeutic option for progressive forms of MS.¹²⁷ However, a Phase III RCT aimed at investigating whether DMF (compared with placebo) slows disability progression not related to relapses in secondary progressive MS has recently been terminated by sponsor decision.¹²⁸

In conclusion, DMF is a promising candidate for newly diagnosed treatment-naïve patients with R-MS, and a possible switching option in some selected cases (especially in cases of poor tolerability or safety concerns with other DMTs).

Disclosure

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