Drug Design, Development and Therapy

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REVIEW

Diroximel Fumarate as a Novel Oral Immunomodulating Therapy for Relapsing Forms of Multiple Sclerosis: A Review on the Emerging Data

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Abstract: Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disorder of the central nervous system. Disease-modifying drugs (DMDs) and subsequent adherence are crucial for preventing reversible episodes of neurological dysfunction and delayed onset of progressive accumulation of irreversible deficits. Yet, side effects may limit their usage in clinical practice. Gastrointestinal (GI) side effects are a significant limitation of the use of dimethyl fumarate (DMF), the most frequently prescribed oral DMD in MS worldwide. Diroximel fumarate (DRF) is a second-generation oral fumaric acid ester (FAE) that was developed as a formulation with better GI tolerability. The improved tolerability is assumed to be related to a lower synthesis of gut-irritating methanol. Other explanations for DRF's lower extent of GI irritation include a more modest off-target activity due to its chemical structure. The superior GI tolerability of DRF compared to DMF could be proven in clinical trials and lead to approval of DRF for the treatment of relapsing forms of MS/relapsing-remitting MS (United States Food and Drug Administration and European Medicines Agency, respectively). Here, we summarize the mode of action of oral FAE and compare the chemical and physiological characteristics of DMF and DRF. Moreover, we discuss the adverse effects of FAE and introduce the emerging preclinical and trial data leading to the approval of DRF in MS. This article additionally reviews our current understanding of coronavirus disease 2019 (COVID-19) and the efficacy of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccination in people treated with FAE.

Keywords: diroximel fumarate, dimethyl fumarate, multiple sclerosis, immunotherapy, SARS-CoV-2, tolerability, adherence

Introduction

The first clinical episode of multiple sclerosis (MS), a chronic immune-mediated disorder of the central nervous system (CNS), typically occurs at 20 to 30 years of age.[1]. An initial relapsing-remitting disease course (RRMS, 85%) is predominant and followed by a phase of insidious and irreversible worsening of neurologic function independent from relapses.[2] A minor proportion of individuals (15%) have a progression from the onset, called primary progressive MS (PPMS).[1] The disease stage developing in the aftermath of relapsing-remitting MS is termed secondary progressive MS (SPMS) and develops after a median of 15 years in a subgroup of untreated individuals.[3] Common neurological manifestations include unilateral optic neuritis, motor and sensory disturbances, and myelopathic, brainstem, and cerebellar syndromes.[4] The symptoms of the relapse resolve within a couple of weeks or months, and there is a higher chance of complete resolution earlier in the disease course. An epidemiological study from South-East Norway evaluated 1032 individuals diagnosed with MS between 1998 and 2017.[5] They found a significantly longer time lag from disease onset to an Expanded Disability Status Scale (EDSS) of 6, which reflects the need for a walking aid, in people with MS (pwMS) who were diagnosed after 2006. Still, 692 (33%) individuals in their cohort had reached

Received: 9 July 2022
Accepted: 3 November 2022
Published: 10 November 2022

EDSS 6, which was after a median time lag of 29.8 (95% confidence interval (CI) 28.5–31.1) years. The clues are continuously growing about the crucial role of environmental, lifestyle, and genetic factors in the condition's occurrence, clinical course, and outcome.[6–10] MS is also associated with numerous comorbidities, which hamper early diagnosis and negatively impact the disease course.[11]

Over the past decade, the number of approved disease-modifying drugs (DMD) for treating MS has substantially increased.[12] The distinct modes of action and levels of efficacy serve as the foundation for selecting the most appropriate DMD. However, proof of prognostic reliability is awaited for combined treatment goals, including 'no evidence of disease activity (NEDA).[13,14] The decision for a certain DMD is aided by the recent individual clinical and radiological dynamics of the inflammatory and degenerative processes within the CNS.[15] The distinction between relapse-dependent and independent progression of long-term disease remission might be an additional variable to consider. In addition, the possibility of a DMD selection according to personal preferences and life circumstances is critical in maintaining adherence.[16] More recently, there have been efforts to develop second-generation therapeutics with an improved risk-benefit profile.[17]

In the pivotal, placebo-controlled Phase III DEFINE and CONFIRM trials in adults with RRMS, twice-daily 240 mg dimethyl fumarate (DMF, Tecfidera®, Biogen, USA) reduced clinical and magnetic resonance imaging (MRI) measures of inflammatory disease activity and improved some aspects of health-related quality of life (HR-QoL).[18,19] The DEFINE study also disclosed reduced disability progression with DMF.[18] Sustained DMF safety/efficacy was observed in patients followed up to 13 years in the long-term follow-up of the ENDORSE trial.[20] In the pivotal trials of DMF, gastrointestinal (GI) adverse events (AE) were reported by 42% of the patients, and 4% discontinued the study medication owing to these events.[18,19] Even higher discontinuation rates of up to 19% are observed in real-life despite the implementation of symptom management and mitigation strategies.[21–23] Of note, more than 560,000 patients have been treated with DMF, representing more than 1.100.000 patient years of exposure.[24] In this regard, diroximel fumarate (DRF, Vumerity®, Biogen USA), a second-generation DMD, was developed to achieve improved gastrointestinal (GI) tolerability and has undergone testing in clinical trials. The United States Food and Drug Administration (FDA) granted marketing authorization for DRF in October 2019 to treat adults with relapsing forms of MS, including clinically isolated syndrome (CIS), RRMS, and active SPMS.[25] The approval of the European Medicines Agency (EMA) in November 2021 respected RRMS.[26] In April 2020, the FDA approved MMF (Bafiertam®, Banner Life Sciences, USA), the active metabolite of DMF and DRF, for relapsing forms of MS.[27] Currently, DMF is being studied in other neurological (amyotrophic lateral sclerosis, glioblastoma multiforme) and non-neurological conditions (cutaneous T cell lymphoma, obstructive sleep apnea, rheumatoid arthritis).[28,29]

In this article, we review the existing scientific evidence for fumaric acid esters (FAEs) and the emerging preclinical and trial data leading to the approval of DRF in MS.

Fumaric Acid Esters: Historical Developments

FAEs were initially extracted from fungi, lichen, and moss (eg Fumaria officinalis). In medieval times, remedies containing FAE were used for blood cleansing, eye disorders, digestive/hepatobiliary complaints, and rheumatoid arthritis in Europe, Asia, and the Middle East.[30] From the late 1950s, FAE was studied for its use in psoriasis, a chronic immune-mediated and non-contagious disease characterized by raised areas of abnormal skin.[31] A mixture of FAEs, primarily consisting of DMF, was approved in Germany to treat psoriasis (Fumaderm®, Fumapharm, Switzerland) in 1994. The understanding of psoriasis as a T-cell-mediated autoimmune disease and the identification of the immunomodulatory activity of FAE as a central mode of action fostered the repurposing of DMF in MS.

Historically, the biocidal activity of FAEs, with the capability to prevent mold growth, was used in the production of clothes, furniture, and shoes. Of note, allergic skin reactions, severe eye irritation, and respiratory irritation can occur on direct contact.[32] Thus, its use for consumer products has been forbidden in the European Union since 1998 under the Biocide Directive 98/8/EC.[33]

Fumaric Acid Esters: Chemistry, Pharmacodynamics, and Kinetics

DMF and DRF are both prodrugs and have distinct chemical structures and molecular weights, as shown in Figure 1. After oral intake, both compounds undergo rapid esterase cleavage into MMF, the only active

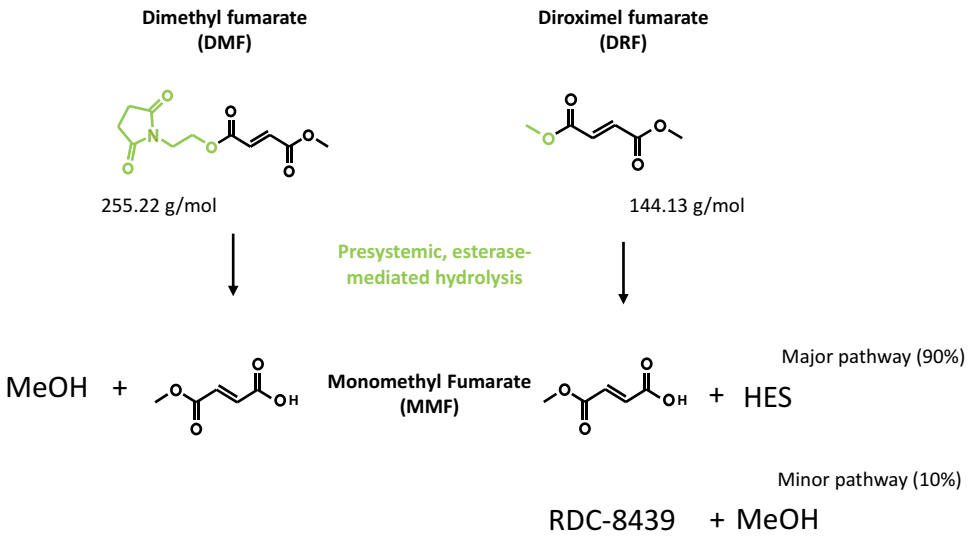

Figure 1 Chemical structure and metabolism of dimethyl fumarate and diroximel fumarate.

metabolite.[34] In detail, DMF undergoes rapid hydrolysis by esterase cleavage within the small intestine. DMF is converted to MMF, and the byproduct methanol (MeOH). In contrast, DRF is hydrolyzed via a major (>90%) and a minor pathway (>10%). The main path leads to the generation of MMF and the inactive metabolite 2-hydroxyethyl succinimide (HES). There is no evidence so far for the pharmacological activity of HES. Around 58–63% of the total dose of DRF is excreted as HES via the renal route. In the minor pathway, DRF metabolizes into the inactive RDC-8349 and MeOH. The stoichiometric ratio of MMF to MeOH is 1:1 after esterase hydrolysis of DMF.[35] In contrast, MMF and MeOH are generated in a balance of 9:1 in the case of DRF metabolism. MMF crosses the BBB and is likely to exert action within the CNS.[36] Drug penetration across the BBB was evaluated in people with SPMS, revealing that CSF MMF concentration was 11% of plasma.[37] Moreover, the Tmax of CSF MMF peaked only 2 hours later than that of plasma.

The terminal half-life of MMF is around one hour.[38] MMF is metabolized by the tricarboxylic acid cycle to carbon dioxide, fumaric acid, citric acid, and glucose. The elimination of MMF is primarily maintained through the exhalation of carbon dioxide (60% of a dose).[39,40] Only a minor proportion is eliminated via the renal (15.5%) or fecal (0.9%) route.

DMF was designed as an oral delayed-release (DR) preparation for optimized pharmacokinetics with predominant release in the small intestine.[40] The compound requires reapplication every 12 hours, ie, twice daily intake (2x240 mg). Most importantly, for DRF, an oral intake at the dose of 2×462 mg results in systemic MMF concentrations that are bioequivalent to DR DMF 2×240 mg.[41] Peak plasma concentrations after oral intake of DR DMF are reached after 2–2.5 hours, and for DRF after 2.5–3 hours.[42] The administration of DR DMF with a high-fat, high-calorie meal does not affect the area under the curve (AUC) of MMF.[25] However, there is a decrease in the peak plasma concentration by 40%, with a delay of 3.5 hours; yet, this does not modify the AUC.[43] Of note, co-administration with food significantly decreases the incidence and severity of nausea, vomiting, and abdominal pain.[44] Indeed, intake of DR DMF with high-fat, high-protein, and low-starch foods can mitigate GI AEs.[45] Moreover, the use of acid secretion blockers, antacids, or antihistamines is among further GI AE management strategies.

A population pharmacokinetic (PK) model for MMF and HES was established with pooled concentration-time data derived from 11 clinical studies of DRF.[46] DRF metabolites showed linear kinetics across dose levels and over time. Variables that impacted PK were meal fat content, evening dosing, body weight, and extent of kidney dysfunction. MMF shows dose-proportional PK, with exposure increasing proportionally over a daily dose range of 462–924 mg. Moreover, MMF does not accumulate in the system over multiple doses of DRF.

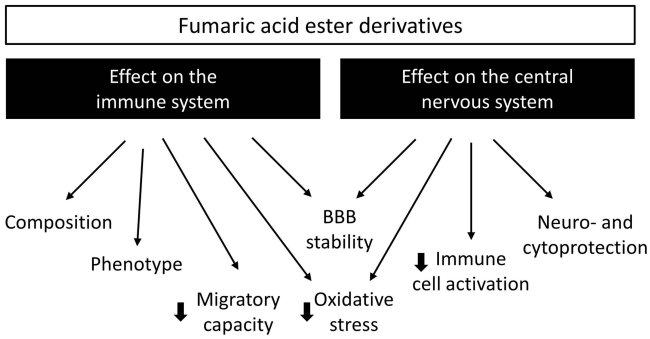

Figure 2 Presumed effect of MMF/DMF/DRF on immune cells and within the central nervous system.

Fumaric Acid Esters: Current Understanding of the Mode of Action

Molecular Pathways

The therapeutic mode of action of FAEs in MS is not entirely unraveled. FAEs are presumed to impact different steps of MS pathophysiology. Both, inflammatory and neurodegenerative properties of immune and brain resident cells are targeted by FAEs, as shown in Figure 2.[47,48]

There is evidence that the cytoprotective effects on neurons and glial cells are, in part, mediated through the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) transcriptional pathway, which leads to the activation of antioxidant and detoxifying genes.[49–51] These include heme oxygenase-1 (HO-1, NAD(P)H quinone dehydrogenase (NQO-1), and glutathione S-transferase-1 (GST-1).[52] While HO-1 activates anti-inflammatory, anti-proliferative, and anti-apoptotic pathways, NQO-1 and GST-1 can prevent cellular oxidative stress.[53,54]

FAEs also activate several Nrf2-independent pathways. MMF is an exogenous ligand for the hydroxycarboxylic acid receptor 2 (HCAR2), also known as the niacin receptor-1. Activation of HCAR2 was shown to inhibit microglia activation and thus attenuate neuroinflammation.[55] Activated HCA2R2 inhibits chemoattractant-mediated macrophage migration via Gβγ/PKC/ERK1/2 pathway and heterologous receptor desensitization.[56] FAE derivatives can inhibit the Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway, which controls cytokine production and cell survival, in an Nrf2-independent manner. MMF can also exert anti-inflammatory action through the 5' adenosine monophosphate-activated protein kinase (AMPK)/NAD-dependent deacetylase sirtuin-1 (Sirt1) pathway.[57]

Mode of Action in Multiple Sclerosis

The treatment with DMF is associated with changes of peripheral immune cell subset composition and activation. Not all subpopulations of immune cells in the peripheral blood are affected equally. There is evidence for anti-inflammatory action, with a relative shift of immune cell populations toward anti-inflammatory phenotypes.[58] DMF also interferes with lymphocyte signaling, attenuating proinflammatory cytokine and chemokine production.[59] In-vivo, a relative decrease of the following immune cell populations is observed: proinflammatory Th1/17 cells, central and effector memory CD4/8 T cells, plasmablasts, IgD± memory, and CD138 plasma cells, $CD56^{dim}$ NK cells. Conversely, a relative increase in the following immune cell populations is observed in-vivo. The subsets involved include anti-inflammatory Th2 cells, naïve CD4/CD8 cells, naïve regulatory T cells, transitional B cells, and $CD56^{bright}$ NK cells. In addition, DMF treatment in MS results in a reduction of terminally differentiated effector memory T cells and decreased numbers of interferon-gamma (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF) producing CD4+ and CD8+ T cells. Moreover, DMF targets the intracellular stress response in activated T cells, thereby restricting mitochondrial function and energetic capacity.[60] The subsequently enhanced mitochondrial reactive oxygen species levels result in enhanced T-cell apoptosis. DMF attenuates the migratory potential of CD4+ T cells, whereas CD8+ T cells are less affected.[61]

There is a decline in the absolute B-cell number with DMF treatment, with preferential depletion of memory B cells and a concurrent increase in naïve B cells.[62] In addition, there is a significant reduction in GM-CSF, tumor-necrosis

factor-alpha (TNF-α), and interleukin-6 (IL-6) secreting B cells with DMF treatment. Treatment with DMF is also associated with decreased expression of costimulatory CD40, antigen presentation molecule major histocompatibility complex class 2 and B cell activating factor receptor on B cells.[63] This anti-inflammatory shift of B cell responses was corroborated in another study.[64]

The understanding of the effects of DMF on the distribution of lymphocyte subsets within the CNS of pwMS is limited. The knowledge about DMF/MMF effects on CNS resident cells derives mostly from in-vitro studies and preclinical models. In people with primary progressive MS, there were reduced numbers of CD4+ T cells and increased concentrations of IL-7 in CSF.[65] IL-7 is a hematopoietic growth factor that stimulates the expansion of CD4+ T cells. Thus, the increase of IL-7 could be related to the peripheral lowering of CD4+ T cell counts by DMF and subsequently reduced transmigration to the CNS or the direct impact of MMF on CD4+ T cells within the CNS. In the CSF, the absolute number of mononuclear cells was significantly lower in DMF-treated pwMS than with other DMDs, and there was a disproportionate decrease of plasmablasts.[66]

Mode of Action in in-vitro Studies and Preclinical Models

After oral DMF administration in rodents, MMF rapidly distributes throughout different organs. MMF is detected in the plasma, brain, kidney, jejunum, and spleen.[67] A recent study in rodents disclosed that FAE derivatives undergo a different biodistribution and may elicit distinct biological responses.[67] In detail, the Nrf2-mediated oxidative stress response pathway was exclusively regulated by DMF, whereas MMF activated apoptosis pathways.

Immune cell migration to the CNS is attenuated by inhibition of the adhesion of immune cells to endothelium.[68] A combined ex-vivo analysis of lymphocytes derived from DMF-treated pwMS and in-vitro MMF treatment of endothelial cells revealed dual action.[55] There was VCAM-1 downregulation on the endothelial side and reduction in T cells with a migratory phenotype on the lymphocyte side. The binding of MMF to brain endothelium and activation of G-protein-coupled receptor HCA2 with subsequent inhibition of NF-κB signaling is involved in this process. An in-vitro study also confirmed a reduced extent of transendothelial migration of monocytes upon MMF treatment and increased levels of endogenous antioxidant proteins in brain endothelial cells.[69]

Preclinical and in-vitro studies corroborate that FAE can protect neurons and oligodendrocytes via activation of the Nrf2 pathway. In-vitro studies found that DMF/MMF alters the function of CNS resident cells, suppresses inflammatory cytokine production by activated microglia and astrocytes, and increases the number of oligodendrocyte precursor cells.[51,70,71] In experimental autoimmune encephalomyelitis (EAE), an experimental model of MS, treatment with DMF was associated with decreased microglial activation in chronic active brain lesions.[72] Moreover, in EAE, the mode of action of DMF includes the suppression of inducible nitric oxide synthetase (iNOS)+ proinflammatory macrophages, complement C3 positive astrocytes, and deposition of C3 in the CNS.[73] DMF acts directly on CD4+ T cells and suppresses GM-CSF-producing Th1 or single GM-CSF+ T cells in EAE.[74] In-vitro, DMF is capable of directly inducing apoptosis of B-cells.[63]

DMF alters lipid metabolism, which may support the ability of cells to survive oxidative stress:[51,75] Most recently, DMF was shown to change the metabolic profile of human CD4+ and CD8+ T cells by restricting their antioxidative properties.[60] The enhanced mitochondrial reactive oxygen species levels result in enhanced T-cell apoptosis and potentially contribute to the immunomodulatory function of DMF.

Clinical Efficacy of Dimethyl Fumarate in Multiple Sclerosis

The efficacy of orally administered DR DMF over two years was demonstrated in the pivotal, placebo-controlled phase III DEFINE and CONFIRM trials in adults with RRMS.[18,19] In the long-term extension trial (ENDORSE), 1736 of 2079 DEFINE/CONFIRM completers participated and followed a median of 8.5 years (range 2.1–10.8).[76] The adjusted annualized relapse rate (ARR) remained low in the extension study (⩽0.20). Moreover, almost 75% remained free of 24-week confirmed disability progression. A posthoc analysis of DEFINE/CONFIRM revealed that a significantly higher percentage of patients treated with DMF (26%) achieved NEDA status over two years compared with placebo (12%).[77] The relative risk reduction was 42.7% (hazard ratio, 0.57; 95% CI, 0.48–0.69; $P < 0.0001$). Results of APEX, a pivotal trial in a predominantly East Asian population, were reassuring of those seen in DEFINE and CONFIRM.[78] Real-world

evidence corroborates the efficacy of DR DMF in RRMS concerning lowering the relapse rate and slowing disability progression. A recent review article identified several observational studies.[79] Amongst were studies with large cohorts (n > 500), which were either prospective (n = 7) or retrospective (n = 11).

Tolerability and Safety of Dimethyl Fumarate in Multiple Sclerosis

The tolerability profile of DR DMF 240 mg twice daily is well studied. Of note, AEs were frequent in the phase III trials regardless of assignment for DMF (86–96%) or placebo/glatiramer acetate (GA, 77–95%) but were mainly in the mild to moderate severity range. The most common AEs (≥10% incidence) of DMF with a ≥ 2% greater incidence vs placebo included flushing (40% vs 6%), nausea (10% vs 5%), abdominal pain (18% vs 10%) and diarrhea (14% vs 11%). MS relapse was the most frequently reported serious AE in the pivotal trials. Relapses occurred in the DMF and placebo/GA arm in 10–11% and 14–15%, respectively. All other serious AEs occurred at a frequency of ≤2%. The absolute lymphocyte count (ALC) declines four weeks after DMF initiation. The ALC declines by 30% on average but remains above the lower limit of normal (LLN; ie, ALC $\leqslant 0.91\times10^9$/L) in about two-thirds of the patients. Severe prolonged lymphopenia developed in 2% of patients; prolonged lymphopenia with moderate severity developed in 10%. Infections were also common in DEFINE (64% for DMF and 65% for placebo) and CONFIRM (56% and 50% for GA, respectively). The most common infections included nasopharyngitis, urinary tract infection, and upper respiratory tract infection. Few patients (≤2%) had serious infections, with no opportunistic infections in the main period of the pivotal trials.

In the long-term extension study of the DEFINE and CONFIRM trials (EXPAND), the incidence of SAEs was 30% among those exposed to DMF after the elimination of the GA-treated patients.[76] The most common SAEs in this follow-up study over nine years were MS relapse, nasopharyngitis, and flushing. There were nine deaths reported in the long-term study. A fatal case of progressive multifocal leukoencephalopathy (PML) developed after severe lymphopenia over 3.5 years. A recent study calculated a DMF-related PML risk of 0.02 per 1000 patients.[80] The FDA label for DMF recommends interruption of DMF therapy in patients with ALCs $<0.5\times10^9$/L, if persisting over more than six months. In real-life, DMF-associated PML occurred in patients with ALCs above the guideline threshold, suggesting that changes in specific subsets might be more important than the total ALC.[80] The peripheral immune cell pattern with DMF is characterized by a relative shortage of T cells in lymphopenic patients.[81] In this regard, CCR4-expressing T helper cells were identified as a prognostic biomarker for developing relevant lymphopenia in patients treated with DMF.[81] Severe lymphopenia is more prevalent in older patients, and age increases the risk for DMF-associated PML.[82] Hepatic complications occurred in 11% of the DMF/DMF-treated patients.[76] Proteinuria, microalbuminuria, and hematuria were the front runners of renal AEs (incidence ⩾5% in any treatment group). The incidence of malignancies was 3% in both treatment groups in the overall safety population and did not exceed the expected background rate.

A recent analysis of the FDA Adverse Event Reporting System disclosed several opportunistic infections beyond PML in causal association with DMF.[83] These included 11 cases of CNS and 23 systemic infections. The first group consisted of five encephalitis cases (Herpes simplex virus n = 1, Varicella-zoster virus (VZV) n = 3, Listeria monocytogenes n = 1), three meningitis cases (West Nile virus, Streptococcus pneumoniae, Cryptococcus neoformans, n = 1 each), two cases of myelitis due to VZV, and one cerebral abscess caused by Nocardia.

GI AE Aspects of Dimethyl Fumarate

DMF-related GI AEs typically emerge shortly after treatment initiation. The real-world incidence of GI AEs was 88% when self-assessed GI symptoms were analyzed.[84,85] The consequences of GI AEs include dose reduction, interruption, or premature discontinuation. In real-world studies with DMF, GI AE-related dose interruption or reduction was carried out in 7–21% of the patients.[22,84] Up to 19% discontinued the treatment due to GI AEs. Such a dosing change or termination is hazardous to sufficient drug levels required for disease control. From a patient's perspective, the successful mitigation of GI AEs is critical for treatment satisfaction.[86] The extent of GI AEs is mitigated by taking DMF with a meal, eg, high-fat food.[87] For some patients, this strategy may be irresolvable or even an offense to their otherwise healthy lifestyle. Of note, treatment with acetylsalicylic acid alleviates flushing associated with DMF, with no adverse or beneficial effects on GI events.[88]

COVID-19 and DMF

Knowledge about the COVID-19 disease course and immune responses to SARS-CoV-2 vaccination in pwMS is critical to maintaining a favorable risk-benefit profile of individual DMDs. In this regard, older age, obesity, progressive MS, and a higher degree of neurological disability are associated with severe COVID-19 outcomes.[89–91] A systematic review of the available literature did not disclose any higher risk of acquiring a SARS-CoV-2 infection for pwMS on DMDs.[92] However, there was an increased risk for severe COVID-19 (ICU admission, mortality) with CD20-depleting therapies. No increased chance for unfavorable outcome was identified so far for DMF treatment in pwMS.[91,93]

DMDs approved for MS differentially affect the development of SARS-CoV-2 vaccine-induced humoral and T-cell immunity.[92,94–96] In this regard, there is consistent study evidence that pwMS treated with DMF can generate robust humoral and T cell responses and are not at a higher chance of COVID-19 breakthrough disease.[97–99]

GI Tolerability of Fumaric Esters

MeOH release upon the esterase hydrolysis of DMF is blamed as the critical determinant for GI-tolerability. Therefore, the aforementioned lower rate of GI irritation with DRF may be related to significantly lower MeOH production in the gut. The lower molecular weight of DMF and subsequent off-target activity on proteins and receptors may be another issue for the occurrence of GI AEs. Moreover, the chemical structure of DRF is more complex and presumably interacts with fewer off-target proteins.[35] Eventually, also the differences in electrophilicity and half-life may be further factors involved in the distinct extent of GI AE.[35]

MMF acts as an agonist of the HCAR2, which is associated with dual action. Activation of the HCAR2 can elicit signals that, on the one hand, dampen cell activation and, on the other hand, promote inflammation. Subsequent gastrointestinal inflammation and skin flushing reaction are the main off-target effects.[57] Differences in DMF and DRF metabolism and systemic uptake may also play a role in the extent and duration of GI side effects.

Lower doses of MMF (95 mg twice a day) than a single dose of 240 mg DR DMF are needed to yield equivalent plasma MMF levels.[100] Promising data concerning tolerability were provided by a randomized, double-blind, head-to-head, 5-week study evaluating the GI AEs of MMF 190 mg vs DMF 240 mg in healthy subjects.[101]

Study Evidence for Diroximel Fumarate: Trials and Real-World Evidence

The clinical efficacy of DRF in relapsing forms or relapsing-remitting MS has not been studied by phase III trials. With proven bioequivalence between DMF and DRF for the active metabolite MMF, the approvals were based on the pivotal trials of DMF.[41,102] In this regard, early scientific evidence corroborates DRF's improved GI tolerability, as shown in Table 1.

EVOLVE-MS-1 is an ongoing, 2-year, open-label, 96-week, Phase 3 study assessing DRF safety, tolerability, and efficacy in adults with RRMS.[35,102,103] For this trial, patients were either newly enrolled or continued from the EVOLVE-MS-2 study. The interim analysis as of March 2018 included 696 patients and referred to a median exposure time of 59.9 weeks (range 0.1–98.9). AEs occurred in 84.6%; the severity of the events mainly was mild (31.2%) or moderate (46.8%).[102] Overall treatment discontinuation was 14.9%; in detail, 6.3% were due to AEs and <1% due to GI AEs. At week 48, the mean number of Gd+ lesions was significantly lower when compared to baseline (−77%; $p < 0.0001$), and the adjusted ARR was low (0.16; 95% confidence interval (CI) 0.13–0.20). Another EVOLVE-1 interim analysis concerned treatment-emergent adverse events (TEAE).[35] GI TEAEs developed in 30.9% of patients; the severity was mild or moderate in the vast majority (96%). When GI AEs did occur, the time of occurrence was early, the duration was short with a median of 7.5 (range 1–87) days, and resolved (88.8%) in most patients. GI TEAEs led to 1% of patients discontinuing treatment. The third interim analysis of EVOLVE-1 comprised 1057 EVOLVE-MS-2 patients (as of September 2020) and evaluated efficacy and safety outcomes in patients continuing on DRF (DRF-rollover) or switching from DMF (DMF-rollover).[103] The control group consisted of patients who previously were on either GA or IFN-β and switched to DRF. Patients continuing on FAE had significantly lower rates of new or recurrent GI AEs. After 2 years of DRF exposure, patients with prior GA, IFN, or fumarate treatment had safety outcomes consistent with previous fumarate studies. The data suggest that transition to DRF from GA, IFN, or DMF is a reasonable treatment strategy, with low rates of discontinuation due to GI AEs.

Table 1 Pivotal Trials of DRF in MS

	Evolve-MS-1 (NCT02634307)	**Evolve-MS-2 (NCT03093324)**
Trial design	Phase III, open-label, single-arm study; non-comparative	Phase III, randomized, double-blind, head-to-head, 5-week study; superiority
Inclusion criteria	Adults aged 18–65 years with a confirmed diagnosis of RRMS and who were neurologically stable with no evidence of relapse in the 30 days before screening	Adults aged 18–65 years with a confirmed diagnosis of RRMS and who were neurologically stable with no evidence of relapse in the 30 days before screening
Intervention(s)	De novo patients • DRF 231 mg BID (Week 1) • DRF 462 mg BID (Weeks 2–96) • Rollover patients from EVOLVE-MS-2 • DRF 462 mg BID over 96 weeks	• DRF 231 mg BID (Week 1) • DRF 462 mg BID (Weeks 2–5)
Comparator	N/A	• DMF 120 mg BID (Week 1) • DMF 240 mg BID (Weeks 2–5)
Endpoints	• Relapse • Disability (EDSS, T25FW) • Disease progression (CDW3M) • Freedom from disease activity (NEDA-3, NEDA-4) • Subclinical disease activity (MRI) • Adverse effects of treatment • Health-related quality of life (EQ-5D, SF-12)	• Adverse effects of treatment • Health-related quality of life (IGISIS, GGISIS)
Enrolment	N=1057 as of September 2020	N=696 as of March 2018, median exposure 59.9 weeks (range: 0.1–98.9)
Results	• Treatment discontinuation: 14.9% • GI TEAEs were reported in 30.9% • GI TEAEs led to <1% of patients discontinuing treatment. • Mild or moderate in severity for the vast majority (96%) • GI AEs occurred early in treatment, mostly resolved (88.8%), and were of short duration [median 7.5 (range 1–87) days] in most patients.	• Treatment discontinuation due to AEs: DRF, 1.6% versus DMF, 5.6% • Treatment discontinuation due to GI AEs: DRF, 0.8% versus DMF, 4.8% • Interference with daily activities (IGISIS): DRF, 9.5% versus DMF, 28.9% • Work productivity (GGISIS): DRF, 6.1% versus DMF, 11.3% • Days with ⩾1 h of missed work: DRF, 43 days versus DMF, 88 days. • Concomitant symptomatic medication use: DRF, 19.3% versus DMF, 30.6%

Abbreviations: IGISIS, Individual Gastrointestinal Symptom and Impact Scale; GGISIS, Global Gastrointestinal Symptom and Impact Scale; DMF dimethyl fumarate; DRF, diroximel fumarate, RRMS, relapsing-remitting MS; MS, multiple sclerosis, BID twice a day, EDSS expanded disability status scale; T25FW timed 25-foot walk; MRI, magnetic resonance imaging; NEDA, no evidence of disease activity; CDW3M, confirmed disability worsening over 3 months; EQ-5D, standardised measure of health-related quality of life developed by the EuroQol Group; SF-12, 12-Item Short Form Survey.

The EVOLVE-MS-2 trial compared the GI tolerability of twice-daily administered DRF 462 mg and DMF 240 mg over five weeks in patients with RRMS.[104,105] This Phase III, randomized-controlled, double-blind, head-to-head comparison study used two self-administered gastrointestinal symptoms scales.[104] These were the Individual Gastrointestinal Symptom and Impact Scale (IGISIS) and the Global Gastrointestinal Symptom and Impact Scale (GGISIS). The primary endpoint was the number of days with an IGISIS intensity score of two or more relative to exposure. Other endpoints included the degree of gastrointestinal symptom severity measured by IGISIS/GGISIS and the evaluation of safety/tolerability. DRF treatment led to a statistically significant reduction in the number of days with an

IGISIS symptom intensity score of two or more compared to DMF (−46%). Furthermore, lower rates of GI AE events, including diarrhea, nausea, vomiting, and abdominal pain, were observed with DRF than with DMF (34.8% vs 49.0%). In addition, treatment discontinuation was less frequent with DRF compared to DMF because of AE (1.6% vs 5.6%) and GI AE (0.8% vs 4.8%). A post hoc analysis elucidated the impact of GI tolerability events on QoL in EVOLVE-MS-2.[105] Patients experienced a lesser effect on daily life and work and required less frequent concomitant symptomatic medication use. Thus, the improved GI tolerability with DRF translated into clinically meaningful benefits in quality-of-life measures.

A retrospective analysis of 160 pwMS from the AcariaHealth Specialty Pharmacy Program evaluated the persistence and adherence in DRF-treated patients in real-world clinical practice.[106] The median patient age was 51 (range 20–79) years, 80.6% were women, and 16.3% had been on DMF treatment. The median treatment duration was 7.6 (range 0.1–10.4) months. The estimated proportion of patients continuing on DRF treatment eight months later was 88.6% (95% CI 82.5–2.7). Overall, 3.8% discontinued DRF due to GI AEs. The frequency of days covered was 91.4% (95% CI 89.1–93.7). Among the patients that switched from DMF to DRF, 92.3% remained on DRF, and 3.8% discontinued DRF due to GI AEs.

Limitations

The tolerability of DMDs and subsequent adherence is crucial for long-term disease control. DRF, a second-generation FAE, showed an improved GI tolerability profile in the EVOLVE-MS trials and a high level of adherence in a real-world study. Therefore, the EVOLVE-MS trials provide a solid basis for corroborating the improved tolerability of DRF in comparison to DMF. However, as a limitation, the GI events are based on patient-reported outcomes and need to be amended by further observations in the clinical routine. Furthermore, the relapse rates were patient-reported at baseline in EVOLVE-MS-1 and the final analysis is eagerly awaited. Importantly, whether the efficacy and safety data are interchangeable with the experience gained for DMF in pivotal trials and in the real-world setting is unclear. While MMF is the presumed active metabolite of both substances and prior studies confirmed MMF bioequivalence of 2×240 DMF and 2×462 mg DRF, emerging preclinical data disclosed a different biodistribution and distinct biological responses of FAE derivatives.

Conclusion

Taken together, DRF is an emerging first- and second-line oral DMD option for relapsing (FDA) and relapsing-remitting MS (EMA) with an improved tolerability profile compared to the precursor DMF. To be considered as a meaningful treatment option, further studies need to clarify, on the one hand, whether patients with initial or ongoing tolerability issues with DMF will benefit from a switch to DRF. On the other hand, DRF's long-term tolerability, efficacy, and safety profiles must be characterized as for any other newly approved DMD. Moreover, direct head-to-head comparison trials and cost-effectiveness analyses will be critical to defining the position of DRF in the emerging spectrum of DMDs for the treatment of relapsing/relapsing-remitting MS. Of note, the FDA approved MMF to treat relapsing forms of MS. Also, the introduction of DMF generics can weaken the unique selling point of DRF. In the meantime, further efforts should be directed toward preventing lymphopenia with FAE treatment and implementing risk stratification algorithms. Also, a better understanding of FAE-related opportunistic infections and the immunopathogenesis of PML is indispensable.

Abbreviations

AE, adverse event; ALC, absolute lymphocyte count; AMPK, 5' adenosine monophosphate-activated protein kinase; AUC, area under curve; ARR, annualized relapse rate; BBB, blood–brain barrier; CNS, central nervous system; COVID-19, coronavirus infectious disease 2019; CSF, cerebrospinal fluid; CUALs, combined unique active lesions; DMF, dimethyl fumarate; DMD, disease-modifying drug; DR, delayed release; DRF, diroximel fumarate; EDSS, expanded disability status scale; FAE, fumaric acid ester; FDA, United States Food and Drug Administration; EMA, European Medicines Agency; EBV, Epstein-Barr virus; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; Gd+, gadolinium-enhancing; GGSIS, Global Gastrointestinal Symptom and Impact Scale; GM-CSF, granulocyte-macrophage colony-stimulating factor; GI, gastrointestinal; HCAR2, hydroxycarboxylic acid receptor 2; HES, 2-hydroxyethyl

succinimide; IGISIS, Individual Gastrointestinal Symptom and Impact Scale; MRI, magnetic resonance imaging; IFN, interferon; IL, interleukin; LLN, lower limit of normal; MeOH, methanol; MMF, monomethyl fumarate; MS, multiple sclerosis; NEDA, no evidence of disease activity; PK, pharmacokinetics; PML, progressive multifocal leukoencephalopathy; PPMS, primary-progressive MS; pwMS people with MS; QoL, quality of life; RMS, relapsing forms of MS; RRMS, relapsing-remitting MS; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; Sirt1, NAD-dependent deacetylase sirtuin-1; SPMS, secondary-progressive MS; TEAE, treatment-emergent adverse events; TNF-α, tumor-necrosis factor-alpha.

Disclosure

LH has nothing to disclose. JS received honoraria for presentations and the assembly of educational material from Alexion, Angelini, BMS, Biogen, Boehringer, Immunic, Janssen, Merck, Novartis, Pfizer, Sandoz and Sanofi. He is a member of scientific advisory boards of Alexion, BMS, Biogen, Boehringer, Novartis, Sandoz and Sanofi.

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