Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Dimethyl Fumarate

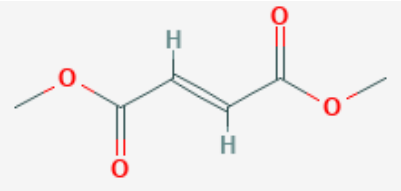
Evidence Summary

May prevent oxidative stress induced cellular damage by boosting the primary endogenous antioxidant pathway, which could prevent neurodegeneration, but may compromise immune function.

Neuroprotective Benefit: Reduces neuroinflammation and may slow the rate of neurodegeneration in MS patients. Strong neuroprotection against oxidative stress damage when used as a preventative therapy in preclinical models.

Aging and related health concerns: Potent anti-inflammatory activity in MS patients. May help overcome endogenous age-related declines in cellular antioxidant activity and prevent new cell damage based on preclinical models.

Safety: Good safety profile relative to other efficacious therapies for MS. Primary side effects are flushing and gastrointestinal-related events. Concern for lymphopenia, liver injury, and an increased risk for infections in people over age 50.

Availability: Rx	**Dose:** 240 mg capsules BID	**Chemical formula:** $C_6H_8O_4$ **MW:** 144.126 g/mol  Source: Pubchem
Half-life: Rapidly metabolized to MMF. MMF half-life approximately 1 hour.	**BBB:** Penetrant	
Clinical trials: Primarily in psoriasis and multiple sclerosis (2 Phase 3 RCTs n=1417/n=1234)	**Observational studies:** Limited to safety and tolerability in MS patients in real-world setting (largest n=735 in Italy)	

What is it? Dimethyl fumarate (DMF) is a methyl ester of fumaric acid with anti-inflammatory, immunomodulatory, and anti-oxidant activity. DMF is an electrophilic compound that covalently modifies cysteine residues on proteins in a process called succination. DMF is generally considered a prodrug since it is rapidly metabolized into monomethyl fumarate (MMF).

DMF, in the form of delayed-release oral capsules under the trade name Tecfidera® (Biogen Idec), was approved by the FDA and European Commission on March 27, 2013 for the treatment of relapsing-remitting multiple sclerosis (RRMS). The FDA also granted orphan status for its use in Fredrich's Ataxia. DMF in combination with three other fumaric esters (Ca, Mg and Zn salts of the monoethylester, ethylhydrogen fumarate), under the trade name Fumaderm®, is approved in Germany for the use in treating severe psoriasis. In June 2017, an oral formulation of DMF under the trade name Skilarence® (Amirall) was approved for use in Europe for the treatment of plaque psoriasis.

While the mechanism(s) of action underlying its clinical efficacy have not been fully established, there are several major processes/pathways that are regulated by DMF and thought to contribute to its cytoprotective and anti-inflammatory activity, including activation of Nrf2, modulation of glutathione levels, inhibition of NF-kB, and agonism of Hydroxycarboxylic acid receptor 2 (HCA2) [1].

Neuroprotective Benefit: Reduces neuroinflammation and may slow the rate of neurodegeneration in MS patients. Strong neuroprotection against oxidative stress damage when used as a preventative therapy in preclinical models

Types of evidence:

- 3 clinical trials (RCTs for Multiple Sclerosis)
- 4 observational studies (Multiple Sclerosis patients treated with DMF)
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Multiple sclerosis (MS) is a neurological autoimmune disease involving both neuroinflammation and neurodegeneration. DMF (Tecfidera®) is currently approved for RRMS, in which disability is primarily driven by inflammatory relapse events. Historically, approximately 90% of RRMS patients develop secondary progressive MS (SPMS) within 20 years. In progressive MS, disability (including cognitive decline) is primarily driven by neurodegeneration (though the underlying mechanisms may be different in MS compared to normal aging and/or dementia).

Prevention of Neurodegeneration: **Potential benefit**

Two Phase 3 double-blind, placebo-controlled, 2-year clinical trials have been conducted testing the efficacy and safety of Tecfidera® in RRMS patients, CONFIRM [2] (NCT00451451) and DEFINE [3] (NCT00420212). Both trials included RRMS patients treated with either: placebo, glatiramer acetate (moderately effective MS therapy), DMF 240mg 2x daily (BID), or DMF 240mg 3x daily (TID). Both trials had positive primary outcomes based on reducing relapse rates, however, they differed on secondary outcome measures related to brain atrophy.

In the **CONFIRM trial** (n=1417, avg age 37, 70% female), the 2-year decrease in whole **brain atrophy as measured by the percent change in brain volume relative to baseline was not significant compared to placebo** (median decrease in atrophy was 30% (BID; **p = 0.0645**) and 21% (TID; p = 0.2636) [4].

In the **DEFINE trial** (n=1234, avg age 38, 73% female), **the 2-year change in brain atrophy just reached statistical significance** in DMF treated patients (decrease in atrophy was 21% (**P = 0.0449**) BID and 5 % (P = 0.6398) TID) [5]. Notably, benefits were only seen with the 2x daily dosage. DMF has been shown to exhibit dose (concentration) dependent effects [6], so better response with BID vs TID may be biologically meaningful.

In the open-label extension trial ENDORSE (NCT00835770), there were no further significant decreases in brain atrophy with continuous DMF treatment 3 years after the end of CONFIRM/DEFINE [7].

However, the rate of brain atrophy in these patients was calculated to be comparable to healthy controls, suggesting DMF may be slowing MS-associated neurodegeneration.

A small retrospective study in a slightly older cohort (DMF n=20, age 46.1 ± 10.2 years) (no treatment n=8, age 42.5 ± 6.6 years) demonstrated a benefit for DMF in reducing whole brain atrophy (brain volume change DMF: −0.37 ± 0.49% vs. No treatment: −1.04 ± 0.67%, p = 0.02) after 1 year, but in the deep gray matter the protective effect was largely restricted to the putamen [8]. It is unclear if this localized effect is clinically meaningful in terms of preserving cognitive function.

Of note, brain atrophy MRI measures in MS are not yet well-standardized, thus making it difficult to make meaningful comparisons across trials. Additionally, RRMS patients, especially young, early stage patients included in RCTs, tend to have slower rates of brain atrophy/neurodegeneration than older patients with progressive MS. Thus, it may be hard to detect neuroprotective benefits in the RRMS cohort.

Preservation/Improvement of Cognitive function: Unclear

In a small observational study of RRMS patients, (n=12) DMF (Tecfidera® 240 mg BID for 12 months) treatment led to an increase in the Paced Auditory Serial Addition Test (PASAT) score, which measures cognitive function, at 3 months relative to baseline, with improvements sustained at 12 months [9]. These results may be specific to MS patients and the study was too small to make meaningful conclusions.

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

The major mechanisms involve regulation of cellular redox balance through:

1. Activation of Nrf2 and oxidative stress associated genes.
2. Modulation of glutathione levels.
3. Inhibition of NF-kb (nuclear translocation and associated signaling).
4. Agonist of HCA2 (a GPCR involved in neutrophil recruitment).

Nrf2 Activation

Most of DMF's beneficial effects are attributed to its activation of the transcription factor Nrf2 and its associated antioxidant signaling pathway [1]. Endogenous activation of Nrf2 occurs under conditions of

elevated oxidative stress. Since the electrophilic activity of DMF involves reactive oxygen species (ROS), it will have more activity/efficacy under conditions with high levels of oxidative stress.

Alzheimer's Disease: Potential benefit (in rodent models).

DMF has been tested in animal and cellular models of Aβ and/or tau mediated neurotoxicity and shown to enhance neuronal survival, reduce levels of phosphorylated tau, and reduce numbers of activated microglia and astrocytes (i.e. reduce reactive gliosis) [10; 11; 12]. DMF treatment induced the Nrf2 pathway leading to induction of antioxidant genes (HO-1, MnSOD and GSH), a reduction in oxidative stress (ROS) and inhibition of pro-inflammatory signaling (NF-kB).

DMF treatment prevented decline in performance in a cognitive task (novel object discrimination, 2.5-fold higher vs vehicle $p< 0.05$) in APP^{V717I}/TAU^{P301L} transgenic mice [11]. Benefits were related to improved neuronal survival and decreased (microglial-mediated) neuroinflammation. In these models DMF treatment (100 mg/kg) was provided at the time of disease induction or in transgenic animals prior to onset of behavioral phenotypes. Benefits of DMF are most apparent when it is present at the time of cell damage causing stressors in order to counteract the stress and prevent damage from occurring. After the damage has occurred, DMF offers less benefit.

Parkinson's Disease: Potential benefit (in rodent models).

DMF has been tested in α-synuclein overexpression and MPTP mouse models of Parkinson's disease (PD) and was shown to protect against loss of dopaminergic (TH+) neurons in a dose-dependent manner (30 mg/kg daily or up to 100 mg/kg required for protection) [13; 14; 15]. The cell protective effect was associated with **decreased oxidative stress** (increased mSOD, increased GSH/GSSG ratio, decreased nNOS, and decreased 3-NT (protein oxidation marker)), **decreased microglial activation** (CD68+) and pro-inflammatory cytokine production (IL-1β, iNOS). Improvements were shown in motor function (reduced bradykinesia and improved performance on rotarod motor tasks) [15]. The neuroprotection was dependent on Nrf2 induction.

MMF is 10-fold less potent in Nrf2 induction *in vitro* but had similar Nrf2 induction capacity and neuroprotective benefit *in vivo* (MPTP model) [13]. Since MMF has lower alkylating activity, if clinically validated, it may provide a safer alternative to DMF for neurodegenerative diseases. However, in a spinal cord injury (SCI) model, DMF was a more effective neuroprotectant than MMF [16].

Traumatic CNS Injury: Potential benefit (in rodent models).

In a spinal cord injury (SCI) [16] and controlled cortical impact (CCI) [17] models, when DMF (30 mg/kg) was administered within 1-hour post-injury, there was a reduction in histological tissue damage (24 hours post-injury) and improved performance on motor (rotarod, $p < 0.0002$ (CCI) or Basso Mouse scale open field score $p < 0.001$ (SCI)) and cognitive tasks (elevated plus maze, $p < 0.0001$ (CCI)). This was associated with less cell loss, induction of the Nrf2 antioxidant pathway, decreased neutrophil infiltration and myeloperoxidase (MPO)-associated oxidative stress, reduced inflammation/microglial activation, and restored growth factor (BDNF, GDNF, NT-3 [16]) levels.

The greatest neuroprotective activity is observed when DMF is available close to time of injury.

Stroke/inflammation-associated cognitive impairment: Potential benefit (in rodent models).

In animal models, DMF administered before or within 1 hour of the onset of insult can prevent/ameliorate the development of neuroinflammation-associated cognitive decline. Protective doses ranged widely from 15 mg/kg– 100 mg/kg 2x daily for mice, and 15 mg/kg in rats [18; 19; 20; 21].

DMF pre-treatment was shown to protect against neurological deficits as measured by the novel object recognition task (in context of LPS-induced inflammation [21] and sepsis [20]) or Garcia test neuroscore (stroke) [19], and the modified neurological severity score (stroke) [18].

Protective benefits were associated with the suppression of pro-inflammatory cytokines by microglia (ex. IL-1β, IL-6, TNFα, but specific cytokines affected varied by study), decreased microglia numbers/reactivity, increase in Nrf2 antioxidant pathway genes (i.e. NQO1, HO-1, SOD), decrease in NF-kB signaling (Nrf2 independent), decreased neutrophil infiltration/myeloperoxidase (MPO)-activity (in sepsis study), and increased cell viability. This leads to less inflammatory oxidative damage to neurons, therefore neuronal activity and cognitive function are preserved. Since the mechanism involves preventing inflammatory damage, to be therapeutically useful, DMF would need to be used prophylactically (may not be practical based on safety profile).

HIV-associated neurotoxicity: Potential benefit (*in vitro* models).

In cell culture studies, treatment of macrophages with DMF or MMF (5 uM-100 uM) rescues macrophage-associated neurotoxicity by inhibiting HIV-replication, inhibiting NF-kB nuclear translocation, increasing the Nrf2 antioxidant response, and preventing lysosomal dysfunction in macrophages [22; 23]. This suggests DMF may be beneficial as an adjunct therapy (to ART-therapy) in HIV patients to prevent neuroinflammation and neurodegeneration.

APOE4 interactions: Unknown.

Aging and related health concerns: Potent anti-inflammatory activity in MS patients. May help overcome endogenous age-related declines in cellular antioxidant activity and prevent new cell damage based on preclinical models.

Types of evidence:

- 3 observational studies (examining blood from DMF-treated RRMS patients)
- Numerous laboratory studies

Metabolism: Potential benefit (cell and animal models)

DMF promotes mitochondrial biogenesis in a tissue dependent manner. In mouse embryonic fibroblasts, DMF (20 uM for 24 hours) increased mtDNA copy number (Cox-1 gene) and complex subunit expression (1-5) [13]. In human fibroblasts, treatment with DMF (10 or 30 uM for 48 hours) increased mtDNA copy number, TFAM expression, expression of mt-complex subunits (1-4), mitochondrial proteins, and mitochondrial OCR (basal and maximal) [24]. DMF was also found to increase mitochondrial biogenesis in RRMS patients. Following DMF treatment for 3 months, mtDNA copy number increased by 71%, ($P < 0.0075$) and subunit expression increased by 88% ($P < 0.05$) (compared to baseline) in PBMCs [24]. Mouse studies indicated that this mitochondrial biogenesis effect is tissue-type specific, as it occurred in brain, liver, and skeletal muscle, but not in heart [24].

Inflammation: **Benefit**

DMF mediates many of its cell protective effects through its anti-inflammatory properties, **by reducing levels of activated microglia/macrophages and pro-inflammatory T-cells.** In humans, DMF's anti-inflammatory activity has primarily been studied in the context of MS.

Microglial activation: Activated immune cells are metabolically distinct from regulatory and non-activated immune cells. DMF can inhibit microglial activation and associated pro-inflammatory cytokine production by inhibiting aerobic glycolysis in activated immune cells [25].

T-cell activation and survival: DMF can modify cysteines on many proteins other than Keap1 (Nrf2). In contrast to other cell types in which DMF primarily induces Nrf2 and is neuroprotective, in T-cells the preferential modification of these other targets contributes to their cell death [26]. DMF also negatively impacts T-cells by interfering with cellular metabolism. Effector T-cells (activated, pro-inflammatory) rely on aerobic glycolysis, which is inhibited by DMF [25]. Memory T-cells rely on fatty acid oxidation, and mitochondrial respiration was found to be decreased by 75% in T-cells in DMF-treated MS patients [27]. Pro-inflammatory T-cells are also highly dependent on NF-kB signaling. DMF

inhibits NF-kB through the inhibition of thioredoxin-1, which induces cell death [28]. Furthermore, DMF interferes with the maturation of the dendritic cells involved in the activation of pro-inflammatory T-cells [29]. In DMF-treated RRMS patients, these processes have led to a decrease in levels of circulating T-cells [9; 30].

Stroke: Potential benefit (rodents)

DMF and MMF have shown efficacy in mitigating tissue damage and improving functional outcomes in mouse models of stroke (primarily MCAO model). Treatment regimen ranged from 3 days prior to damage (15 mg/kg 2x daily) [31], to 15 min (30 mg/kg 2x daily sustained for 7 days) [18], 30 min (20 mg/kg 1x) [32], or 1 hour following injury (100 mg/kg 1x) [19]. In all conditions, treatment reduced or prevented: edema, microglial activation and inflammatory cytokine production, cell loss, and loss of BBB integrity (cell-cell adhesion). Notably, DMF/MMF had no effect on infarct lesion size acutely (within 1-2 days), but in 1 study led to a minor reduction later (3-7 days after injury) [18]. Protective effects are dependent on the activation of Nrf2 and Casein Kinase 2 (CK2) [19].

Greatest protective benefits occurred with pre-treatment or very early (and sustained) intervention, which may not be clinically feasible. There is a need to determine whether DMF synergizes or interferes with existing early intervention measures (tPA or thrombectomy).

Cardiovascular: Potential benefit (in animal models).

Hypertension: Polymorphisms in the Nrf2 promoter have been associated with reduced vasodilation and increased arterial pressure [33], suggesting Nrf2 can modulate vascular function in humans. In rodent models, DMF treatment has been demonstrated to prevent hypoxia [34], drug (isoproterenol) [35], or diabetes [36; 37; 38; 39] induced cardiac hypertrophy and hypertension (systolic pressure) and promote vasodilation. DMF reduced inflammation (NF-kB), cardiac muscle histological damage, levels of oxidative stress (NADPH oxidase), and cardiac [38] and lung fibrosis [34] (fibrotic gene expression).

Pre-treatment (preventative intervention) was more effective than treatment after onset of damage (therapeutic intervention).

Vascular calcification: DMF (25 or 50 mg/kg daily) pre-treatment was also able to dose-dependently prevent vascular calcification in a mouse model of Vitamin D3 induced calcification in a Nrf2 dependent manner [40].

Anemia: DMF induces expression of gamma-globin genes, fetal hemoglobin, and haptoglobin (sequesters extracellular Hb- and reduces vascular inflammation) in erythrocytes and was beneficial in a mouse model (100 mg/kg daily for 6 weeks) of anemia [41].

Diabetes: **Potential benefit (in rodent models).**

Vasodilation: Nrf2 is downregulated in the context of diabetes [42]. DMF treatment restores Nrf2 expression and antioxidant signaling in blood vessels in diabetic mouse models [36; 37; 38]. BK channels (large calcium activated-potassium channels) are important for vasodilation, and these channels are downregulated in diabetes. DMF treatment restores BK channel levels by preventing degradation of the channel protein BK-b1 [36; 37], which in turn restores vasodilation and reduces blood pressure.

Glucose regulation: DMF treatment (25 mg/kg daily) was able to reduce body weight and blood glucose levels in a high-fat diet induced Type 2 diabetes model [37], but not in a Type I (streptozotocin-induced) diabetes model (with10 mg/kg daily DMF) [38]. There were no effects on these measures in non-diabetic mice.

Wound closure: DMF (20 mg/kg) treatment also improved the rate of wound closure in diabetic mice (streptozotocin-induced) but had no effect on wound closure latency in non-diabetic mice [43].

Cognitive decline: The Streptozotocin injection model for diabetes also induces cognitive impairment/Alzheimer's disease (AD)- like changes in the rodent brain. In streptozotocin injected rats, the effects of DMF varied depending on whether the rats were young (4 months) or aged (22 months) [44]. Older animals showed more severe neurodegeneration, cognitive decline (water maze test performance), and more microglia activation in response to AD induction than younger animals. **DMF offered more benefit for older animals.**

Preferential Efficacy in Older or Diabetic Animals: This may be related to higher baseline levels of oxidative stress and age-related decline in endogenous damage-mediated induction of Nrf2, suggesting use of exogenous Nrf2 activators could protect against age-related increases in oxidative stress cellular damage. Similarly, differences in effects of DMF in diabetic and non-diabetic animals is likely due to higher ROS and lower endogenous Nrf2 signaling in the high-glucose environment of diabetes. In normal conditions, endogenous antioxidant processes are capable of mitigating damage, while impairment of these processes in diabetes promotes pathology. Therefore, a potent exogenous Nrf2 activator (DMF) is needed to combat the excessive damage-inducing oxidative stress in diabetic conditions.

Cancer: **Potential benefit (*in vitro* models).**

DMF has shown may be effective in limiting proliferation and inducing apoptosis in a variety of cancer cell lines [45], including: breast cancer [46], colon cancer [47], glioblastoma [48], melanoma [49], and T-cell lymphoma [28]. Cancer cells with KRAS mutations are particularly sensitive to the pro-apoptotic effects of DMF [45].

DMF exhibits these anti-cancer effects through several mechanisms.

- ***Metabolic regulation*** -by inhibiting aerobic glycolysis and the glycolysis-derived metabolites that promote cell proliferation [25; 45].
- ***NF-kB regulation***- by inhibiting NF-kB which leads to induction of apoptosis in cancer cells [28].
- ***Nrf2 regulation***- inhibiting Nrf2 in cancer cells through covalent modification of DJ-1 [45]. The resulting loss of antioxidant capacity makes the cancer cells susceptible to oxidative stress and death.

Neuropathy: Potential benefit (*in vitro* models).

DMF was shown to prevent chemotherapy-induced neuropathy in a cell culture system. Co-treatment of PC12 cells or rat dorsal root ganglia (DRGs) with chemotherapeutic agents (oxaliplatin, cisplatin, or bortezomib) and DMF for 24 hours prevented neurite shortening but had no effects on general pro-neurite outgrowth or the ability to reverse damage [50]. Notably, Nrf2 binding activity was only increased in the presence of chemotherapeutic agents.

Safety: Good safety profile relative to other efficacious therapies for MS. Primary side effects are flushing and gastrointestinal-related events. Concern for lymphopenia, liver injury, and an increased risk for infections in people over age 50.

Types of evidence:

- 3 meta-analyses/systematic reviews (Cochrane review (included 2 Phase 3 RCTs), 1 systemic review (2 Phase 3), 1 integrated analysis (Phase 2b +2 Phase 3 RCTs + extension)
- 13 clinical trials (9 not included in reviews)
- 5 observational studies
- Numerous laboratory studies

Adverse Events

The safety and efficacy of DMF in the oral delayed release form (Tecfidera®) has been tested in patients with RRMS, psoriasis, or sleep apnea. These studies have included Phase 2 and Phase 3 RCTs, as well as real-world observational studies from the open-label and post-market period. In all trials **the most common adverse events (AE) were flushing and gastrointestinal-related events**, including nausea, diarrhea, and abdominal pain [51; 52]. These AEs were most common immediately after starting treatment on Tecfidera® and reduced in severity over time. Based on meta-analysis of the 2 Phase 3 RCTs, at BID dosage (n=1540), the risk for AE was significantly higher than placebo (Risk ratio (RR): 1.37, 95% Confidence Interval (CI) 1.25 to 1.49, P < 0.00001)[52].

Flushing results from DMF's effects on HCA2. It was the most common AE, occurring at a frequency of approximately 40% of adults (47% in Phase 2b [53], 31% and 38% in Phase 3 [2; 3], 14% (Japan) [54], 37% (Italy) [55] and 7% (Kuwait) [56] in real-world studies) and 45% of pediatric RRMS patients [57]. In adults with psoriasis (2 studies), flushing occurred in 65% [58] and 18% [59] of study participants. In adults with sleep apnea flushing occurred in 56% of participants [60]. Flushing can be minimized by taking aspirin 30 min prior to DMF according to a study in heathy volunteers [61].

Gastrointestinal-related events were the most common cause of intolerance to Tecfidera® in real-world studies. The frequency of gastrointestinal-events was 55% in pediatric RRMS patients [57], 32% (Japan) [54], 31% (Italy) [55] and 13% (Kuwait) [56] in adult real-world studies, and nausea (10%, 15%/13%,) diarrhea (9%, 15%/19%), abdominal pain (9%, 10%/12%) in Phase 2b [53] and Phase3 [2; 3] trials in adults. In adults with psoriasis gastrointestinal-events occurred in 58% of study participants [58] including diarrhea (39%), nausea (11%), and abdominal pain (20%) [59]. Nausea occurred in 9% of sleep apnea trial participants [60]. Gastrointestinal-event severity can be minimized by taking gastrointestinal-symptomatic *medications* [62] (loperamide).

On Treato.com, the top concerns for DMF (Tecfidera®) from RRMS patients are progressive multifocal leukoencephalopathy, nausea, itching, hair loss, and depression.

Serious Adverse Events

The FDA package insert [63] for Tecfidera contains safety warnings for:

1. **Anaphylaxis and Angioedema** (if allergic or become allergic to the drug)

2. **Progressive Multifocal Leukoencephalopathy (PML):** PML is a progressive demyelinating and neurodegenerative disease caused by the infection of oligodendrocytes by the JC virus. PML is an

opportunistic infection that usually occurs in the context of immunosuppression. It is usually fatal, and survivors have long-term neurological disability. 5 cases of PML can be attributed to Tecfidera use in RRMS patients. Risk for DMF-associated PML is highest in patients >50 years of age and with Grade 2/3 lymphopenia.

3. Lymphopenia: In RCTs, lymphopenia was a common AE, with lymphocyte counts decreasing 30% on average during the first year of treatment in RRMS patients and then stabilizing. The absolute lymphocyte levels (ALC) of 61% of patients remained within normal range following treatment [64]. Of the patients who had sub-normal ALC levels, 9% had Grade 1, 21% had Grade 2, 7% had Grade 3, and <1% had Grade 4 lymphopenia. 2.2% had ALCs <500 mm^3 persisting for ≥6 months [64]. It was found that lymphopenia was more common in patients ≥55 years old who had low baseline ALC [65]. According to a Cochrane systematic review based on 2 Phase 3 RCTs (n=1540 patients), the risk ratio for lymphopenia with DMF was RR:5.69 (95%CI 2.40 to 13.46) with a moderate quality of evidence [52].

*Due to the risk for PML the FDA and EMA have issued safety guidelines stating that Tecfidera® should be discontinued if lymphocyte counts drop below 0.5X10^9/L for ≥6 months.

The lymphocytes from MS patients were shown be more sensitive to the apoptotic effect of DMF than those from healthy controls [9]. This may be related to a higher proportion of activated immune cells in MS patients. Therefore, MS patients may be at higher risk for DMF-associated lymphopenia and opportunistic infections than in people without autoimmune disease.

4. Liver injury: Elevated liver aminotransferase levels were detected in 3% of RRMS patients during the DEFINE trial. A real-world retrospective study analyzing the FAERS database identified 151 reports of DMF-associated liver injury, 137 were due to mild serum transaminase abnormalities. There were 14 cases of severe liver injury, 6 were moderate to moderate-severe, 10 required hospitalization, and none resulted in death or liver transplant [66].

5. Flushing

Risk for Infections: Age dependent

In RCTs and real-world observational studies treatment with DMF was not associated with an overall increased risk for infections [52; 64]. A Phase 2 clinical trial examining response to vaccines found that DMF treated RRMS patients had similar response to tetanus and diphtheria toxins (recall efficiency), anti-pneumococcal (T-cell independent), and meningococcal (neoantigen) [67]. Productive response was defined as ≥2-fold increase in IgG antibody levels 4 weeks post vaccination. However, in this study

the mean age was 45.3 years (range 27-55), while the risk for lymphopenia and PML increases at ≥55 years.

A single-center retrospective study (n=50) found that there was a higher incidence of infections in patients over 50 [68].

**Older patients (≥55 years) specifically may be at higher risk for infections.*

Electrophilic activity concerns

Due to its electrophilic activity, DMF can react (alkyl thiolation) with glutathione (GSH) resulting in a temporary reduction in GSH levels [69; 70], leading to elevated oxidative stress (ROS) and reduced cell viability. The thiol reactivity profile of DMF will depend on the protein composition and ROS levels in a given cell type. The covalent modification of some of DMF's non-Keap1 targets could potentially be harmful and induce side effects in certain cell types or under certain conditions.

Drug interactions

According to Drugs.com, there are 95 drugs known to interact with DMF (29 major and 66 moderate). Due to the immunomodulatory activities, most of these interactions fall into two categories: Immunosuppressant drugs and Live viral vaccines.

Clinical dosing guidelines

DMF is available by prescription in an oral delayed-release formula as capsules taken daily under the trade name Tecfidera® (BG-12) from Biogen Idec approved in the U.S. and Europe for the treatment of RRMS.

The recommended dosing for Tecfidera® in RRMS patients (based on MS clinical guidelines) is one 120mg capsule 2x a day for 1 week then one 240 mg capsule 2x per day afterwards. Taking with food can reduce risk of gastrointestinal-related events.

Dose-dependent effects: DMF has been shown to exhibit dose-dependent gene modulation in the brain and peripheral tissues in mice [6]. The DMF transcriptional profile was also tissue specific. The largest gene modulation occurred in the kidney, and only a small subset of (Nrf2 associated) genes were significantly modified in the brain (NQO1, Osgin1, and BDNF). Therefore, there is likely to be an optimal therapeutic dose that varies depending on organ system that is being targeted.

Pharmacodynamics: Since DMF is not found at quantifiable levels in the plasma, all pharmacokinetic data for Tecfidera® was obtained by measuring MMF [63]. The median T_{max} of MMF is 2-2.5 hours. Following administration of Tecfidera® 240 mg twice a day with food, the mean C_{max} of MMF was 1.87 mg/L and AUC was 8.21 mg.hr/L in MS patients. The terminal half-life of MMF is approximately 1 hour and no circulating MMF is present after 24 hours [1]. MMF is metabolized via the TCA cycle. Accumulation of MMF does not occur with multiple doses of Tecfidera®.

Research underway:

According to Clincaltrials.gov there are currently 12 trials active but not recruiting, 18 trials actively recruiting, 2 trials not yet recruiting and 1 trial with enrollment by invitation underway for DMF. The majority of these trials are in MS patient or psoriasis patients.

Notable trials include:

A Phase 2 RCT (NCT02959658) examining the efficacy of DMF in primary progressive MS (PPMS) patients based on levels of neurodegeneration using the biomarker of CSF levels of neurofilament light (NFL) and measures of clinical disability (EDSS). Estimated completion is December 2019.

A Phase 4 open label study (NCT03092544) examining the mechanism of neuroprotection for DMF in RRMS and SPMS. This will be a 6-month study monitoring changes in plasma biomarkers (neuronal bioenergetics, change in CSF biomarkers (neuronal bioenergetics, NFL, ceramide sphingosine and lipids), and changes in microbiota composition associated with DMF treatment and disease activity. Estimated completion is December 2018.

A Phase 1 study (NCT02981082) in Pulmonary Arterial Hypertension (PAH) Associated with Systemic Sclerosis and is expected to be completed in May 2020.

A Phase I study is examining the use of DMF as an adjunct therapy for Glioblastoma "Dimethyl Fumarate, Temozolomide, and Radiation Therapy in Treating Patients with Newly Diagnosed Glioblastoma Multiforme" (NCT02337426). Estimated completion was September 2018, but results have not been posted yet.

Search terms:

Pubmed, Google: Dimethyl fumarate + neurodegeneration, Alzheimer's, aging, cardiovascular, neuroprotection, diabetes, inflammation, safety, metabolism, Nrf2, meta-analysis

Websites visited for Dimethyl fumarate:

- Clinicaltrials.gov
- Treato.com
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Patientslikeme.com
- Cafepharma

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