Dimethyl fumarate for relapsing MS

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Summary

Dimethyl fumarate (DMF) is the latest oral therapy approved for relapsing-remitting multiple sclerosis (RRMS). In 2 placebo-controlled phase III trials, twice daily DMF demonstrated a 44%–53% reduction in annualized relapse rate and 71%–90% reduction in new MRI lesions. In one trial, DMF slowed the accumulation of disability, but not in the other trial. The main side effects of DMF include gastrointestinal symptoms (nausea, abdominal pain, vomiting, and diarrhea) and skin flushing, which peak at treatment initiation. There was no increased risk of opportunistic infections. Recommended safety monitoring includes complete blood count prior to treatment and annually while on treatment. Appealing aspects of DMF include potent efficacy, oral administration, and good safety and tolerability profiles. Altogether, DMF is an attractive option for first-line treatment, breakthrough disease activity, intolerance to other therapies, and possibly natalizumab-treated patients with positive JC virus serology.

Dimethyl fumarate (DMF; Biogen Idec; formerly called BG-12) is a new oral disease-modifying therapy approved in March 2013 to treat relapsing forms of multiple sclerosis (MS). This review summarizes its mechanism of action, clinical trial results, and expected clinical use.

Brief history of DMF

The history of DMF is a story of archetypal medicine, where treatment development stemmed from theoretical thinking and clinical observation. In the 1950s, German chemist Walter Schweckendiek turned to his professional background to find a treatment for his own psoriasis vulgaris. After postulating a Krebs cycle dysfunction, he found that fumaric acid appeared clinically effective. A decade earlier, fumaric acid began use as a food acidulant, so its oral safety and tolerability was known. Fumaric acid ester salts were added to improve gastrointestinal tolerability. A standardized formulation was then studied in 900 psoriasis patients.¹ The proprietary fumaric acid formulation Fumaderm was approved for treatment of psoriasis in Germany in 1994, where it continues widespread use for psoriasis.

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The most frequent adverse events associated with DMF included skin reactions (mostly flushing, but also erythema and pruritus) and gastrointestinal events (e.g., diarrhea, nausea, abdominal pain, vomiting).

The application of fumaric acid therapy to MS is credited to neurology chair Horst Przuntek and his dermatology colleague Peter Altmeyer, both of St. Josef Hospital, Ruhr University, Bochum, Germany, who noticed improvement in 2 patients with MS treated with Fumaderm for their coexisting psoriasis. An open-label phase I study in relapsing-remitting MS (RRMS) followed,² which then led to a successful placebo-controlled phase II trial using an enteric-coated, microtablet preparation of dimethyl fumarate to improve gastrointestinal tolerability.³

Mechanism of action

Preliminary experiments suggested that the immunomodulatory effects of DMF may include shifting dendritic cell differentiation and inhibiting proinflammatory pathways.^{4,5} DMF also exhibits potential neuroprotective effects in experimental models of neurodegeneration and oxidative stress, which is mediated through activation of the nuclear factor (erythroid-derived 2)–like 2 (Nrf2) antioxidant response pathway.^{6,7} These pathways represent novel mechanisms not shared by other MS disease-modifying therapies, although it remains unclear whether Nrf2 is responsible for the treatment effect seen in MS.

Efficacy results in clinical trials

DMF was evaluated in 2 phase III randomized, double-blind, placebo-controlled, 2-year trials: the Determination of the Efficacy and Safety of Oral Fumarate in RRMS (DEFINE) trial (1,237 patients)⁸ and the Comparator and an Oral Fumarate in RRMS (CONFIRM) trial (1,430 patients).⁹ In both studies, 2 dosing regimens of DMF (240 mg twice and thrice daily) were compared with placebo. Since both regimens demonstrated similar efficacy, only twice daily was submitted for regulatory approval and will be described here. Glatiramer acetate was included as a reference comparator in CONFIRM, in accordance with European regulatory requirements.

Both studies showed robust efficacy. DMF was associated with a 53% reduction in annualized relapse rate in DEFINE and 44% reduction in CONFIRM (both $p < 0.001$). The proportion of relapsing patients over 2 years was reduced by 49% in DEFINE ($p < 0.001$) and 34% in CONFIRM ($p = 0.002$). Although not yet published, a post hoc analysis found that the onset of clinical and MRI efficacy was apparent by 10–12 weeks.¹⁰ Glatiramer acetate performed similarly to its original phase III trial, with a 29% reduction in both relapse rate and proportion of relapsing patients, each compared to placebo.

Sustained accumulation of disability was reduced by 38% with DMF compared to placebo in DEFINE ($p = 0.005$), but only a trend of 21% was observed in CONFIRM ($p = 0.25$). The lack of a significant effect in CONFIRM in part may have been secondary to a lower disability progression rate in CONFIRM (13%–17% among the treatment groups) compared to DEFINE (16%–27%).

MRI measures also showed a robust reduction in disease activity. Across the 2 studies, gadolinium-enhancing lesions were reduced by 74%–90%, new or enlarging T2 lesions by 71%–85%, and T1 hypointense lesions by 57%–72% (all $p < 0.001$). Again, glatiramer acetate showed similar efficacy to previous trials, with 61% reduction in gadolinium-enhancing

The 20 years of experience with Fumaderm to treat psoriasis in Europe, along with the very good safety profile of DMF in MS clinical trials, makes DMF an attractive treatment option.

lesions, 54% reduction in new T2 lesions, and 41% reduction in new T1 hypointense lesions. Although not yet published, initial reports of atrophy progression over 2 years found a 21% reduction in median % change in whole brain volume in DEFINE ($p < 0.05$) and a trend of 30% reduction in CONFIRM ($p = 0.065$).

In post hoc comparisons of DMF vs GA in CONFIRM, significant differences favoring DMF were observed in annualized relapse rate (thrice daily DMF only), new or enlarging T2-weighted hyperintense lesions (both DMF doses), and new T1-weighted hypointense lesions (thrice daily DMF only) (all $p < 0.05$).

Safety

In both trials, study drug discontinuation rates because of adverse events were similar across groups: 10%–13% in placebo and 10%–16% with DMF. A total of 5.8%–9.7% of DMF-treated subjects discontinued their participation in the trial because of adverse events. The most frequent adverse events associated with DMF included skin reactions (mostly flushing, but also erythema and pruritus) and gastrointestinal events (e.g., diarrhea, nausea, abdominal pain, vomiting). Gastrointestinal side effects were reported over the first 3 months of treatment in 27% of DMF-treated subjects and 17% of placebo-treated subjects. The peak incidence of flushing and gastrointestinal events was in the first month of treatment and may improve if DMF is taken with food. Over-the-counter treatments for gastrointestinal side effects were used with some patients, but optimal management of gastrointestinal side effects is not clearly understood. Aspirin can help prevent flushing. The frequency of infections and serious infections was similar among the treatment groups. No opportunistic infections were reported in any DMF group, although rare cases of progressive multifocal leukoencephalopathy (PML) have been reported with other fumaric acid preparations in other autoimmune disorders. Prolonged, marked lymphocytopenia may be a risk factor for PML in this setting, which emphasizes the importance of periodic monitoring of complete blood count. The overall incidence of malignant neoplasms was <1% in all groups. The overall incidence of serious adverse events was similar across all groups. Mean peripheral white cell and lymphocyte counts decreased with DMF during the first year and then plateaued thereafter.

Use in practice

DMF 240 mg twice daily is approved to treat relapsing forms of MS. The 20 years of experience with Fumaderm to treat psoriasis in Europe, along with the very good safety profile of DMF in MS clinical trials, makes DMF an attractive treatment option. In the United States, DMF will likely be considered a first-line therapy option given its good efficacy, safety, and tolerability. In addition, DMF is likely to be considered a treatment option for patients with MS with sub-optimal response to, or intolerance to, injectable and other oral MS therapies. DMF also may be an alternative treatment to natalizumab in JC virus seropositive patients, in whom the risk/benefit ratio for natalizumab may have become unfavorable, although there have not been formal studies of DMF in this patient population. However, patients should be encouraged to continue their current disease-modifying therapy and not change to DMF if they are clinically stable on that therapy, are tolerating it well, and are not at increased risk of complications from that therapy.

Table The clinical use of DMF

Pharmacology and drug interactions	The approved dose is 240 mg by mouth twice daily.
	Absorption and elimination are not affected by food, ethnicity, sex, or mild to moderate hepatic or renal impairment. However, gastrointestinal side effects may be reduced by taking DMF with food.
	DMF is not known to have any significant drug interactions.
	DMF is approved as monotherapy; there are no published data on the safety or efficacy of combining DMF with other disease-modifying therapies.
	Washout from other MS therapies is not established. It is likely that patients can switch directly from IFN- β 1 and GA to DMF without need for washout. Washout period from fingolimod, natalizumab, and teriflunomide is at the clinician's discretion.
Laboratory testing	DMF modestly lowers lymphocyte counts. Complete blood count is recommended prior to starting therapy, annually thereafter, and when clinically indicated.
Cutaneous and gastrointestinal effects	The most frequent side effects associated with DMF are skin reactions (mostly flushing, but also pruritus and erythema) and gastrointestinal events (e.g., diarrhea, nausea, abdominal pain, vomiting), which may be reduced by taking DMF with food. Gastrointestinal side effects typically improve after 2–4 weeks; skin flushing may continue intermittently and is reduced by aspirin.
Infection	No increased risk of infection or opportunistic infection was observed in phase III clinical trials. Rare cases of PML have been reported with other fumaric acid preparations in other disorders. Prolonged, marked lymphocytopenia may be a risk factor for PML in this setting.
Cancer	No increased risk of cancer was observed in phase III clinical trials.
Pregnancy	Category C; DMF is not recommended in pregnant patients or those considering pregnancy.
Children	No data are available concerning use of DMF in children or adolescents, although postmarketing requirements include pediatric studies.
Elderly	Experience with DMF in patients >55 years of age is limited.
Abbreviations: DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; PML = progressive multifocal leukoencephalopathy.	

The practical aspects related to clinical use of DMF are summarized in the table. Gastrointestinal symptoms are common with initial treatment, but typically improve after several weeks. DMF should be used as monotherapy, since there are limited data concerning safety and efficacy in combination with other MS disease-modifying therapies.

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