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MONOGRAPH

BG-12

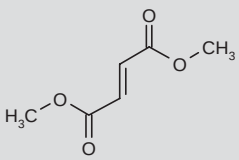
NF-κB Activation Inhibitor
Treatment of Multiple Sclerosis

Dimethyl fumarate
AZL-O-211089
BG-00012
DMF
FAG-201

2(*E*)-Butenedioic acid dimethyl ester

Fumaric acid dimethyl ester

InChI: 1S/C6H8O4/c1-9-5(7)3-4-6(8)10-2/h3-4H,1-2H3/b4-3+



$C_6H_8O_4$
Mol wt: 144.1253
CAS: 624-49-7
CAS: 23055-10-9
EN: 306774

SUMMARY

BG-12 is an oral second-generation formulation of dimethyl fumarate (DMF), a fumaric acid ester (FAE). FAEs are licensed in some countries for the therapy of severe psoriasis. Due to their immunomodulatory effects, FAEs were proposed as a treatment for multiple sclerosis (MS). In a recent phase II clinical trial in patients with relapsing–remitting (RR) MS, BG-12 was shown to reduce Gd^+-enhancing lesions and newly enlarging T2 lesions on MRI. To explore the long-term efficacy and safety, two international multicenter phase III trials are ongoing. Here we summarize the findings from clinical trials and many in vivo and in vitro studies on the mechanisms of action of BG-12. Both immunomodulatory and potential neuroprotective mechanisms have been proposed. The results of the phase III clinical trials need to be awaited until the role of BG-12 in the treatment of MS can be definitively assessed.

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BACKGROUND

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) with a putative autoimmune etiology. The neuropathological hallmarks are focal demyelination, inflammation and subsequent axonal loss, leading to neurological deficits (1). MS is the most common cause of neurological disability in young adults. The clinical course can be alleviated by so-called immunomodulatory drugs. These are, in particular, interferon beta, the copolymer glatiramer acetate and a monoclonal antibody against α_4 integrin, natalizumab (2-5). However, all these treatments bear the disadvantage that they require a parenteral route of administration, either s.c., i.m. or i.v. Thus, there is a need for a more convenient, preferably oral treatment.

Fumaric acid esters (FAEs) were introduced as therapeutic agents by the German chemist Schweckendiek, who proposed them as treatments for psoriasis (6), an autoimmune disease characterized by inflammation of the skin with cellular infiltrates, including lymphocytes, monocytes and dendritic cells (DCs). Schweckendiek himself suffered from psoriasis. He assumed that a disturbance in the citrate cycle might be the cause due to a critical dependency of immune cells on energy supply. A mixture of dimethyl fumarate (DMF) and three salts of ethyl hydrogen fumarate (EHF) was developed and licensed in 1994 under the brand name Fumaderm® (Table I) in Germany by Fumapharm as oral therapy for chronic plaque psoriasis. This has become the most prescribed systemic treatment for chronic plaque psoriasis in Germany and is also used in the U.K., Switzerland and the Netherlands (7), representing more than 30,000 patient-years without drug-associated long-term adverse reactions and only minor side effects. Its mode of action is thought to be mainly immunomodulation, with DMF representing the main active component (8-10). To reduce gastrointestinal side effects, an enteric-coated microtablet in gelatin capsules, BG-12, was designed as a monosubstance containing DMF only.

Table I. *Contents of one tablet of Fumaderm® initial© (used to improve tolerance in the first 3 weeks of therapy), Fumaderm® and BG-12.*

	Fumaderm® initial(C)	Fumaderm®	BG-12
Dimethyl fumarate	28.6% (30 mg)	55.8% (120 mg)	100% (120 mg)
Ethyl hydogen fumarate Ca salt	63.8% (67 mg)	40.5% (87 mg)	–
Ethyl hydogen fumarate Mg salt	4.8% (5 mg)	2.3% (5 mg)	–
Ethyl hydrogen fumarate Zn salt	2.8% (3 mg)	1.4 (3 mg)	–

PRECLINICAL PHARMACOLOGY

Although the pharmacology and the mode of action of FAEs have been investigated in various in vitro and in vivo studies, they still are not well understood. There is evidence that FAEs effectively influence several cell types of the immune system, as well as epithelial cells and glial cells (Table II). The most common hypothesis involves the cellular redox system, which can be modulated by DMF and alters the concentration of thiols. This leads to an increase of reduced glutathione (11). Increased levels of intracellular glutathione result in inhibition of the translocation of the nuclear factor NF-kappa-B (NF-κB) into the nucleus. This reduction of translocation of NF-κB decreases the expression of NF-κB-dependent genes that regulate a cascade of inflammatory cytokines, chemokines and adhesion molecules (12) involving different cell types of the immune system and the endothelium. In one of the first psoriasis clinical studies, treatment with FAE led to a reduction in human T cells in the blood (13). This effect was confirmed by the observation of a 50% reduction in $CD4^+$ T cells in epidermal inflammatory infiltrates (14). Treumer et al. also demonstrated the apoptotic effect of DMF on human T cells in an in vitro experiment (15). Moreover, analysis of the cytokine profile showed a shift from a proinflammatory Th1 to an anti-inflammatory Th2 cytokine profile with production of interleukins IL-4 and IL-5 (16). The observed apoptotic effect was also seen in human B cells (11) and DCs, which play an important role by regulating inflammatory responses in autoimmune diseases such as psoriasis and MS (17). It appears that the beneficial effect of FAE in psoriasis results at least partly in the reduction of these immunological cell populations. Another in vitro study that focused on interferon gamma (IFN-γ)- and lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells (PBMCs) showed an influence of FAE on the secretion of various cytokines, such as IL-10, IL-4, IL-5, TNF-α and IL-1RA, and downregulation of the chemokines CXCL8, CXCL9 and CXCL10 (12). Zhu et al. showed superoxide anion upregulation in human monocytes in response to zymosan (18).

Further information on the mechanisms of action of FAE emerged from studies with human keratinocytes, which are part of the inflammatory response in psoriasis. In an in vitro study with human keratinocytes and T cells in co-culture, DMF increased the production of IL-10 and decreased the production of IFN-γ, IL-6 and transforming growth factor α (TGF-α) (19). At the same time, another study (20) using the HaCat keratinocyte cell line showed a suppression of intercellular adhesion molecule 1 (ICAM-1) and the human leukocyte antigen HLA-DR. A recent study in human keratinocytes demonstrated inhibition of CXCL8, CXCL9 and CXCL10 protein production (12). These proteins participate in the chemoattraction of T cells, macrophages and neutrophilic granulocytes. The observed inhibitory effect is also present in human umbilical vein endothelial cells (HUVECs). Incubation of these cells with DMF led to an inhibition of ICAM-1, vascular cell adhesion molecule 1 (VCAM-1) and E-selectin.

Table II. *Effect of fumaric acid ester (FAE) in different cell types.*

Cell type	T cells	PBMCs	B cells	Dendritic cells	Endothelial cells	Glial cells	Keratinocytes
FAE	MMF/DMF	DMF	n.d.	MMF/DMF	DMF	DMF	DMF
Cytokines and other molecular changes	IL-2↓ TNF-α↓ IFN-γ↓ IL-5↑ IL-10↑ IL-12↑ Heme oxygenase 1 (HO-1)↑	CXCL8, 9, 10↓ TNF-α↑ IL-10↑ IL-1RA↑ IL-4↑, IL-5↑	n.d.	IL-12↓	Prevent NF-κB translocation CXCL8, 9, 10↓	TNF-α↓ IL-1β↓ IL-6↓ NAD(P)H: quinone oxidoreductase↓ Cellular glutathione↓ NO↓	IFN-γ↓ IL-10↑ HLA-DR↓ ICAM-1↓
Effect	"Th1" "Th2" shift Apoptosis $CD4^+$ (90%↓) $CD8^+$ (53%↓)	Superoxide anions↑	Apoptosis	Induce apoptosis Cell differentiation↓		Putative cyto-protection	
Reference	(13, 15, 16)	(18, 19, 34)	(11)	(17, 35)	(36)	(21)	(12, 19, 20)

MMF, monomethyl fumarate; DMF, dimethyl fumarate; PBMCs, peripheral blood mononuclear cells; n.d., not determined; NO, nitric oxide.

Another possible mechanism of action has focused on a potential detoxification effect observed when DMF was tested in mouse glial cells (21). Microglia and astrocytes stimulated with LPS and treated with DMF showed a decrease in the expression of TNF-α, IL-1β, IL-6 and nitric oxide (NO). Interestingly, there was also an upregulation of NAD(P)H:quinone oxidoreductase (QR1) and cellular glutathione synthesis, which is part of the glial detoxification machinery. Recent investigations suggested a role for NF-E2-related factor 2, a transcription factor that controls the transcriptional activity of QR1 and regulates the expression of more than 200 genes encoding for both antioxidant and anti-inflammatory proteins by binding to the antioxidant response element (ARE) in gene promoters (22). A study using the experimental autoimmune encephalomyelitis (EAE) mouse model of MS showed that FAE attenuated the disease (23). There was a reduced infiltration of activated macrophages into the CNS and a reduction of axonal loss. Preliminary studies in a rat EAE model showed that DMF inhibits the disease by preventing astrogliosis and macrophage activation. In vitro experiments also revealed a reduction of proinflammatory gene expression in rat astrocytes and macrophages after LPS stimulation (24, 25).

PHARMACOKINETICS AND METABOLISM

Almost all available data derive from clinical studies on the mechanisms of FAE in the treatment of psoriasis. These studies demonstrate that after oral intake DMF is rapidly hydrolyzed by esterases to its most bioactive metabolite monomethyl fumarate (MMF). MMF is then absorbed completely in the small intestine (26) and can interact with cells of the immune system in the blood circulation (27). In the citrate cycle, most of the MMF is further metabolized to carbon dioxide and water. The rest will be excreted via urine and feces (28). The MMF concentrations reach the maximum 5-6 h after oral intake (27). The measured half-life of DMF is approximately 12 min (29) and the half-life of MMF is about 36 h, but it has a biological impact that endures longer.

SAFETY

The best data on the safety of BG-12 have been documented in the phase II study in MS patients (30). The side effect profile is consistent with studies on FAE in the treatment of psoriasis. The most common adverse events are gastrointestinal symptoms, flushing, diarrhea, headache and a mild increase in liver enzymes (Fig. 1). All these adverse events were mild and reversible.

CLINICAL STUDIES

The clinical efficacy and safety profile of FAE was first evaluated in a single-center, 12-month, open-label observational trial including 83 patients with severe psoriasis vulgaris. In this study FAE revealed an antipsoriatic effect, with a mean reduction of 76% in the Psoriasis Area Severity Index (PASI) (13). A prospective multicenter study in 101 patients where the dose ranged from 1 low-dose tablet (Fumaderm® initial©, containing a mixture of DMF and MHF salts; see Table I) to 6

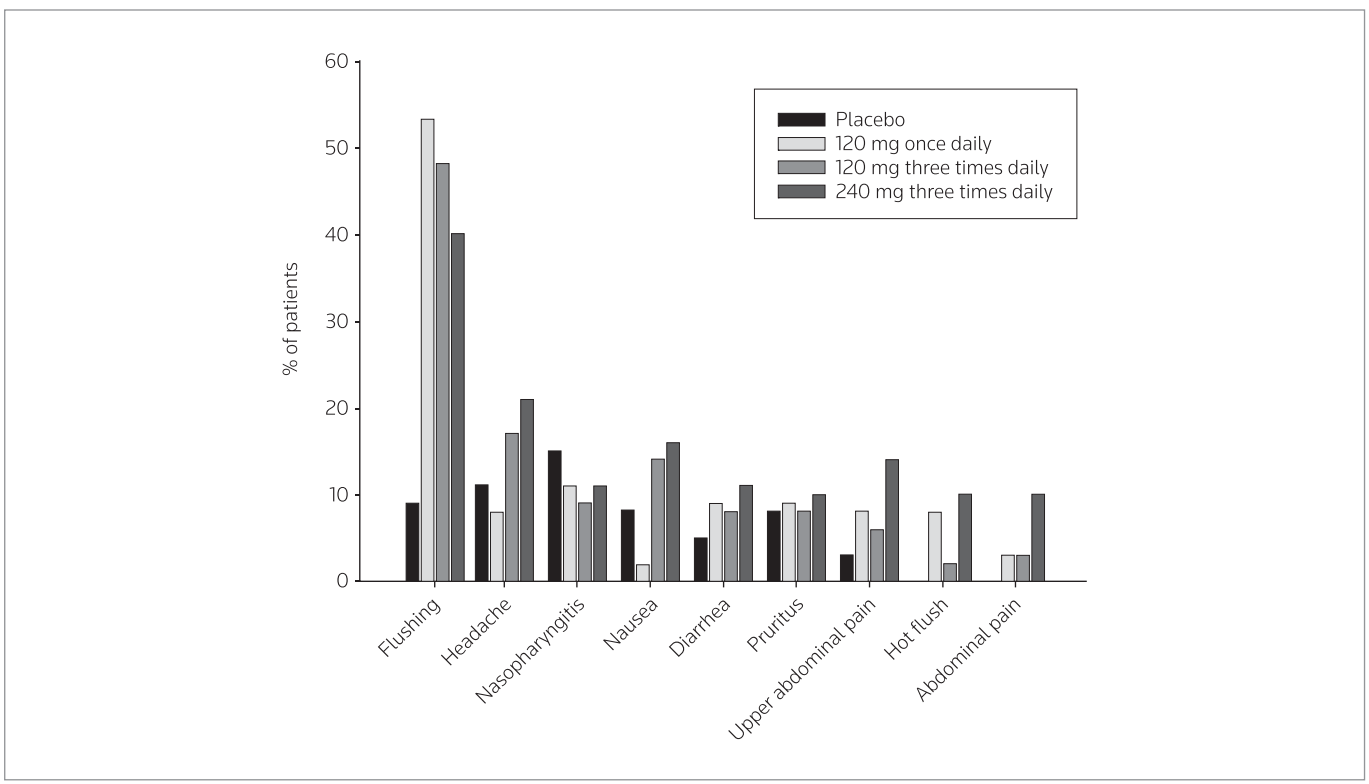

Figure 1. Adverse events of the placebo-controlled phase II study (30). The figure includes adverse events during the first 24 weeks. During this period, the patients were randomly assigned to four groups receiving placebo, oral BG-12 120 mg once daily, 120 mg BG-12 three times daily and 240 mg BG-12 three times daily, respectively. Only adverse events reported in 10% or more in any group were included.

Table III. *Summary of clinical studies in multiple sclerosis.*

Study type	Study year	Patients included	Main results	Reference/study name
Pilot study	2006	10	Reduction of Gd^+ lesions (98%*)	(31)
Phase II	2007	257	Gd^+ lesions: 69% reduction New or enlarging T2 lesions: 49% reduction Relapse rate: 32% reduction	(30)
Phase III	2007-2011	> 2,000	In progress	DEFINE/CONFIRM
Phase III	2009-2013	1,700 (subjects participating in and completing as per protocol DEFINE/CONFIRM studies)	In progress	–

*Post-hoc calculation from intraindividual observation in a crossover design.

high-dose tablets (Fumaderm®) confirmed these results, showing a reduction of 80% in the PASI (10).

An exploratory, prospective, open-label study with FAE (Fumaderm©, containing a mixture of DMF and MHF salts) included 10 patients with RR-MS (31). After a baseline run-in period, patients were treated for 18 weeks with 720 mg/day, followed by a 4-week washout period and another treatment phase with a reduced dose of 360 mg/day for 48 weeks. Inclusion criteria were an Expanded Disability Status Score (EDSS) of 2.0-6.0 and at least one gadolinium-enhancing (Gd^+) lesion on T1-weighted magnetic resonance imaging (MRI). The primary endpoint was the number and volume of Gd^+-enhancing lesions. Secondary clinical outcomes included ambulation index (AI), the nine-hole peg test (9-HPT) and a detailed cytokine profile. There was a significant reduction of 98% in the number and volume of Gd^+-enhancing lesions after the first treatment phase. Due to the small number of patients included, this was calculated post hoc from intraindividual observations in a crossover design. The effect persisted during the second treatment phase after the 4-week washout phase. A slight but nonsignificant improvement of AI and 9-HPT compared to baseline was observed. Immunological investigations revealed a small increase in IL-10 and a greater apoptosis rate of $CD4^+$ lymphocytes.

These promising results led to further systematic investigation of FAE in MS therapy (Table III). A multicenter, double-blind, placebo-controlled phase II trial in 257 RR-MS patients was designed to evaluate the safety, efficacy and dose range. In this study (30) the second-generation FAE, BG-12, consisting of DMF as a monosubstance (32, 33), was used. The patients were randomized into 4 groups treated either with placebo or BG-12 at different doses (120, 360 or 720 mg/day) for 24 weeks. The treatment phase was followed by another 24 weeks of a dose-blinded safety extension study where the placebo group received 720 mg/day. The primary endpoint was the total number of Gd^+-enhancing lesions on brain MRI scans at weeks 12, 16, 20 and 24. Secondary endpoints included the cumulative number of new Gd^+-enhancing lesions (weeks 4-24), new or enlarging T2-hyperintense lesions, new T1-hypointense lesions at week 24 and annualized relapse rate. A total of 235 of 257 randomized patients completed the first placebo-controlled phase (24 weeks) of the study and 219 also completed the dose-blinded extension phase. MRI scans showed a significant dose-dependent decrease in the number of Gd^+-enhancing lesions. In the 720 mg/day group there was a statistically significant reduction of 69% in the mean number of Gd^+-enhancing lesions, as measured by the combined monthly MRI scans between weeks 12 and 24. Moreover, this group had a reduction of 48% in newly enlarging T2-hyperintense lesions and a 53% reduction in newly T1-hypointense lesions compared to the placebo group at week 24. Finally, although the study was not designed to demonstrate such an effect, there was a trend towards a reduction of the annualized relapse rate of 32% in the 720 mg/day group.

In order to further investigate the long-term safety and efficacy of BG-12, two phase III studies are in progress: the DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS, NCT00420212) and the CONFIRM (Comparator and an Oral Fumarate in Relapsing-Remitting MS, NCT00451451) study. These trials started recruiting in 2007 and are expected to be completed in 2011. They are designed as international, multicenter, 2-year, randomized, double-blind, placebo-controlled, dose-comparison studies. The DEFINE study contains three groups in a ratio of 1:1:1 receiving BG-12 at a dose of 720 mg/day, 480 mg/day and placebo, respectively. The CONFIRM trial includes a fourth group treated with glatiramer acetate. The endpoints in both studies are the evaluation of relapse rate, progression of disability and various MRI parameters. Another phase III trial (NCT00835770) is enrolling patients from the above studies to evaluate the long-term safety and efficacy of BG-12 in RR-MS, with an estimated enrollment of 1,700 patients and an estimated completion date of June 2013.

DRUG INTERACTIONS

No drug interactions have been reported so far. Until now, no studies have been performed to investigate specific drug interactions.

SOURCE

Biogen Idec, Inc. (US).

DISCLOSURES

Dr. Stangel is an investigator in a clinical trial with BG-12. He has received research support and honoraria for lectures and travel expenses from Biogen Idec.

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