EDITED BY JEFFREY A. COHEN
AND RICHARD A. RUDICK

# MULTIPLE SCLEROSIS THERAPEUTICS

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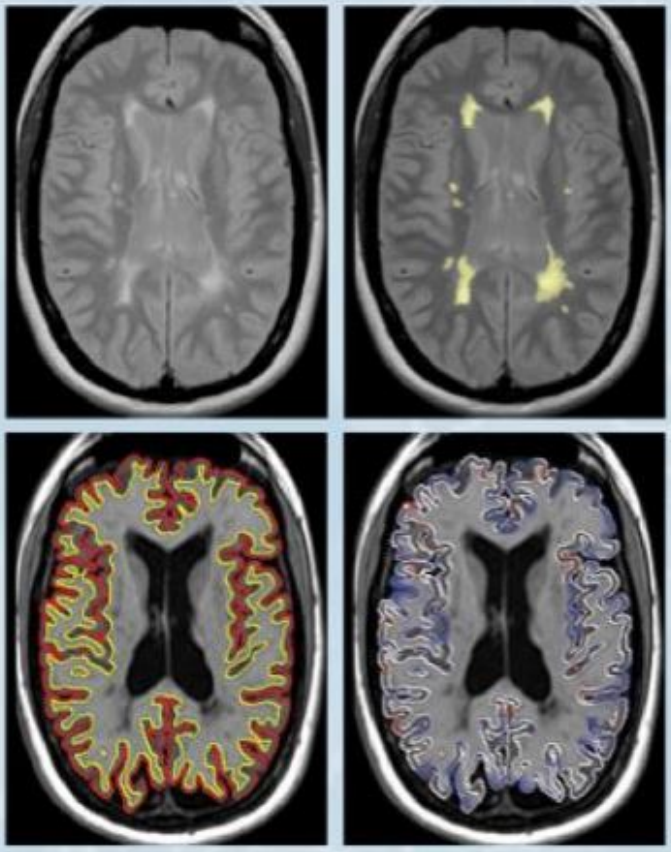

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Chapter 31

# Dimethyl fumarate to treat multiple sclerosis

Robert J. Fox and Ralf Gold

## Unmet need for multiple sclerosis therapies

For over 15 years, approved multiple sclerosis (MS) disease-modifying therapies were limited to parenteral routes of administration – subcutaneous, intramuscular, and intravenous modalities. These routes are not only unpleasant for patients because of needle-stick pain, but also lead to skin reactions such as rubor, pruritus, lipoatrophy, and rarely infection. Intravenous administrations are inconvenient because they require routine visits to an infusion center or with a home care nurse.

The US Food and Drug Administration approval of fingolimod in 2010 marked the beginning of a new period of oral MS treatment. In addition to fingolimod, at least four additional oral long-term MS disease-modifying therapies were in late Phase III trials in 2010. These oral therapies promise to lead to dramatic shifts in treatment patterns for relapsing forms of MS. As in any therapeutic area, a successful oral therapy will need to demonstrate convincing efficacy, reasonable safety, and convenience in administration. An emerging additional consideration for MS disease modifying therapies is their potential neuroprotective effects. MS is thought to be not only a neuroinflammatory disease, but also a superimposed neurodegenerative disease. The detailed interplay between these two pathophysiologies is not well understood, but one potential model is that neuroinflammation in the early years sets up a cascade of accelerated neurodegeneration in later years. Whatever the cause, a gradually progressive clinical disorder becomes manifest in the later years of the MS course, and this stage of MS has been uniformly recalcitrant to currently available immunotherapies. If new anti-inflammatory therapies are also effective against the neurodegenerative component of MS, they would meet a hitherto unmet need in MS therapeutics. Dimethyl fumarate is an oral therapy in development for MS which may meet these needs.

## History of fumaric acid

Fumaric acid is the common name of an unsaturated dicarbonic acid (Fig. 31.1). In turn, the salts of this acid are named fumarate. In the Krebs cycle, succinate is converted via a specific dehydrogenase into fumarate, which subsequently is metabolized to maleate. To date, there is no known disease which arises from inborn errors of this pathway.

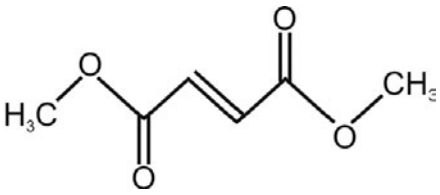


**Fig. 31.1.** Molecular structure of dimethyl fumarate.

In the late 1950s, the German chemist Walter Schweckendiek postulated that the pathogenesis of psoriasis vulgaris was due, at least in part, to a disturbed Krebs cycle. Thus, he aimed at modulating this pathway by exogenous administration of fumaric acid. He first used fumaric acid on his own psoriatic skin and preferred application as an ointment of fumaric ester. He continued studies on himself by swallowing fumaric esters and published its success in 1959.[1] Later, he used a combination of monomethyl fumarate and dimethyl fumarate (DMF), and by changing the galenic pharmacological formulation and adding a tablet coating, he achieved delayed release in the duodenum, leading to reduced side effects (Table 31.1). Further systematic studies demonstrated the efficacy of fumaric acids for the treatment of psoriasis.[2,3] The Swiss company Fumaderm obtained German regulatory approval in 1994 for this fumaric acid formulation (called Fumaderm) for treatment of severe psoriasis. Since then, Fumaderm is the preferred systemic treatment of severe psoriasis in German-speaking countries.[4] Thus, more than 100 000 patient–years of experience have accumulated with minimal serious complications. The mixture of these fumarate esters has been found safe for long-term therapy.

**Table 31.1.** *Constituents of fumaric acid preparations*

| | Fumaderm | BG00012 |
|---|---|---|
| Dimethyl fumarate | 120 mg | 120 mg |
| Ethylhydrogen fumarate Ca-salt | 87 mg | |
| Ethylhydrogen fumarate Mg-salt | 5 mg | |
| Ethylhydrogen fumarate Zn-salt | 3 mg | |

*Multiple Sclerosis Therapeutics, Fourth Edition*, ed. Jeffrey A. Cohen and Richard A. Rudick. Published by Cambridge University Press.

The successful use of fumaric acid in dermatology eventually led to its translational use in neurology. Since it was postulated that fumarates induce a so-called $Th_2$-shift,[5] Peter Altmeyer, dermatology chair at the Ruhr University of Bochum, inspired Horst Przuntek, his neurologist colleague, to test fumaric acids in active relapsing MS. From this study, the first small systematic observation on ten patients was published (see below), ultimately leading to a successful Phase 2 trial, the acquisition of Fumapharm by Biogen Idec, and finally the subsequent MS Phase 3 studies described below.[6]

## Mechanism of action of fumaric acid

### Immunomodulation

In the past, dermatological investigators performed a wide array of studies focusing on the adaptive immune system. During clinical trials a reduction of peripheral blood leukocytes, mainly CD4+ T-cells (up to 90%) and CD8+ T-cells (up to 53%), was observed as a putative consequence of apoptosis.[7] In addition, a shift from $Th_1$ to $Th_2$ cytokine production was also detected.[5] While levels of pro-inflammatory cytokines, tumor necrosis factor-alpha (TNFα) and interferon-gamma (IFNγ), levels were reduced, the levels of anti-inflammatory $Th_2$ type cytokines, namely interleukin (IL)-4, IL-5 and IL-10, were markedly increased.

In vitro experiments showed that an increased secretion of $Th_2$ cytokines up to ten-fold over normal was observed in CD45R0+ T-cells.[5] In addition, other blood cells were modulated. For example, dendritic cells, which play a central role in regulation of inflammatory processes, were down-regulated and secreted less IL-12. Apoptosis was also detected in dendritic cells.[5] Immunological effects of DMF were also observed in keratinocytes where major histocompatability complex class II gene products and the adhesion molecule, ICAM-1, were found to be down-regulated.[8,9] The immunomodulatory effects of DMF were shown to be functionally relevant in a rat model of organ transplantation, where transplant rejection was successfully modulated by fumarates.[10] Fumaric esters were shown to inhibit acute and chronic rejection in rat kidney transplantation models, providing further evidence of its immunosuppressant properties.[11]

Nonetheless, the molecular mechanisms of DMF have not been fully unraveled. In vitro studies in human endothelial cells have shown that DMF acts via transcriptional downregulation of TNF-induced genes as well as inhibition of TNF-induced nuclear entry of nuclear factor kappa B (NFκB).[12] DMF inhibits NFκB-dependent chemokines such as CXCL8, CXCL9 and CXCL10. Most studies involving the molecular effects of fumaric esters have focused on T-cells, and there is very little information available on their effects on B-cells.

### Neuroprotection

Recently, novel potentially neuroprotective effects of DMF were observed in rodent glial cells and neurons, both in vitro and in vivo.[13] Since an oral formulation of DMF had demonstrated beneficial effects on MRI markers of axonal destruction in a Phase 2 MS trial,[14] one of us (RG)[15] studied immune effects and potential axonal protection in experimental autoimmune encephalomyelitis (EAE) induced by immunization with myelin oligodendrocyte glycoprotein peptide.[16] In C57BL/6 mice, preventive DMF treatment given twice a day by oral gavage, afforded a significant beneficial effect on the EAE disease course and a strongly reduced macrophage inflammation in the spinal cord as revealed by histology.[17] Multiparameter cytokine analysis from blood detected an increase of IL-10, an anti-inflammatory cytokine, in the treated animals. Thus, the underlying biological activity of DMF in EAE appears to be complex.

We then studied chronic EAE using the same C57BL/6 mouse EAE model.[13] Treatment with DMF improved preservation of myelin, axons, and neurons (Fig. 31.2). In vitro, the application of fumarates increased neuronal survival and protected human astrocytes against oxidative stress. Additional studies evaluated the functional pathway of fumarates and found that application of fumarates led to direct modification of a protein called Kelch-like ECH-associated protein 1 (Keap-1) which is an inhibitor of nuclear-factor- E2-related factor-2 (Nrf2). This modification of Keap-1 caused stabilization of Nrf2, activation of Nrf2-dependent transcription, and a concomitant accumulation of prototypical Nrf2 target proteins. In turn, there was induction of several substances which enhance cellular resistance to free radicals such as glutathione and NAD(P)H dehydrogenate quinine 1 (NQO1). DMF treatment resulted in increased Nrf2 immunoreactivity in neuronal subpopulations, oligodendrocytes, and astrocytes. These DMF-mediated beneficial effects were completely abolished in Nrf2 deficient mice. Human autopsy studies have observed up-regulation of Nrf2 in MS lesions within the spinal cord lesions, suggesting that the Nrf2 pathway may be activated through the body's endogenous protective mechanisms. Altogether, these observations suggest that DMF treatment may be effective in tissue preservation and protection in MS. The ability of DMF to activate Nrf2 may thus offer a novel cytoprotective modality that is not known to be targeted by other MS therapies. Fig. 31.3 illustrates the putative mechanism through which DMF may exert immunomodulating and neuroprotective effects.

## Phase 1 clinical trial

Fumaric acids were first studied in MS in a Phase 1, open-label, baseline-controlled trial using the combination fumaric acid ester preparation Fumaderm. Ten patients with relapsing remitting (RR) MS and at least one relapse within the prior year were enrolled in the study. A 6-week untreated baseline phase was followed by an 18-week treatment phase, then a 4-week washout phase, and finally a second 48-week treatment phase. With each treatment phase, fumaric acid esters were titrated over 9 weeks. Primary efficacy outcome was the number and volume of triple-dose (0.3 mmol/kg body weight) gadolinium (Gd)-enhancing lesions.

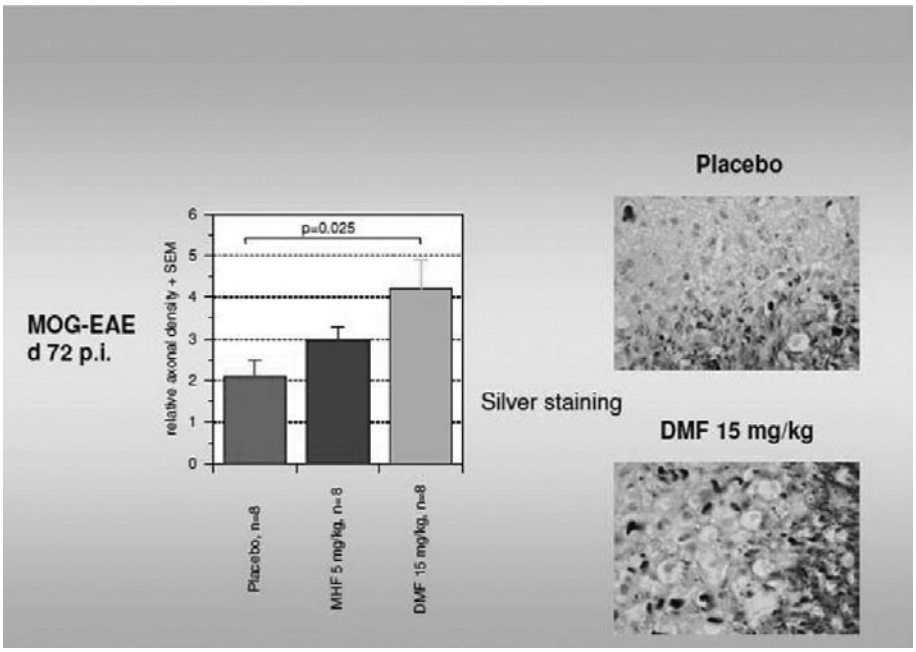


**Fig. 31.2.** Quantification of axonal density in EAE lesions of carrier-fed mice ("placebo"), or recipients of MHF or DMF. As illustrated in the Bielschowsky stain (right side) there are more black axonal profiles preserved under DMF treatment (see also color plate section).

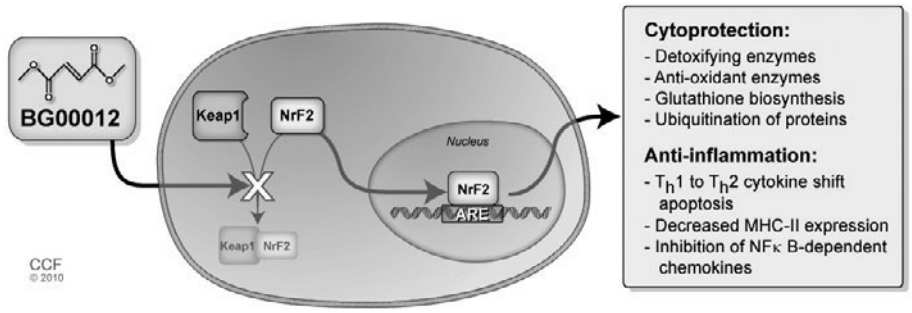


**Fig. 31.3.** Illustration of how dimethyl fumarate may exert both immunomodulatory and neuroprotective effects.

Of the ten patients enrolled, six completed the study. One patient each stopped because of unplanned pregnancy, gastrointestinal side effects, lack of compliance, and loss to follow-up. The most common adverse events were flushing and gastrointestinal symptoms (diarrhea, nausea, cramps), which were reported by almost all patients during the initial phase of the study. In general, symptoms improved over 6 weeks.

After 18 weeks of treatment, a significant reduction in Gd-enhancing lesions was observed. There were a mean of 11.3 Gd-enhancing lesions per patient at baseline, which decreased to 1.5 per patient at 18 weeks. Gd-enhancing lesions reduced further during the second treatment period, decreasing to a mean of 0.28 per scan per subject. The volume of Gd-enhancing lesions also decreased from 245 $mm^3$ at baseline, to 26.1 $mm^3$ at 18 weeks, to 2.1 $mm^3$ at 70 weeks. Clinical scores showed modest, non-significant improvements over the course of the study, including Expanded Disability Status Scale (EDSS), Ambulation Index, and nind-hole peg test. Two relapses were observed – one at week 18 and one at week 46. Immunologic studies on peripheral blood of these patients during the first 28 weeks showed similar findings to that from dermatology: an increase in IL-10 from CD4+ T-cells during treatment, as well as a transient increase in apoptosis of CD4+ T-cells. No change in IFNγ was observed over the course of treatment.

## Phase 2 clinical trial

Based upon the encouraging Phase 1 results, Fumapharm partnered with Biogen Idec to conduct a Phase 2 trial of DMF in RRMS. To improve gastrointestinal tolerability, they used only dimethyl fumaric acid (rather than the multiple fumaric acid esters which constitute Fumaderm) and employed enteric-coated microtablets. This preparation of DMF is currently designated BG00012.

The Phase 2, multicentered, placebo-controlled clinical trial was performed to provide proof-of-concept evidence of DMF's efficacy in relapsing MS.[14] In this trial, 257 RRMS patients were enrolled and randomized to one of four treatment groups: 120 mg BG00012 once daily (and matching placebo twice daily), 120 mg BG00012 thrice daily (360 mg daily dose), 240 mg BG00012 thrice daily (720 mg daily dose), and placebo thrice daily. One patient did not receive treatment, so all results were based upon 256 patients. The high-dose group was titrated to

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