Multiple sclerosis (MS) is a slowly progressive, immunologically mediated disease of the central nervous system characterised by inflammation and demyelination of white matter in the brain and spinal cord. In MS an autoimmune response is evoked that causes the body to attack its own myelin sheath which deteriorates to scleroses at multiple regions. It is the commonest progressive neurological disease worldwide. The disease incidence ranges from 2 to 10 per 100,000 population per year, with prevalence in US approximately 100 cases per 100,000 population and approximately 130 cases per 100,000 population in UK. There are no large scale epidemiological studies from India but Hospital-based studies in India, over the last decade have projected a prevalence of 3 per 100,000, supported by the Multiple Sclerosis International Federation World MS Atlas. The clinical course of MS is categorized into 4 patterns: Benign Multiple Sclerosis; Relapsing-Remitting Multiple Sclerosis (RRMS); Primary Progressive Multiple Sclerosis (PPMS); and Secondary Progressive Multiple Sclerosis (SPMS), with majority of patients (80%) suffering from RRMS. Classical symptoms of MS vary, ranging from optic neuritis (usually an early symptom), trigeminal neuralgia and constitutional symptoms, spinal cord symptoms like spasticity, autonomic dysfunction, cognitive changes and cerebellar symptoms like dysarthria, ataxia and tremors to hemiparesis or paraparesis.

In recent years, a number of oral agents have emerged as potential therapeutic options in MS, with beneficial effects demonstrated in large, multicentre phase III clinical trials. Dimethyl fumarate (DMF) marketed as Tecfidera® is a novel oral drug that has shown promise with respect to clinical efficacy and safety in relapsing MS patients, and was recently approved by the Food and Drug Administration (FDA). This review will clarify the role of DMF in the context of current MS treatment options by

INTRODUCTION

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summarizing relevant points on the pharmacologic properties, clinical trials, safety and tolerability of DMF.

**Table 1: Current treatment modalities for MS.**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Clinical application</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta</td>
<td>First line therapy in RRMS, treatment of SPMS</td>
<td>↓ T-cell proliferation and migratory potential  ↓ IFN-γ induced upregulation of MHC class II expression  ↓ production of pro-inflammatory cytokines  ↑ Production of anti-inflammatory cytokines</td>
</tr>
<tr>
<td>Interferon beta-1a (Rebif)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon beta-1a (Avonex)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon beta-1b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Betaseron&amp;Extavia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>First-line therapy in RRMS</td>
<td>Activation and tolerance induction in CNS antigen specific T cells  Induction of GA-reactive regulatory T cells that mediate local suppression  Secretion of neurotropic factors by GA-reactive T cells</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Treatment of active forms of RRMS and SPMS</td>
<td>Potent immunosuppressive agent  ↓ Proliferation of macrophages, B cells and T cells  ↑ T suppressor functions  ↑ apoptosis of B cells and other antigen-presenting cells  ↓ Production of pro-inflammatory cytokines</td>
</tr>
<tr>
<td>Monoclonal Antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natalixumab (Tysabri)</td>
<td>Reapproved in 2006 as monotherapy for treatment of MS</td>
<td>Binds to CD49, the alpha4 unit of antigen-4.  Prevents the adhesion between the endothelial cell and the immune cell  Block the migration of leukocytes in CNS</td>
</tr>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>Approved in 2010 as first oral disease-modifying agent for managing RRMS</td>
<td>Fingolimod-phosphate (active form) is a sphingosine 1-phosphate receptor (S1PR) modulator.  Inhibits egress of lymphocytes from lymph nodes and their recirculation.  Potentially reduces trafficking of pathogenic cells into the central nervous system.  May have direct effects on neural cells</td>
</tr>
<tr>
<td>Teriflunomide (Aubagio)</td>
<td>Approved in 2012 as an oral drug option for the management of RRMS</td>
<td>Is an immunomodulatory drug.  Inhibits pyrimidine de novo synthesis by blocking the enzyme dihydroorotate dehydrogenase.  Reduces the activity of high-avidity proliferating T lymphocytes and B lymphocytes and thus is likely to attenuate the inflammatory response to autoantigens in MS  Basic homeostatic functions of resting and slowly dividing cells appear to be preserved.</td>
</tr>
<tr>
<td>Glucocorticoids (as Disease</td>
<td>Intravenous pulse therapy for treatment of acute attacks</td>
<td>↓ T-activation  ↓ Production of pro-inflammatory cytokines  ↓ Adhesion of neutrophils to endothelial cells  ↓ production of anti-inflammatory cytokines  ↓ endothelial cell activation  Sealing of the blood brain barrier</td>
</tr>
<tr>
<td>modifying therapy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous Immunoglobulin</td>
<td>Second line therapy in RRMS</td>
<td>Anti-idiotype antibodies  Blockade of Fc receptors on phagocytes  ↑ production of anti-inflammatory cytokines  ↓ endogenous production of immunoglobulins  ↓ complement mediated effects</td>
</tr>
<tr>
<td>Other cytotoxic agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Escalating treatment in severe forms of MS</td>
<td>Immunosuppressive agents  ↓ activation, proliferation and differentiation of T cells and B cells  Immune shift from TH1 to TH2</td>
</tr>
<tr>
<td>Azathioprine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
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</tbody>
</table>
CURRENT TREATMENT MODALITIES FOR MULTIPLE SCLEROSIS

The National MS society has listed more than 136 ongoing clinical trials testing different treatments for Multiple Sclerosis. There are currently 9 FDA approved Disease Modifying Agents (DMDs) for relapsing forms of Multiple sclerosis. These include four preparations of Interferon-beta (Avonex, Rebif, Betaseron and Extavia), Glatiramer acetate (Copaxone), Mitoxantrone (Novantrone), Natalizumab (Tysabri) and the recently approved oral medications Fingolimod (Gilenya) and Teriflunomide (Aubagio) (Table 1). Out of these, only Interferon-beta (IFN-β), Glatiramir acetate, Mitoxantrone, and the very recently launched Natalizumab (Tysabri) are currently available in India.

DEVELOPMENT OF DIMETHYL FUMARATE (DMF)

Dimethyl fumarate (DMF) is the methyl ester of Fumaric acid (FAE) group of compounds that have been used in the treatment of psoriasis since 1959, originally introduced by the German chemist Schweckendiek. In 1994, a mixture of compounds consisting of DMF and three salts of Ethyl hydrogen fumarate (EHF) was developed and licensed in Germany in as an oral therapy for severe psoriasis under the brand name Fumaderm®. Over the past 15 years, there have been many clinical trials that demonstrated the immunomodulatory efficacy and safety of oral FAE in this indication. Due to its immunomodulatory potential, Biogen Idec, an American biotechnology company began an exclusive development and evaluation of DMF as a potential treatment for RRMS in 2003. Based on the positive results from 2 global clinical studies conducted, FDA approved DMF to be marketed as Tecfidera® capsules for the management of adults with RRMS on March 27, 2013.

MECHANISM OF ACTION OF DIMETHYL FUMARATE IN MS

Many research studies have supported the role of several immunological pathways in the pathogenesis of MS. T helper (Th) cells, specifically Th1 and Th17, are believed to play a crucial role. After activation of naïve (‘Th0’) cells, these cells get differentiated into Th1 and Th2 by the help of a protein Interleukin12 which is seen to be high in MS lesions. According to the pathogenesis, derived from the experimental autoimmune encephalomyelitis, autoreactive peripherally activated CD4+ T cells recognize autoantigens within the CNS parenchyma in the context of class II molecules of the major histocompatibility complex (MHC) expressed by both local glial antigen-presenting cells and dendritic cells, which commit T cells toward a ‘Th1’ phenotype. Th1 cells produce mainly pro-inflammatory cytokines like interleukin (IL)-2, tumour necrosis factor alpha (TNF-α) and interferon-gamma, (IFN-γ) cytokines which cause myelin disruption and further recruit additional unspecific inflammatory cells and specific antemyelin antibody-forming B cells that amplify tissue injury. In contrast, anti-inflammatory ‘Th2’ cells are characterized by the production of IL-4 and IL-5, and in part also IL-10 which positively modulate the outcome of the lesion. Antimyelin antibodies such as activated macrophages or microglial cells, dendritic cells and natural killer (NK) cells are believed to cooperate in producing demyelination.

Figure 1: Proposed mode of action of DMF on NFκB-regulated gene transcription.

![Figure 1](https://example.com/figure1.png)

Figure 2: DMF activates the transcription factor Nrf2 and induces Nrf2 target genes.

NQO1= NADPH (nicotinamide adenine dinucleotide phosphate) quinone oxidoreductase: prototypical Nrf2 target gene
HO1= Heme oxygenase-1: catalyzes the breakdown of heme into the antioxidant biliverdin
GCLC= Glutamate-cysteine ligase catalytic subunit – catalyses the rate limiting step in the synthesis of Glutathione, a powerful endogenous antioxidant

The exact mechanism of action by which the oral formulations of DMF and Mono methyl fumarate (MMF), its primary metabolite, exert their effects in MS is still unclear. In vitro experiments mimicking Multiple Sclerosis (model showing the effects of FAE in myelin oligodendrocyte glycoprotein induced experimental autoimmune encephalomyelitis) have indicated three
potential pathways of action: First, DMF has been able to switch the T-helper response from Th1 to Th2 phenotype. Whereas Th1 cytokine interferon gamma (IFN-γ) remains unaffected. DMF also inhibits NFκB translocation (Figure 1) that regulates the expression of a cascade of inflammatory cytokines, chemokines, and adhesion molecules. This affects different types of cells in the immune system (Table 2) and their counterparts like the endothelium. However at higher concentration DMF may induce apoptosis in all cell types. The second pathway indicated, is the activation of the nuclear factor E2-related factor 2 (Nrf2) mediated antioxidative transcriptional pathways via direct interaction of MMF with Kelch-like ECH-associated protein 1 (Keap 1) (figure 3). This ultimately raises the levels of the important intracellular antioxidant glutathione which has been shown to protect glial cells as well as neuronal cells against metabolic and inflammatory stress. On the other side, the Nrf2 is shown to have neuroprotective capabilities such as inhibition of excitotoxic and oxidative neuronal damage, BBB protection, and significant preservation of myelin and axonal integrity. Through the third pathway, DMF is shown to almost completely inhibit the TNF-induced CD62E, responsible for the accumulation of blood leukocytes at sites of inflammation by mediating the adhesion of cells to the vascular lining.

Table 2: Summary of the Effect of Dimethyl Fumarate in Different Cell Types.

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Cytokine/Signalling Effect</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cells</td>
<td>IL-10↑, IL-5↑</td>
<td>“TH1” “TH2” shift, HO-1↑ reduced CD4+, CD8+ numbers</td>
</tr>
<tr>
<td>PBMC</td>
<td>CXCL8, 9, 10↑, TNF-α↑, IL-10↑, IL-1RA↑, IL-4↑, IL-5↑</td>
<td>Superoxide anions↑</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>IL-12↓</td>
<td>Induce apoptosis, prevent cell differentiation</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td></td>
<td>TNFa↓, ICAM-1↑, E-selectin↑ VCAM-1↑</td>
</tr>
<tr>
<td>Glia cells</td>
<td>TNF-α↓, IL-1β↓, IL-6↓</td>
<td>NQO-1↑, cellular Glutathion↑, NO↓</td>
</tr>
</tbody>
</table>

**ADVERSE EFFECTS**

No serious adverse effects have yet emerged in the clinical trials demonstrating the efficacy of DMF in Multiple Sclerosis. The most common adverse events reported were gastrointestinal symptoms (diarrhea, cramps and nausea), mild increase in liver enzymes and flushing which usually decreased after the first 6 weeks of the treatment. In general, DMF appears to have a promising efficacy and safety profile. No evidence exists to suggest that this agent may have any clinically important drug interactions, given the lack of cytochrome P450 metabolism. A word of caution with DMF is it may decrease lymphocyte counts during the first year of treatment as reported in the clinical studies, but remain stable thereafter. Therefore patients taking DMF should have a complete blood count (CBC) before starting treatment to...
measure lymphocyte count and an annual follow up CBC investigation.

DMF has a Pregnancy Category C and there are to date no adequate studies of the safety of the drug in pregnant women. Therefore, it should only be used during pregnancy if the potential benefits outweigh any possible risks. Additionally, it is not known whether DMF is secreted into human breast milk and therefore should be avoided in lactating mothers.

**EFFICACY OF DMF (Tecfidera) IN MULTIPLE SCLEROSIS**

A first exploratory, prospective open-label study of Fumaric acid esters (FAE) in Multiple Sclerosis investigated the efficacy of the FAE compound Fumaderm (mixture of DMF and MHF salts) in 10 RRMS patients. The study showed significant decrease in number and volume of Gadolinium (Gd) – enhancing lesions after initiation of FAE therapy. This pilot study opened the way for further systematic investigations of FAE in Multiple Sclerosis.

The FDA approval of DMF is based on data from a robust clinical development program that include DEFINE (Determination of the Efficacy of Oral Fumarate in Relapsing-Remitting MS) and CONFIRM (Comparator and an Oral Fumarate in Relapsing- Remitting MS), 2 global phase III studies that enrolled more than 2,600 patients (Table 3). An on-going Phase III extension trial (ENDORSE) has been designed to evaluate long term (up to 5 years) efficacy and safety of dimethyl fumarate and is scheduled to be completed in June 2016.

**Table 3: Results of phase 3 trials in comparison to placebo.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arm</th>
<th>Annualized relapse rate reduction</th>
<th>Risk of relapse</th>
<th>Disability progression</th>
<th>Reduction in mean new or newly enlarging T2 lesions</th>
<th>Reduction in mean new T1 lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFINE</td>
<td>DMF twice daily</td>
<td>53%* (0.40-0.66)</td>
<td>HR 0.51</td>
<td>HR 0.62 (0.44-0.87)</td>
<td>85%*</td>
<td>72%*</td>
</tr>
<tr>
<td>DEFINE</td>
<td>DMF 3 times daily</td>
<td>48%* (0.39-0.65)</td>
<td>HR 0.50</td>
<td>HR 0.62 (0.44-0.87)</td>
<td>74%*</td>
<td>63%*</td>
</tr>
<tr>
<td>CONFIRM</td>
<td>DMF twice daily</td>
<td>44%*</td>
<td>Reduction 34%, P&lt;003</td>
<td>Reduction 21% NSS</td>
<td>71%*</td>
<td>57%*</td>
</tr>
<tr>
<td>CONFIRM</td>
<td>DMF 3 times daily</td>
<td>51%*</td>
<td>Reduction 45%, P&lt;0001</td>
<td>Reduction 24% NSS</td>
<td>73%*</td>
<td>65%*</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>29%, P&lt;02</td>
<td>Reduction 29%, P&lt;01</td>
<td>Reduction 7% NSS</td>
<td>Reduction 6% NSS</td>
<td>54%*</td>
<td>41%, P&lt;003</td>
</tr>
</tbody>
</table>

*P<0001 versus placebo

**DEFINE** was a randomized, double-blind, 2 year trial that enrolled patients aged 18 to 55 years with RRMS and a baseline Expanded Disability Status Scale (EDSS, a standard scale that measures disability) score of 0 to 5 and having had at least 1 relapse in the past 12 months or a Gadolinium-enhanced (Gd+) MRI lesion activity within 6 weeks of randomization. A total of 1,237 patients were randomly assigned to receive DMF 240 mg 3 times daily or 240 mg twice daily, or placebo. There was a significant reduction in the proportion of people on DMF who experienced relapses at 2 years, compared with those on inactive placebo. For those on the approved twice-daily dose, 27% experienced relapses versus 46% of those on placebo showing a 49% reduction in the risk of relapse. All secondary outcomes were also met in the DMF groups, including significant impact on disease activity detected...
with MRI, and reduction in the risk of confirmed progression of disability. The proportion of clinical or radiologic disease-free patients was significantly higher in both the DMF groups compared to placebo over the 2-year period. In the group receiving DMF twice daily and in the group receiving it 3 times daily, clinical/radiological disease-free progression was achieved in 63%/45% and 59%/39%, respectively, versus 39%/27% of patients in the placebo group. Both clinical and radiologic disease-free progression was achieved in 28% of those receiving DMF twice daily and in 26% of those receiving it 3 times daily, versus 15% of patients receiving placebo. The Annualized Relapse Rate (ARR) was also decreased in both groups compared to placebo (DMF twice daily, 53%, and 3 times daily, 48%). The proportion of those who progressed over two years was 16% for twice-daily DMF compared with 27% for placebo, a 38% reduction in the risk of disability.39

In the CONFIRM trial (similar to DEFINE), a total of 1,417 patients were randomly assigned to receive DMF240 mg 3 times daily, twice daily, placebo, or Glatiramer acetate 20 mg daily. There was a significant reduction in the average annual number of MS relapses (ARR) in the DMF groups compared with the placebo group. For those on the approved twice-daily and 3 times daily doses, ARRs were reduced by 44% and 51% respectively compared with placebo. Glatiramer also reduced the ARR significantly versus placebo (29%). Results for secondary endpoints included significant reductions in disease activity on MRI and in the proportion of patients experiencing relapses in the DMF groups compared with those in the placebo group. Disability progression was not reduced significantly in the DMF groups compared with the placebo group in this trial.40

DMF: POTENTIALLY THE BEST ORAL TREATMENT OPTION

DMF (Tecfidera) is the third FDA approved oral drug for MS following Fingolimod (Gilenya) and Teriflunomide (Aubagio). Most neurologists expect dimethyl fumarate to be the best oral option as Fingolimod now carries new safety recommendations against use in patients with heart disease41 and Teriflunomide can have negative effects on blood pressure, bone marrow and may cause significant birth defects if used during pregnancy. It now carries a black-box warning about an increased risk of hepatotoxicity.10 DMF on the other hand produces far milder side effects. On the efficacy side, Fingolimod cut patient’s relapse rate by about 54% in trials, Teriflunomide reduces frequency of relapses by about 30%. DMF was found to reduce that rate by 44% and 53% in the 2 major trials conducted.34

DMF is therefore expected to be preferred over Teriflunomide because of superior efficacy and to be preferred over Fingolimod because of superior safety.

APPROVED DOSAGE AND ADMINISTRATION

DMF marketed as Tecfidera capsules have been approved by the US FDA to be taken orally twice per day. The approved dosage is 240mg. The patient will initially be started with a reduced dose of 120 mg twice daily for a week and thereafter a maintenance dose of 240 mg twice daily. The medication can be taken with or without food, but taking it with food may reduce the risk of flushing.34

CONCLUSION

With the recent FDA approval, DMF has offered the MS community (especially patients with Relapsing forms of MS) a treatment with strong efficacy, additional antioxidant and neuroprotective benefits and a favorable safety profile in the convenience of a pill. It has recently been approved by European Union and Canada and is under evaluation by the regulatory agencies of Australia and Switzerland.

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Conflict of interest: None declared
Ethical approval: Not required

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38. Biogen Idec press release. Oral BG-12 (dimethyl fumarate) significantly reduced multiple sclerosis (MS) relapses and disability progression in DEFINE phase 3 clinical trial. October 21, 2011.Available at:


