Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20131239

New Drug Update

Dimethyl fumarate: a new oral treatment option for multiple sclerosis

Sarjana S. Atal[1]*, Shubham S. Atal[2]

[1]Senior Lecturer, Department of Pharmacology, Modern Dental College and Research Centre, Indore, Madhya Pradesh, India
[2]Assistant Professor, Department of Pharmacology, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India

Received: 12 October 2013
Accepted: 27 October 2013

***Correspondence to:**
Sarjana S. Atal,
Email: sarjanamantri@gmail.com

ABSTRACT

Multiple Sclerosis (MS) is a slowly progressive, immunologically mediated disease of the CNS. The recent years have witnessed great efforts in establishing new therapeutic options for multiple sclerosis. There is a clear need for more effective, safe and at the same time orally available treatment options. Here we review the recently approved drug Dimethyl fumarate (DMF, Tecfidera®) as a new therapeutic option for MS and its role in context to the existing oral treatment options for MS. Dimethyl fumarate is the methyl ester of fumaric acid and has been claimed to possess immunomodulatory properties and is already in clinical use as Fumaderm for severe systemic psoriasis. In addition, Dimethyl fumarate was also shown to act on the blood-brain barrier and exert neuroprotective properties via activation of anti-oxidative pathways and displayed beneficial effects in experimental autoimmune encephalomyelitis (EAE), a model mimicking many aspects of MS. Based on two global phase III studies. Dimethyl fumarate has been clinically proven to significantly reduce important measures of disease activity, including relapses and development of brain lesions, as well as to slow disability progression over time, while demonstrating a favourable safety and tolerability profile.

Keywords: Fumaric acid, Tecfidera, Multiple sclerosis, Immunomodulation, Neuroprotective effects

INTRODUCTION

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.[1] 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[2] and approximately 130 cases per 100,000 population in UK.[3] 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.[4] 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.[5]

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.[6] 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

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

Table 1: Current treatment modalities for MS.[8,9]

Agent	Clinical application	Mechanisms
Interferon beta Interferon beta-1a (Rebif) Interferon beta-1a (Avonex) Interferon beta-1b (Betaseron&Extavia)	First line therapy in RRMS, treatment of SPMS	↓ 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
Glatiramer acetate (Copaxone)	First- line therapy in RRMS	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
Mitoxantrone	Treatment of active forms of RRMS and SPMS	Potent immunosuppressive agent ↓ Proliferation of macrophages, B cells and Tcells ↑ T suppressor functions ↑ apoptosis of B cells and other antigen-presenting cells ↓ Production of pro-inflammatory cytokines
Monoclonal Antibodies Natalixumab(Tysabri)	Reapproved in 2006 as monotherapy for treatment of MS	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
Fingolimod (Gilenya)	Approved in 2010 as first oral disease-modifying agent for managing RRMS	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
Teriflunomide (Aubagio)	Approved in 2012 as an oral drug option for the management of RRMS	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.
Glucocorticoids (as Disease modifying therapy)	Intravenous pulse therapy for treatment of acute attacks	↓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
Intravenous Immunoglobulin	Second line therapy in RRMS	Anti-idiotype antibodies Blockade of Fc receptors on phagocytes ↑production of anti-inflammatory cytokines ↓endogenous production of immunoglobulins ↓complement mediated effects
Other cytotoxic agents Cyclophosphamide Azathioprine Methotraxate	Second line therapy in MS Escalating treatment in severe forms of MS	Immunosuppressive agents ↓ activation , proliferation and differentiation of T cells and B cells Immune shift from TH1 to TH2

CURRENT TREATMENT MODALITIES FOR MULTIPLE SCLEROSIS

The National MS society has listed more than 136 ongoing clinical trials testing different treatments for Multiple Sclerosis.[7] 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).[8,9] Out of these, only Interferon-beta (IFN-β), Glatiramir acetate, Mitoxantrone, and the very recently launched Natalizumab (Tysabri) are currently available in India.[10]

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.[11] 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.[12] 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.[13]

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.[14] 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.[15] 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,[16] 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 antimyelin antibody-forming B cells that amplify tissue injury.[17] 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.[17] Antimyelin antibodies such as activated macrophages or microglial cells, dendritic cells and natural killer (NK) cells are believed to cooperate in producing demyelination.[18]

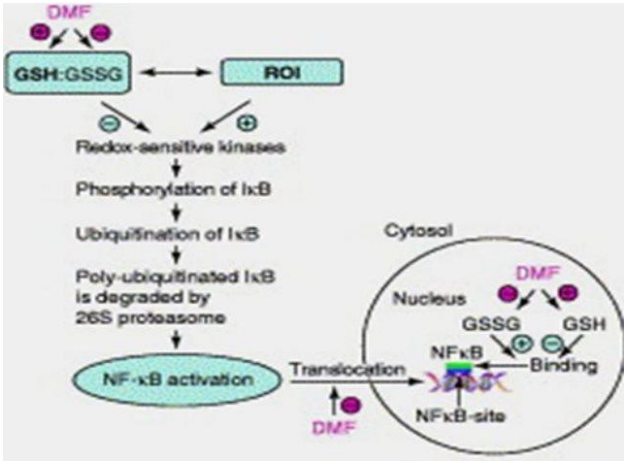

Figure 1: Proposed mode of action of DMF on NFκB-regulated gene transcription.

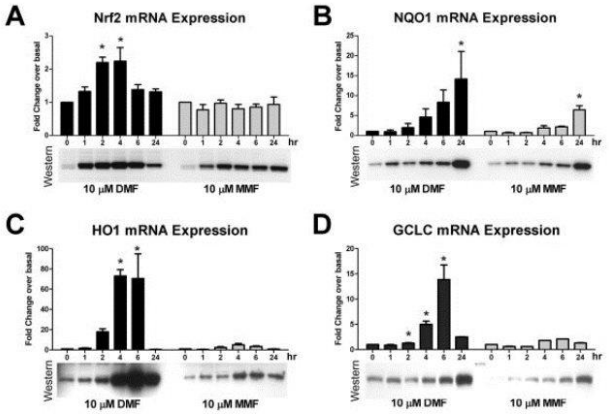

Figure 2: DMF activates the transcription factor Nrf2 and induces Nrf2 target genes.

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[19] have indicated three

potential pathways of action: First, DMF has been able to switch the T-helper response from Th1 to Th2 phenotype.[20] 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.[14] 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 (figure 2)[22] via direct interaction of MMF with Kelch-like ECH-associated protein 1(Keap 1) (figure 3).[23] 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.[24] On the other side, the Nrf2 is shown to have neuroprotective capabilities such as inhibition of excitotoxic and oxidative neuronal damage,[23] BBB protection, and significant preservation of myelin and axonal integrity.[25] 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.[26]

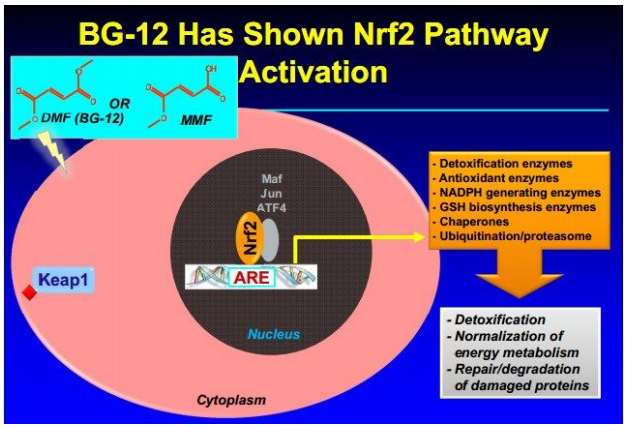

Figure 3: Diagrammatic presentation of activation of Nrf2 pathway by Dimethyl fumarate (BG-12).

Keap1 - Kelch-like ECH (erythroid cell–derived protein with CNC homology)–associated protein 1
ARE – Antioxidant Response Element

Table 2: Summary of the Effect of Dimethyl Fumarate in Different Cell Types.[14]

Cell type	Cytokine/Signalling Effect	Effect
T-cells	IL-10↑, IL-5↑	"TH1" "TH2" shift, HO-1↑ reduced $CD4^+$, $CD8^+$numbers
PBMC	CXCL8, 9, 10↓,TNF-α ↑,IL-10↑, IL-1RA↑,IL-4↑, IL-5↑	Superoxide anions↑
Dendritic cells	Il-12↓,	Induce apoptosis, prevent cell differentiation
Endothelial cells	prevent NF-κB translocation	TNFα↓, ICAM-1↑,E - selectin↑ VCAM-1↑
Glia cells	TNF-α↓, IL-1β↓, IL-6↓	NQO-1↑, cellular Glutathion↑, NO↓

PHARMACOKINETICS

After oral intake, DMF is completely absorbed in the small intestine[27] and is rapidly hydrolyzed by esterases to its most bioactive metabolite Mono methyl fumarate (MMF). MMF is further metabolized in the citrate cycle to carbon dioxide and water and finally eliminated mainly though breathing, while only small amounts of intact MMF are excreted through urine or feces.[28] The half-life of DMF and MMF are about 12 minutes and 36 hours, respectively, yet biological effects tend to last much longer. The peak concentration of MMF in human serum is reached 5 to 6 hours after oral intake. While MMF displays a protein binding of 50%, DMF does not show any binding activity to serum proteins which may further contribute to its rapid turnover in the circulation.[29] There is no evidence for a cytochrome P450-dependent metabolism in the liver.[30]

ADVERSE EFFECTS

No serious adverse effects have yet emerged in the clinical trials demonstrating the efficacy of DMF in Multiple Sclerosis.[31] 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.[32] 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.[33] 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.[34] Additionally, it is not known whether DMF is secreted into human breast milk and therefore should be avoided in lactating mothers.[35]

EFFICACY OF DMF (Tecfidera) IN MULTIPLE SCELROSIS

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.[32] 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).[35] 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.[36]

Table 3: Results of phase 3 trials in comparison to placebo.[35]

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

DMF, Dimethyl fumarate; HR, hazard ratio; NSS, not statistically significant
*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.[37] 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 disease[11] 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.

Funding: None
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Annapurna A, Krishna Kumar V, Murali Mohan RaoP, SomeswaraRao K and Rajasekhar J. Multiple Sclerosis: The disease and its treatment. Indian Journal of Pharmacology 2002; 34:3-15.
2. Olek M. Epidemiology and clinical features of multiple sclerosis in adults. 2013. Available at http://www.uptodate.com/contents/epidemiology-and-clinical-features-of-multiple-sclerosis-in-adults. Accessed 10 June 2013.
3. Pugliatti M, Rosati.G, Carton H, Riise T, Druvolic J, Vecsei L et al. The epidemiology of multiple sclerosis in Europe. European Journal of Neurology 2006, 13:700-22.
4. Neurological disorders: A public health approach. In: Neurological Disorders: Public Health Challenges. World Health Organization. Geneva, Switzerland: WHO Press; 2007. Available at http://www.who.int/mental_health/neurology/neurodiso/en/index.html. Accessed 2 August 2013.
5. Lublin F and Reingold S. Defining the clinical course of multiple sclerosis: Results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology.1996; 46:907–911.
6. Marriott J and O'Connor P. Emerging therapies in Relapsing-Remitting Multiple sclerosis. Rev Recent Clin Trials 2010; 5:179-88.
7. Loma I and Heyman R. Multiple sclerosis: Pathogenesis and treatment. Current Neuropharmacology 2011; 9:409-416.
8. FDA Approves oral Teriflunomide – Brand name Aubagio – as Disease Modifying therapy for Relapsing MS, 2012. Available at http://www.nationalmssociety.org/news/news-detail/index.aspx?nid=6864. Accessed 4 March 2013.

9. Update FDA approves Fingolimod – Brand Name Gilenya – First oral Disease Modifying Therapy for Relapsing MS- Now available by prescription, 2010. Available at http://www.nationalmssociety.org/news/news-detail/index.aspx?nid=3871. Accessed 4 March 2013.
10. Pandit L and Murthy J. Treatment of multiple sclerosis. Ann Indian Acad Neurol 2011; 14(l1):65–69.
11. AntonieR ,Kristian R and Almut B. Use of fumaric acid esters in psoriasis.Indian Journal of Dermatology, Venereology and Leprology 2007; 73(2): 133-137.
12. Mrowietz U and Asadullah K. Dimethylfumarate for psoriasis: more than a dietary curiosity. Trends in Molecular Medicine 2005; 11(1):43-48.
13. Biogen Idec's TECFIDERATM (Dimethyl fumarate) approved in US as a First-line oral treatment for Multiple sclerosis. Biogen Idec Press Release.2013 Mar 27. Available at http://www.biogenidec.com/press_release_details.aspx?ID=5981&ReqId=1801165. Accessed 5 March 2013.
14. Fransson M, Liljienfeldt L, Fagius J, Totterman T and Loskog A. The T-cell pool is anergized in patients with multiple sclerosis in remission. Immunology 2009; 126(1):92-101.
15. Hafler D. Multiple sclerosis. J Clin Invest. 2004; 113(6): 788–794.
16. Inglesea M. Multiple sclerosis: New Insights and Trends. AJNR May 2006, 27: 954-957.
17. Link H. The cytokine storm in multiple sclerosis. Multiple Sclerosis 1998, 4:12-15.
18. Steinman L. Multiple Sclerosis: a two-stage disease. Nature Immunology 2001, 2(9):762-64.
19. Schilling S, Goelz S, Linker R, Luehder F and Gold R. Fumaric acid esters are effective in chronic experimental autoimmune encephalomyelitis and suppress macrophage infiltration. Clinical and Experimental Immunology 2006, 145:101-7.
20. De Jong R, Bezemer A, Zomerdijk T, Van de Pouw-Kraan T, Oteenhoff T and Nibbering P. Selective stimulation of T helper 2 cytokine responses by the anti-psoriasis agent mono methyl fumarate. Eur J Immunol 1996, 26(9):2067-74.
21. Wilms H, Sievers J , Rickert U , Rostami-Yazdi M , Mrowietz U and Lucius R.Dimethylfumarate inhibits microglial and astrocytic inflammation by suppressing the synthesis of nitric oxide, IL-1β, TNF-α and IL-6 in an in-vitro model of brain inflammation. Journal of Neuroinflammation 2010, 7:30:1-8.
22. Scannevin R, Chollate S, Jung M , Shackett M, Patel H, Bista P, et al. Fumarates Promote Cytoprotection of Central Nervous System Cells against Oxidative Stress via the Nuclear Factor (Erythroid-Derived 2)-Like 2 Pathway . JPET 2012, 341:274–284.
23. Linker R, Lee D, Ryan S, Van Dam A, Conrad R , Bista P, et al. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. Brain 2011, 134(3):678-92.
24. Albrecht P , Bouchachia I, Goebels N, Henke N, Harald H, Issberner A et al. Effects of dimethyl fumarate on neuroprotection and immunomodulation. Journal of Neuroinflammation 2012,9:163:1-10.
25. Zhao J, Moore A, Redell J and Dash P. Enhancing expression of Nrf2-driven genes protects the blood brain barrier after brain injury. J Neurosci 2007; 27(38):10240-8.
26. Loewe R, Pilinger M, Martin R, Mrowietz U, Groger M , Holnthoner W et al . Dimethylfumarate inhibits Tumor-Necrosis-Factor-Induced CD62E Expression in an NF-KB-Dependent manner. The Journal of Investigative Dermatology 2001, 117(6):1363-68.
27. Werdenberg D , Joshi R, Wolffram S, Merkle H and Langguth P. Presystemic metabolism and intestinal absorption of antipsoriatic fumaric acid esters. Biopharm Drug Dispos 2003, 24(6):259-73.
28. Khiabani D, Linker R, Gold R and Stangel M. Fumaric acid and its esters: An Emerging treatment for Multiple Sclerosis. Curr Neuro pharmacol 2009, 7(1):60-64.
29. Lee D, Linker R and Gold R. Spotlight on Fumarates. The International MS Journal 2008, 15:12-18.
30. Mrowietz U, Christophers E and Altmeyer P. Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. The German Fumaric acid ester Consensus Conference. Br J Dermatol 1999, 141(3):424-9.
31. Phillips J and Fox R. BG-12 in Multiple Sclerosis. Semin Neurol 2013; 33:56–65.
32. Phillips J, Fox R, Miller D, Kita M, Hutchinson M, Havrdova E. et al. Safety and Tolerability of BG-12 in patients with Relapsing – Remitting Multiple Sclerosis (RRMS): Analyses from the CONFIRM study (S41.005).
33. Litjens N, Burggraaf J, Van Strijen E, Gulpen C, Mattie H , Schoemaker R et al. Pharmacokinetics of oral fumarates in healthy subjects. Br J Clin Pharmacol 2004, 58(4):429-32.
34. Gold R, Phillips J, Havrdova E, Bar-Or A, Kappos L, Yuan H et al. BG-12(Dimethyl Fumarate) and pregnancy: Preclinical and clinical data from the clinical development program. Neurology 2013.
35. Sobieraj D and Coleman C. Dimethyl fumarate: A fumaric acid ester under investigation for treatment of relapsing-remitting multiple sclerosis. Formulary 2012, 47:386-91.
36. ClinicalTrials.gov/. Long-term safety and efficacy study of oral BG00012 monotherapy in relapsing-remitting multiple sclerosis 2012.NCT00835770. Available at http://www.clinicaltrials.gov/ct2/show/NCT00835770?term=BG-12&rank=5/. Accessed 5 March 2013.
37. Gold R, Arnold D, Kappos L, et al. Baseline characteristics of patients in the DEFINE trial: A randomized, multicenter, double-blind, placebo-controlled, randomized, phase 3 study of BG-12 in relapsing-remitting multiple sclerosis. Neurology 2010; 74(9 Suppl 2):546–47.
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:

http://www.biogenidec.com/press_release_details.aspx?ID=5981&ReqID=1619878/. Accessed 5 April 2013.

39. Giovannoni G, Gold R, Kappos L, et al. BG-12 increases the proportion of patients free of clinical and radiologic disease activity in relapsing-remitting multiple sclerosis: Findings from the DEFINE study (PD5.005). Available at http://www.neurology.org/cgi/content/meeting_abstract/78/1_MeetingAbstracts/PD5.005/. Accessed 3 September 2013.
40. Fox R, Miller D, Phillips T, et al. Baseline characteristics of patients enrolled in a randomized, multicenter, placebo-controlled and active comparator trial evaluating efficacy and safety of BG-12 in relapsing-remitting multiple sclerosis: The CONFIRM trial. Neurology 2010; 74(9 Suppl 2):A549.

doi:10.5455/2319-2003.ijbcp20131239
Cite this article as: Atal SS, Atal SS. Dimethyl fumarate: a new oral treatment option for multiple sclerosis. Int J Basic Clin Pharmacol 2013;2:849-56.