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New Drug Update

Dimethyl fumarate: a novel drug for multiple sclerosis

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ABSTRACT

Dimethyl fumarate (DMF) is a novel oral immunomodulatory and neuroprotective drug that was approved by FDA for relapsing forms of multiple sclerosis (MS). The initial use of DMF was for the treatment of psoriasis where its long-term use was safe and efficacious, and it also got German approval for the same. It was found that the anti-inflammatory actions of DMF contributed to its efficacy in psoriasis. This anti-inflammatory action of DMF created interest using DMF in other auto-immune or inflammatory diseases, including MS. DMF acts by decreasing production and release of inflammatory molecules. DMF also activates the nuclear factor-erythroid 2 related factor pathway which induces the transcription of various genes, including anti-oxidative ones, reduces oxidative neuronal death and helps maintain myelin integrity. Thus, DMF acts via two pathways: by down-regulating oxidative stress and corresponding cellular injury, as well as by inhibiting pro-inflammatory cytokines. DMF is an orally administered, enteric-coated microtablet preparation. There was a 44-53% reduction in annualized relapse rate with the use of DMF in patients with relapsing form of MS. The most common adverse reactions reported are flushing, abdominal pain, diarrhea, and nausea, which are more prominent during initial treatment and usually decrease over time. No serious adverse events were seen during the phase II and III trials, including no increased risk of opportunistic infections or cancer. DMF seems to approach the ideal combination of safety, efficacy and well-tolerability to other approved oral therapies for MS.

Keywords: Dimethyl fumarate, Fumaric acids, Multiple sclerosis, Nuclear factor-erythroid 2-related factor 2

INTRODUCTION

Dimethyl fumarate (DMF) is a novel oral immunomodulatory and neuroprotective drug which was approved by FDA for relapsing forms of multiple sclerosis (MS) and by EMA for adult patients with relapsing-remitting MS (RRMS).[1,2] The initial use of DMF was for the treatment of psoriasis where its long-term use was safe and efficacious, and it has also got German approval for the same. It was found that the anti-inflammatory actions of DMF contributed to its efficacy in psoriasis. This anti-inflammatory action of DMF created interest using DMF in other auto-immune or inflammatory diseases including MS.[3]

MS is an inflammatory demyelinating disease of axons in central nervous system. Although the cause of MS is unknown, accumulating evidence suggests that it is an autoimmune disorder mediated by autoreactive myelin-specific CD4+T cells.[4] DMF is one of the drugs for MS given by oral route. There are other approved drugs such as teriflunomide and fingolimod, which can also be given by oral route for the treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and delay the accumulation of physical disability.[5,6] There are many approved drugs, which can be given by parenteral route such as beta-interferons, glatiramer acetate, natalizumab other than the drugs administered by oral route for MS.[7] The ideal drug for treatment should control symptoms, decrease the frequency of exacerbations, slow down or stop the progression of the disease, reverse pre-existing neurological damage, improve the patient's quality of life and have excellent safety profile.[7] The course of MS has a wide variation and unpredictability. MS is categorized into four different classes depending on course of the disease as follows:[8]

1. RRMS
   RRMS consist of 80-85% of patients with MS. It is characterized by unpredictable relapses or deterioration of symptoms as well as appearance of new symptoms.
2. Secondary progressive MS
   It is characterized by progressive stage of disease after long period of relapsing-remitting disease.

3. Primary progressive MS
   The patients with primary progressive MS have gradual deterioration with relatively little inflammation. The primary progressive form comprises of about 15% patients with a diagnosis of MS.
4. Progressive relapsing MS
   Progressive relapsing form is least common form of MS and is characterized by disease that develops from beginning with deterioration of symptoms. The primary progressive form comprises of about 5% patients with a diagnosis of MS.

There are a number of approved therapies for relapsing MS given in Table 1 along with their corresponding pharmacologic category and adverse drug reactions.

MECHANISM OF ACTION

DMF is an ester of fumaric acid, which is rapidly hydrolyzed to monomethyl fumarate (MMF). The exact mechanisms of action of DMF are not fully known. However, the detoxification and anti-inflammatory capabilities of DMF are responsible for its beneficial effects in RRMS (Figure 1).

PHARMACOKINETICS

DMF is available as a delayed-release capsule. After oral intake, DMF is rapidly hydrolyzed pre systemically by esterases within the alkaline environment of a small intestine to form its biologically active metabolite, MMF. As DMF is rapidly hydrolyzed into MMF, which can be detected in serum 60 mins after oral DMF ingestion and this metabolite is responsible for all pharmacological effects. In fasting healthy individuals, MMF is estimated to have peak serum levels (mean 6 μM, range 3-10 μM) at about 3 hrs after 120 mg of oral DMF (95 mg of MMF). There is variability in serum MMF concentrations after consumption of DMF with fatty meals although AUC remains same. MMF is further metabolized through the tricarboxylic acid cycle to form water and carbon dioxide, carbon dioxide being excreted through respiration. Small amounts of non-metabolized MMF are excreted through urine and faeces.[10]

COMPARATIVE EFFICACY OF DMF IN VARIOUS CLINICAL TRIALS

On the basis of encouraging results of phase II trial results, two phase III trials were conducted:

- Determination of the efficacy and safety of oral fumarate in RRMS (DEFINE)
- Comparator and an oral fumarate in RRMS (CONFIRM).

Both DEFINE and CONFIRM were 2 years, randomized, placebo-controlled trials, evaluating clinical relapses, progressive disability, and MRI disease activity in a subset of patients. The DEFINE study enrolled and dosed 1234 patients from North and Central America, Europe, and Asia who were randomized to two different doses of DMF 240 mg 3 times daily orally (720 mg/day) and 240 mg twice daily orally (480 mg/day with placebo given for mid-day dose) and were compared with placebo given 3 times a day in an intent to treat cohort.[11]

The primary outcome of DEFINE trial annualized relapse rate (ARR) decreased by 53% with DMF twice daily and by 48% with DMF 3 times daily compared with placebo (p=0.001) at 2 years. Proportion of relapsing patients at 2 years in the intent-to-treat cohort was 27% in the twice-daily group and 26% in the 3-times-daily DMF groups who had at least one relapse, compared with 46% in the placebo group (p=0.01, for both comparisons) based on Kaplan–Meier estimates.[11]

The CONFIRM study enrolled and dosed 1417 (including the additional Glatiramer acetate arm) from North and Central America, Europe, and Asia who were randomized in four groups. Group 1 was treated with oral DMF 240 mg twice daily along with mid-day placebo given orally and an injection of placebo subcutaneously. Group 2 patients were given oral DMF 240 mg 3 times daily along with subcutaneous injection of placebo and Group 3 patients were administered injection glatiramer acetate 20 mg once daily

Table 1: FDA approved drug therapies for relapsing MS.[9]

Drug	Pharmacologic category	Adverse effects
Fingolimod	Sphingosine 1-phosphate receptor modulator	GI upset, back pain, cough, elevated liver enzymes
GA	Immunomodulator	Injection-site reactions, palpitations, allergic reaction, lipoatrophy
IFN-β-1a	Interferon	Flu-like symptoms, injection-site reactions, depression, hepatic dysfunction and rarely anaemia, lymphopenia, thrombocytopenia
IFN-β-1b	Interferon	Flu-like symptoms, injection-site reactions, depression, hepatic dysfunction and rarely anaemia, lymphopenia, thrombocytopenia
Natalizumab	Monoclonal antibody, selective adhesion molecule inhibitor	Infusion reactions, progressive multifocal leukoencephalopathy
Teriflunomide	Dihydro-orotate dehydrogenase inhibitor	GI upset, hair thinning, leukopenia, elevated liver enzymes

GI: Gastrointestinal, MS: Multiple sclerosis, IFN-β-1a: Interferon beta-1a, GA: Glatiramer acet

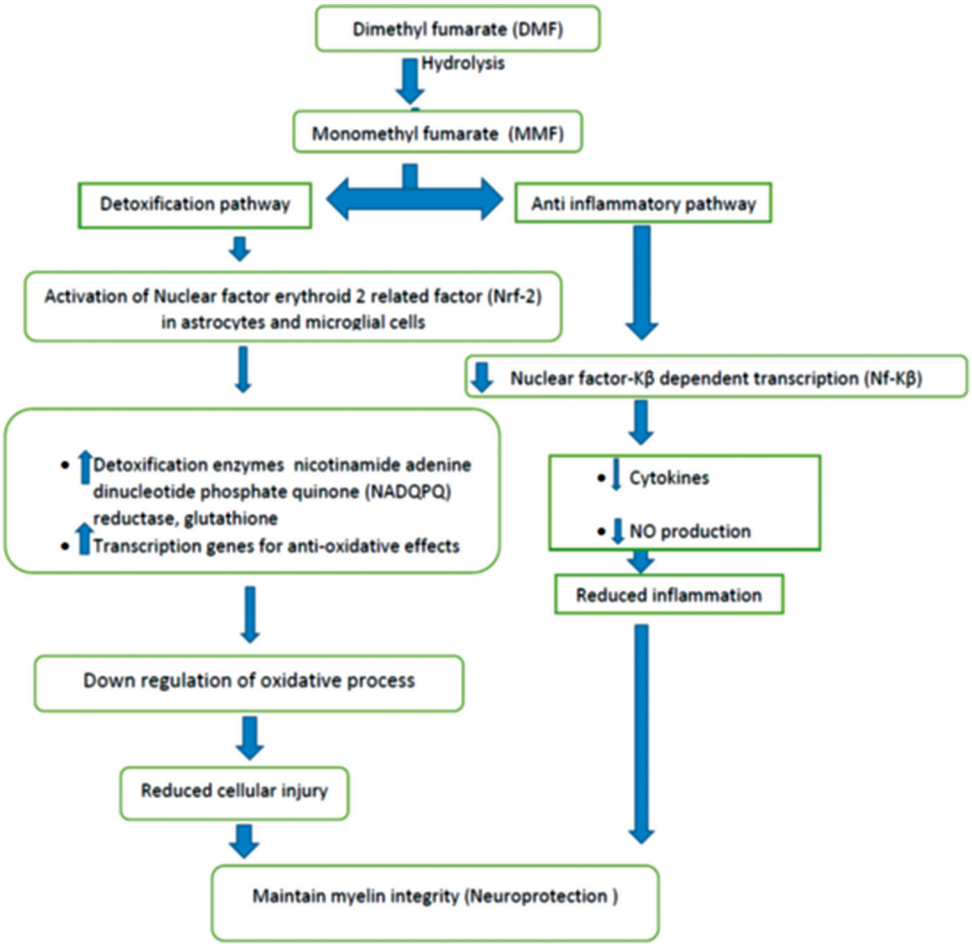

Figure 1: Mechanism of action of dimethyl fumarate.

subcutaneously and placebo orally 3 times a day whereas Group 4 was given placebo orally three times a day along with injection of placebo sub cutaneously for 96 weeks.[11]

The ARR in CONFIRM trial decreased by 44% with DMF twice daily and by 51% with DMF 3 times daily compared with placebo (p=0.001) at 2 years in the intent-to-treat cohort. Glatiramer acetate decreased the ARR by 29% (p=0.01 vs. placebo). Based on Kaplan-Meier estimates, 29% of patients in the twice-daily DMF group, 24% in the 3-times-daily DMF group, and 32% in the glatiramer acetate group had at least one relapse, compared with 41% in the placebo group.[11]

Both DEFINE and CONFIRM trials showed DMF to be more effective than placebo in decreasing the relapse rate in patients with RRMS over 2 years. Both dosages of DMF produced similar improvements and appeared more effective than glatiramer acetate therapy. Table 2 gives details of efficacy of FDA-approved drugs for RRMS.

Adverse reactions

The most common adverse reactions reported are flushing (40%), abdominal pain (18%), diarrhea (14%), and nausea (12%). Flushing symptoms range from mild to moderate severity manifesting as warmth, redness, itching, which are more prominent during initial treatment and usually decrease over time. Flushing led to discontinuation of therapy in 3% of patients.[11]

The incidence of serious gastrointestinal adverse events was 1%. There were episodes of abdominal pain, diarrhea and nausea. These adverse events can be reduced by administering the drug with meals.[11]

Hepatic transaminases were elevated in few patients, primarily during the initial 6 months of treatment. Most of the patients had concentrations <3 times the upper limit of normal hepatic transaminases. The therapy was discontinued in <1% in both DMF and placebo group due to elevated hepatic transaminase levels.[11]

Transient increases in mean eosinophil counts were reported during the first 2 months of therapy. DMF was found to be associated with lymphopenia. DMF decreased mean lymphocyte counts by approximately 30% during the 1st year of treatment in clinical trials, and then remained stable. Lymphocyte count increased in 4 weeks after discontinuation of therapy, but did not return to baseline. The incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in both groups treated with DMF and placebo, respectively. Both DEFINE and the CONFIRM studies have

Table 2: Efficacy comparison of phase III trials of various FDA approved drugs for RRMS.

Drug	Study	Route	Patients	ARR (% decrease compared to placebo)
DMF	Gold et al.[12] Three arms (104 weeks duration)	Oral		
	Placebo: tds		123	0.92
	DMF 240 mg: bid+placebo: od		125	0.8
	DMF 240 mg: tds		124	0.66
Fingolimod	Kappos et al.[13] Three arms (104 weeks duration)	Oral		
	Placebo: od		418	0.4
	Fingolimod 0.5 mg: od		425	0.18
	Fingolimod 1.25 mg: od		429	0.16
GA	Johnson et al.[13] Two arms (104 weeks duration)	S/C		
	Placebo: od		126	0.84
	GA 20 mg: od		125	0.59
IFN-β-1b	Jacobs et al.[13] Two arms (104 weeks duration)	I/M		
	Placebo: od		143	0.9
	IM-IFN 30 mg: od		158	0.61
IFN-β-1b	Paty et al.[13] Three arms (156 weeks duration)	S/C		
	Placebo: od		123	0.92
	IFN-β 0.05 mg: od		125	0.8
	IFN-β 0.25 mg: od		124	0.66
Natalizumab	Polman et al.[14] Two arms (116 weeks duration)	I/V		
	Placebo: od		627	0.73
	Natalizumab 300 mg: od		942	0.23
Teriflunomide	O'Connor et al.[15] Three arms (108 weeks duration)	Oral		
	Placebo: od		363	0.54
	Teriflunomide 7 mg: od		365	0.37
	Teriflunomide 14 mg: od		368	0.37

GA: Glatiramer acetate, IFN-β-1a: Interferon beta-1a, RRMS: Relapsing remitting multiple sclerosis, DMF: Dimethyl fumarate

similar incidence of infections in DMF and placebo groups. The incidence of infection in DEFINE study was 65% in the placebo group, 64% in the twice daily DMF group and 68% in the 3-times-daily DMF group. The commonly seen infections in DEFINE trials were nasopharyngitis, upper respiratory tract infection, urinary tract infection, and influenza. CONFIRM study has shown the incidence of infection to be 50% in the placebo group, 65% in the DMF group and 50% in the glatiramer acetate group. The commonly seen infections in the CONFIRM trial were nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, sinusitis, and gastroenteritis.[11]

Contraindications

There are no contraindications reported till now.[1]

Warnings and precautions

A recent (within 6 months) complete blood count (CBC) is must before initiating therapy to identify patients with pre-existing low lymphocyte counts. Routine CBC is recommended throughout the treatment. DMF therapy should be withheld if the patient develops a serious infection.[1]

DMF is classified in pregnancy category C and should only be used during pregnancy if the anticipated benefit overweight the risk to the fetus. A pregnancy registry monitors outcomes in women who are treated with DMF during pregnancy and such patients should be encouraged to register in Tecifedra Pregnancy Registry.[1]

It is not known yet whether DMF or MMF is excreted in human milk, and caution should be exercised if the drug is used by a lactating mother. The effectiveness and safety of DMF in pediatric patients are also not known yet.[1]

Drug interactions

No drug-drug interactions have been identified.[1]

Dosing

The recommended starting dosage of DMF is 120 mg orally twice a day for 7 days. The dosage is then increased to the recommended maintenance dosage of 240 mg orally twice a day. DMF can be administered with or without food. However, the incidence of flushing is reduced on administration with meals.[1]

Storage conditions

DMF was approved by FDA in March 2013 as Tecfidera, is available as a hard gelatin delayed release capsule containing 120 or 240 mg of DMF. It is recommended to be stored at 15-30°C. The capsules must be stored in the original packing and protected from light. Once the pack is opened, the contents should be used within 90 days.[1]

CONCLUSION

In spite of all the advances in treatment options for RRMS, there is a need for an effective, safe and well tolerated MS disease modifying therapy. DMF seems to approach this ideal combination, with comparable efficacy to other approved oral therapies for MS. Over 20 years of extensive clinical experience with the fumaric acid in psoriasis suggests that DMF should have strong long-term safety. The mechanisms of DMF action are unique and appear to involve both immunomodulatory as well as separate neuroprotective components. Altogether, DMF appears to be a very promising and ideal addition to the therapeutic options for relapsing remitting MS.

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