Dimethyl fumarate for relapsing-remitting multiple sclerosis

Steve Chaplin BPharm, MSc, Klaus Schmierer PhD, FRCP

Dimethyl fumarate is the third oral disease-modifying treatment for people with RRMS. Steve Chaplin presents the data relating to its efficacy and adverse events and Klaus Schmierer outlines its place in therapy.

**KEY POINTS**
- dimethyl fumarate (Tecfidera) is licensed for the treatment of adults with relapsing-remitting multiple sclerosis
- it has anti-inflammatory properties but its mechanism of action is uncertain
- the recommended dosage is initially 120mg then 240mg twice daily orally with food
- a month’s treatment on the maintenance dose costs £1373
- compared with placebo, it significantly reduced relapse rates and new brain lesions after two years’ treatment
- a reduction in disability progression has not consistently been shown in the two pivotal phase 3 trials, although post hoc analyses suggest such an effect
- common adverse effects include flushing and gastrointestinal events, low white cell count, pruritus, rash and proteinuria

**Dimethyl fumarate**

DMF has been licensed by the EMA and FDA for treatment of adults with RRMS. Its mechanism of action is uncertain but appears to be mediated via activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway, promoting anti-inflammatory activity and inhibiting pro-inflammatory cytokines and adhesion molecules.

Treatment is initiated at a dosage of 120mg twice daily with food, increased to 240mg twice daily after one week. Renal and hepatic function should be assessed before treatment, after three and six months, and then every six to 12 months. DMF may decrease the lymphocyte count; a full blood count is recommended before treatment, after six months, and then every six to 12 months.

No dose adjustment is recommended for the elderly, nor in patients with impaired renal or hepatic function, however DMF should be prescribed with caution in older people. It is contraindicated in patients with severe renal or hepatic impairment or severe active gastrointestinal disease, and during pregnancy.

**Clinical trials**

Two phase 3 trials have compared DMF 240mg twice daily with placebo: DEFINE (n=1234) and CONFIRM (n=1417). Both trials included a three times daily treatment arm, but only data for the twice daily
dose are discussed here. CONFIRM included GLAT 20mg per day as a ‘reference’ but was not designed to assess whether DMF was superior or non-inferior.

Both trials included patients aged 18–55 with RRMS, and a score of ≤5 on the Expanded Disability Status Scale (EDSS), plus at least one clinically documented relapse in the previous 12 months or at least one gadolinium-enhancing lesion up to six weeks before randomisation. The primary endpoint of DEFINE was the proportion of patients who had a relapse by two years; for CONFIRM, it was the annualised relapse rate (ARR) at two years. About 20 per cent of patients in each study discontinued treatment.

In DEFINE, relapses occurred in significantly fewer patients treated with DMF (27 vs 46 per cent with placebo; \(p<0.001\)); the ARR after two years was 0.17 compared to 0.36 with placebo (\(p<0.001\)). DMF prolonged the time to first relapse (87 vs 38 weeks with placebo in the 25th percentile of patients) and reduced the risk of confirmed disability progression over two years (hazard ratio 0.62, 95 per cent CI, 0.44–0.87; \(p=0.005\)). On MRI, DMF reduced the mean numbers of new or enlarging T2-weighted lesions at two years (2.6 vs 17.0 with placebo) and gadolinium-enhancing T1-weighted lesions (0.1 vs 1.8).

In CONFIRM, the ARR was 0.22 with DMF and 0.40 with placebo (\(p<0.001\)); the ARR for GLAT was 0.29. The proportions of patients with relapse after two years were 29, 41 and 32 per cent, respectively. Neither DMF nor GLAT significantly reduced disability progression at six months. The mean number of new or enlarging T2-weighted lesions on MRI at two years was reduced by DMF (3.0 vs 7.0 with placebo; 4.1 with GLAT); it also reduced the number of gadolinium-enhancing lesions on T1-weighted MRI (0.5 vs 2.0; 0.7 with GLAT).

**Adverse events**
The most frequently reported adverse events are flushing (affecting one third of

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patients vs 4 per cent with placebo), diarrhoea, abdominal pain and nausea (10–14 per cent vs 6–10 per cent with placebo). These usually begin in the first month of treatment and intermittently thereafter, causing 3–4 per cent of patients to stop treatment. Flushing and adverse gastrointestinal effects may be reduced by lowering the dosage to 120mg twice daily for up to one month. Other common adverse events include low white cell count (not associated with an increased risk of infection), pruritus, rash, proteinuria and raised liver enzymes.

References

Declaration of interests
Steve Chaplin has none to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics

Place in therapy

Klaus Schmierer

DMF is a welcome addition to the new batch of disease-modifying treatments (DMTs) for people with RRMS. It is the third oral DMT available to patients on the NHS, and the second first-line DMT following the recent release of teriflunomide (fingolimod is licensed only for RRMS failing treatment with first-line injectable DMT).

DMF reduces the relapse rate across a broad spectrum of people with RRMS, however its potential is probably greatest in recently diagnosed patients, ie not in people with rapidly evolving or highly active RRMS, for whom other treatments (natalizumab, alemtuzumab) will be more appropriate.

While there is unequivocal evidence for a significant effect on relapses (about 50 per cent reduction relative to placebo), efficacy on disability endpoints has so far been less convincing and awaits confirmation following longer term observation. However, taking into account the significant effect of DMF on relapses and MRI predictors of disability, such as the number of T2 hypo-intense lesions (‘black holes’), and brain atrophy (30 per cent relative reduction compared to placebo between months 6 and 24), it is likely that DMF will also be effective in limiting disability progression. The data collected so far suggest that DMF is more effective than GLAT and – albeit not compared directly – beta-interferons. It is therefore likely that the use of first injectable DMT (GLAT and beta-interferons) will diminish substantially.

Key adverse effects of DMF are flushing, abdominal pain, diarrhoea, nausea, pruritus, proteinuria and lymphopenia. Although these appear manageable in most cases, and gastrointestinal side-effects diminish over about one month, one should expect that about 20 per cent of patients will not tolerate DMF long term.

The twice-daily dosing frequency is a slight disadvantage compared to drugs that need to be taken only once daily. However, neither this minor inconvenience, nor the overall modest side-effect profile are likely to impact on the uptake by UK neurologists eager to prescribe DMF to their patients with RRMS.

As this article goes into press a case of progressive multifocal leukencephalopathy (PML) has been reported in a patient with MS who eventually died of pneumonia. Apparently, the patient had been taking DMF for more than five years and developed significant long term lymphopenia. Lymphopenia is a known risk factor for PML, and our empiric advice at this stage would be to prevent the lymphocyte count in patients treated with DMF from dropping lower than 0.8x10⁹ per litre (WHO grade 1–2 toxicity).

References

Declaration of interests
Dr Schmierer has received speaker fees and honoraria from, and/or served on advisory boards for Novartis, Biogen, Teva, Merck-Serono and Merck Inc, and has received travel support from Genzyme.

Reader in Clinical Neurology and Consultant Neurologist (Hon) at the Blizzard Institute (Neuroscience), Queen Mary, University of London and The Royal London Hospital, Barts Health NHS Trust