New drugs

Dimethyl fumarate

Approved indication: multiple sclerosis
Tecfidera (Biogen Idec)
240 mg modified-release capsules
Australian Medicines Handbook section 16.5

Dimethyl fumarate is a hazardous chemical, but has been studied in Germany as a treatment for psoriasis. It was observed that a few patients who also had multiple sclerosis improved when their psoriasis was treated. This prompted research into dimethyl fumarate as a treatment for multiple sclerosis.

When taken orally, dimethyl fumarate is rapidly hydrolysed to monomethyl fumarate. This active metabolite is further metabolised and has a terminal half-life of only one hour. Most of the dose is exhaled as carbon dioxide. How the chemical works in multiple sclerosis is uncertain.

A phase II trial randomised 257 patients with relapsing-remitting multiple sclerosis to take dimethyl fumarate 120 mg once daily, 120 mg three times daily, 240 mg three times daily, or placebo. After 24 weeks the patients taking 240 mg three times daily had a significantly better response than those taking placebo. They had developed an average of 3.7 new gadolinium-enhancing lesions on MRI of the brain compared with 6.6 lesions in the placebo group. The responses with other doses were not significantly different from placebo, so formulations of 240 mg have been used in phase III trials.[1]

The DEFINE study was a placebo-controlled trial involving 1234 patients with relapsing-remitting multiple sclerosis. This assessed dimethyl fumarate 240 mg two or three times a day. After two years the annual rate of relapse had been reduced by 53% with twice-daily treatment and by 48% with three-times-daily treatment. Compared to placebo, there were fewer new lesions on MRI and less progression of disability (see Table 1).[2]

The CONFIRM study, involving 1417 patients, also compared 240 mg twice or three times daily with placebo, but also included glatiramer acetate as an active control. After two years the reductions in relapse rates, compared with placebo, were 44% with twice-daily and 51% with three-times-daily treatment. Glatiramer reduced the annual rate by 29% relative to placebo. All the active treatments significantly reduced the number of new lesions on MRI, but there was no significant effect on the progression of disability (see Table 2).[3]

In the phase III trials treatment was discontinued by 35–36% of the placebo group, 30–31% of the dimethyl fumarate twice-daily group and 28–31% of the three-times-daily group. Adverse events led to the withdrawal of 10–13% of the placebo group and 12–16% of the dimethyl fumarate groups.[2,3] Adverse reactions to dimethyl fumarate include flushing, abdominal pain, nausea, vomiting and diarrhoea. Taking the capsules with food may reduce the irritant effects of dimethyl fumarate on the gut. An annual measurement of the full blood count is recommended as dimethyl fumarate can cause lymphopenia. This could increase the risk of infection. There have been case reports of progressive multifocal leukoencephalopathy in patients treated with dimethyl fumarate for psoriasis.[4] Some patients develop raised liver enzymes or proteinuria, and annual urinalysis is recommended.

Live vaccines are not recommended during treatment. The safety of dimethyl fumarate in pregnancy and lactation is uncertain.

The relative reductions in relapse rates were significant, but the effect on disability was less clear. For some outcomes, dimethyl fumarate appears to have better efficacy than glatiramer. It also has the advantage that it does not have to be injected like glatiramer and the interferons. A comparison between twice-daily dimethyl fumarate and once-daily oral fingolimod or teriflunomide would be useful.

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Table 1 **Outcomes of the DEFINE trial** [2]

	Treatments (number of patients)		
Outcomes	**Placebo** (408)	**Dimethyl fumarate** 240 mg twice daily (410)	**Dimethyl fumarate** 240 mg three times daily (416)
Proportion who relapsed by two years	46%	27%	26%
Annualised relapse rate	0.36	0.17	0.19
Mean number of new or enlarging hyperintense lesions on MRI	17	2.6	4.4
Proportion with progressive disability	27%	16%	18%

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Table 2 **Outcomes of the CONFIRM trial** [3]

Outcomes	Treatments (number of patients)			
	Placebo (363)	**Dimethyl fumarate** 240 mg twice daily (359)	**Dimethyl fumarate** 240 mg three times daily (345)	**Glatiramer acetate** 20 mg daily (350)
Proportion who relapsed by two years	41%	29%	24%	32%
Annualised relapse rate	0.40	0.22	0.20	0.29
Mean number of new or enlarging hyperintense lesions on MRI	17.4	5.1	4.7	8.0
Proportion with progressive disability	17%	13%	13%	16%

T manufacturer provided the product information

REFERENCES *

1. Kappos L, Gold R, Miller DH, MacManus DG, Havrdova E, Limmroth V, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet 2008;372:1463-72.
2. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367:1098-107.
3. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012;367:1087-97.
4. Mrowietz U, Reich K. Case reports of PML in patients treated for psoriasis [letter]. N Engl J Med 2013;369:1080-1.

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).