Dimethyl fumarate for the treatment of plaque psoriasis

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Dimethyl fumarate (Skilarence) is an oral therapy licensed for the treatment of moderate to severe plaque psoriasis in adults when systemic treatment is indicated. This article discusses its efficacy, adverse effects and place in therapy.

KEY POINTS

- Dimethyl fumarate is an oral immunomodulator indicated for the treatment of adults with moderate to severe plaque psoriasis who need systemic therapy
- NICE recommends it as an option for severe plaque psoriasis when non-biological systemic therapies are unsuitable or have failed
- Treatment is initiated at a low dosage (30mg daily) and titrated upwards over nine weeks
- The 16-week phase 3 BRIDGE trial showed that dimethyl fumarate is non-inferior to Fumaderm (a fixed combination of fumaric acid esters)
- Common adverse events included diarrhoea, abdominal pain, flushing and nausea; about 10% of patients developed lymphopenia
- A month's treatment at the maximum dosage of 240mg three times daily costs about £382

NICE recently updated its 2012 clinical guideline on the diagnosis and management of psoriasis.[1] It found no new evidence to alter its recommendations but it incorporated the many treatment options into a single guideline. Topical therapies (steroids, vitamin D analogues, dithranol and tar preparations) are recommended as first-line treatments. Phototherapy with UVB and psoralen UVA, and systemic non-biological agents (ciclosporin, methotrexate, acitretin) are second-line alternatives. If these are unsuccessful, further options for psoriasis or psoriatic arthritis are apremilast and biological agents (adalimumab, certolizumab pegol, etanercept, infliximab, ixekizumab, secukinumab and ustekinumab). The guideline also recommends trying a second biological agent if the first fails.

In a separate technology appraisal, NICE recommends dimethyl fumarate (Skilarence) as an option for adults with severe plaque psoriasis (defined as a total Psoriasis Area and Severity Index [PASI] ≥10 and a Dermatology Life Quality Index [DLQI] >10) when systemic non-biological therapies (including ciclosporin and methotrexate) and PUVA have failed, or are contraindicated or not tolerated.[2] Treatment with a biological agent is not a prerequisite. As with other psoriasis treatments, dimethyl fumarate should be discontinued if the response is inadequate after 16 weeks (not achieving a 75% reduction in PASI score, or 50% reduction in PASI and a 5-point reduction in DLQI from when treatment was started).

Indications and dosage

Dimethyl fumarate is a fumaric acid ester with immune modulating and anti-inflammatory properties. Its mechanism of action has not been fully elucidated but it is thought to involve a reduction in the production of inflammatory cytokines, promoting apoptosis, inhibiting keratinocyte proliferation, reducing expression of adhesion molecules and lowering inflammatory infiltrate in psoriatic plaques.

Dimethyl fumarate is licensed (as Skilarence) for the treatment of moderate to severe plaque psoriasis in adults when systemic treatment is indicated. It is also licensed (under the brand name Tecfidera) for the treatment of multiple sclerosis.

Skilarence is available as 30mg and 120mg gastroresistant tablets. Treatment should be initiated at a dosage of 30mg daily, increasing over nine weeks to a maximum of 240mg three times daily, according to efficacy and tolerability (details are provided in the summary of product

characteristics). Although clinical experience is limited, no dosage adjustment is recommended for patients aged over 65 years. No dosage adjustment is needed in patients with mild or moderate renal or hepatic impairment; however, there is no experience of its use in severe renal or hepatic impairment and Skilarence is contraindicated in these patients. The product is also contraindicated in severe gastrointestinal disorders, pregnancy and breastfeeding.

There is a risk of opportunistic infection with dimethyl fumarate and a full blood count should be carried out prior to initiating treatment and every three months; treatment should be discontinued if leukopenia or lymphopenia occurs. No drug interaction studies have been carried out, but the product characteristics state there is no evidence that dimethyl fumarate will interact with medicines metabolised by cytochrome P450 enzymes.

Efficacy

Evidence for the efficacy of dimethyl fumarate in psoriasis is provided by the phase 3 BRIDGE trial (n=704), in which it was compared with Fumaderm (a fixed combination of fumaric acid esters) and placebo.[3] (NB Fumaderm is licensed in Germany but not the UK, though it is used in some specialist centres.) Patients with moderate to severe chronic plaque psoriasis were treated for 16 weeks after a nine-week titration phase. The primary endpoints were the proportion of patients achieving ≥75% improvement of PASI score (PASI 75) and the proportion achieving a Physician's Global Assessment (PGA) score of 0 or 1 ('clear' or 'almost clear') at week 16.

Patients had a mean PASI score at baseline of about 16 (10 is NICE's threshold for severe psoriasis), with a mean body surface area affected of about 21%; up to 14% had previously received systemic therapy, a small number had received biological therapy and approximately 30% had undergone phototherapy.

About 37% of patients discontinued treatment with dimethyl fumarate (*vs* 38% with Fumaderm and 29% with placebo); adverse events accounted for discontinuation in 23%, 25% and 4% of patients respectively; and lack of efficacy for 4%, 3% and 15%.

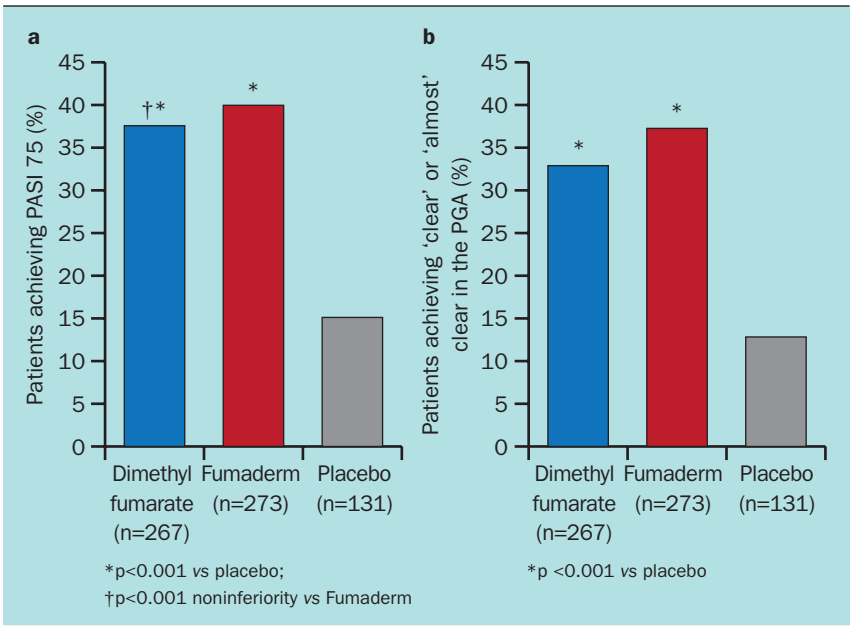

Figure 1. Primary endpoints at 16 weeks with dimethyl fumarate, Fumaderm and placebo in the BRIDGE trial.[3] a. % patients achieving ≥75% improvement in Psoriasis Area and Severity Index score (PASI 75); b. % patients with Physician's Global Assessment (PGA) rating of 'clear' or 'almost clear'

After 16 weeks treatment, dimethyl fumarate was significantly more effective than placebo and non-inferior to Fumaderm (see Figure 1). The body surface area affected began to decrease after three weeks, with a significant reduction at week 8 compared with placebo, which continued to improve up to week 16. Two months after treatment was discontinued, the symptom rebound rate was 1.1% with dimethyl fumarate, 2.2% with Fumaderm and 9.3% with placebo.

NICE's technology appraisal concluded that dimethyl fumarate improves severe psoriasis more than placebo but indirect comparisons suggest it is less effective than systemic biological therapies and apremilast.[2]

Adverse events

The overall incidence of adverse events with dimethyl fumarate was similar to that with Fumaderm (approximately 84% for each) and higher than with placebo (60%). The nature of adverse events associated with the two active treatments was similar. Diarrhoea (39% with dimethyl fumarate *vs* 17% with placebo), upper abdominal pain (20% *vs* 8% respectively), abdominal pain (20% *vs* 5%), flushing (18% *vs* 2%) and nausea (11% *vs* 4%) were the most frequent adverse events.[3] Lymphopenia occurred in 10% of patients taking dimethyl fumarate and 9% had eosinophilia (*vs* none with placebo); white cell counts recovered after treatment ended.

References

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3. Mrowietz U, *et al*. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm- and placebo-controlled trial (BRIDGE). *Br J Dermatol* 2017;176:615–23.

Declaration of interests

None to declare.

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