ORIGINAL RESEARCH

Dimethyl fumarate titration for the systemic treatment of moderate-to-severe plaque psoriasis

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Abstract

Background: Dimethyl fumarate (DMF) is an oral systemic agent approved for the treatment of moderate-to-severe psoriasis vulgaris. It has a favourable tolerability profile, but it is associated with a high incidence of mild and reversible adverse events. The aim of the article is to describe a clinical experience aimed at increasing tolerability.

Patients and methods: A group of patients was treated with DMF with a titration schedule, according to clinical practice, although a personalization of the step-up timing was allowed. The highest dose was the minimal effective dose or the maximal tolerated doses.

Results: DMF treatment was effective in reducing the disease severity and improving the quality of life. DMF was well tolerated as only mild, mainly gastrointestinal, adverse events occurred in these patients. In addition, the up-titration schedule seemed to provide a reduced incidence of adverse events compared with the fixed dose.

Conclusion: Our experience suggested that the recommended up-titration schedule of DMF, adjusted and personalized according to patient needs and physician opinion, provided a relevant clinical benefit and was well tolerated.

Keywords: dimethyl fumarate, plaque psoriasis, systemic conventional treatment.

Citation

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Introduction

Plaque psoriasis is the most common subtype of psoriasis, a chronic, recurrent inflammatory skin disease.¹ Mild disease is treated with topical therapy but systemic agents, either conventional or biological, are available for moderate-to-severe cases.

Fumaric acid esters are amongst the conventional oral systemic agents recommended by current guidelines, with acitretin, cyclosporine and methotrexate.² They have anti-inflammatory and antioxidative capacities; however, the mechanism involved in psoriasis treatment is not clear.³ Dimethyl fumarate (DMF) as well as monoethyl fumarate and its salts are the derivatives of fumaric acid useful for oral therapy. Fumarates were first registered for moderate-to-severe psoriasis in Germany as a proprietary combination (Fumaderm®, Biogen Idec, Cambridge, MA, USA), which was reported to be as effective as other systemic agents, including methotrexate.⁴ DMF is the main active ingredient of Fumaderm® and, in 2017, it was registered by the European Medicines Agency as a single agent for the treatment of moderate-to-severe psoriasis vulgaris.⁵ Their prolonged clinical use has led to a favourable safety profile of fumarates. Nevertheless, usually mild adverse events (AEs), most of which commonly include gastrointestinal symptoms, such as diarrhea, stomachache and cramps, increased frequency of stools, nausea and vomiting, are reported in up to two-thirds of patients.⁶–⁸ Other common AEs include flush, leukocytopenia, lymphopenia and reversible peripheral eosinophilia.⁹,¹⁰

The early clinical studies demonstrating the efficacy of DMF were not placebo controlled and were without a comparator arm.¹¹–¹⁵ Recently, a phase III, double-blind, placebo-controlled, non-inferiority trial (BRIDGE, NCT01726933, EudraCT 2012-000055-13) demonstrated the efficacy and safety of DMF in comparison with Fumaderm® and placebo.¹⁶ At week 16,
a Psoriasis Area Severity Index (PASI) score of 75 was achieved by 37.5% of patients who were treated with DMF, by 15.3% of patients who received placebo (p<0.001) and by 40.3% of patients who received Fumaderm® (non-inferiority for DMF versus Fumaderm®; p<0.001). DMF was also superior to placebo and non-inferior to Fumaderm® in terms of disease clearance in the Physician Global Assessment measure at week 16. In this trial, most treatment-related AEs were classified as ‘mild’. The high incidence of events, although usually mild and reversible, may represent a limit to the use of DMF. A correct management of treatment with DMF could increase tolerability and allow the use of this effective therapy in a wider proportion of patients. Therefore, we report our experience with 36 patients with moderate-to-severe plaque psoriasis who received DMF, amongst whom 17 were administered a personalized titration schedule aimed at reducing the incidence of AEs.

Patients and methods

Our clinical experience was conducted in the hospital setting, following clinical practice. Consecutive adult out-patients affected with moderate-to-severe plaque psoriasis (PASI ≥10) and eligible for systemic treatment with conventional agents were included. DMF was prescribed following the physician’s decision and according to the prescribing recommendations. Pregnant or breastfeeding patients and patients with baseline leucocyte counts of <3 × 10⁹ cells/L and/or lymphocyte counts of <1 × 10⁹ cells/L were excluded. All patients signed an informed consent form.

Treatment

According to the prescribing recommendations, treatment was started with 30 mg/day of DMF for 7 days and up-titrated by 30 mg/day every 7 days, up to the maximal admitted dose of 720 mg. The dose increase could be delayed at the discretion of the investigator and the maximal dose for each patient was chosen based on efficacy and tolerability, with a shared decision by the patient and investigator.

The investigator could start the treatment with a full-dose schedule, when they deemed it necessary, on the basis of the clinical condition and of the patient’s reliability to adhere to a complex schedule. Topical treatment was admitted during therapy with DMF.

Assessment

The endpoint was disease improvement by 4 and 12 months of treatment. All assessments were recorded at baseline and at follow-up visits and after 4 and 12 months of DMF therapy. Disease severity was scored by PASI. The reduction of PASI score by 75% and 90% (PASI 75 and PASI 90, respectively) was recorded at each visit.

A 10-mm visual analogue scale (VAS), ranging from 0 (no complaints) to 10 (worst complaints), was used for patients’ assessment of psoriasis activity at each visit. The change in quality of life was assessed by the Dermatology Life Quality Index (DLQI) score. DLQI is based on 10 questions about symptoms, feelings, daily activities, leisure, work, school, personal relationships and treatment; the score ranges from 0 to 30. An index of 0–1 indicates no effect, 2–5 a small effect, 6–10 a moderate effect, 11–20 a very large effect and 21–30 an extremely large effect on a patient’s life.

Statistical analysis

An observed analysis of data is presented. For continuous characteristics, the number of non-missing values (n), mean and standard deviation (SD) are reported. For proportions, absolute and relative frequencies are reported. In order to test differences of parameters over time, the Friedman test or the McNemar test were computed. For all the statistical tests, a p<0.05 significance level was considered.

Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Approval was obtained by the pertaining Ethical Committee.

Results

Baseline characteristics of patients are shown in Table 1. Overall, 36 patients with plaque psoriasis were treated with DMF and followed up to 12 months. Mean age was 55.7±14 years, 25 (69%) were men and the mean BMI was 26.5±4.5 kg/m². Mean age of psoriasis onset was 38.7±18.7 years and a family history of psoriasis was reported by 5 (15%) patients. Nine (25%) patients were affected by diabetes mellitus and 9 (25%) by hypertension at baseline. Psoriasis was localized in difficult-to-treat areas in 12 patients (1 in the genital area, 10 in the palmoplantar area and 1 on the face). A total of 30 (83%) patients had previously received topical therapy for psoriasis, 16 (44%) had received systemic conventional treatment and 4 (11%) had been treated with biological agents.

Drug administration

Information about dosage titration is available for 29 patients (Table 2). The dose of DMF was up-titrated as reported in the Patients and Methods section in 17/29 (59%) patients, whilst the full dose was administered since the start of therapy in 12/29 (41%) subjects. The maximal dose administered at the end of up-titration was 240 mg/day because a satisfactory improvement had been obtained according to both the patient and the physician. A further increase of the dose was not attempted to prevent unnecessary risk of adverse events. Patients who received a fixed dose were administered 90–360 mg/day DMF.
**Table 1. Baseline demographic and clinical characteristics of patients (n=36).**

| Baseline demographic and clinical characteristics | Mean ± SD/n (%) |
|--------------------------------------------------|-----------------|
| Age (years)                                       | 55.7±14.01      |
| Weight (kg)                                       | 76.4±14.38      |
| BMI (kg/m²)                                       | 26.5±4.50       |
| Men                                              | 25 (69.4)       |
| Age of onset (years)                              | 38.7±18.72      |
| PASI                                             | 14.9±4.9        |
| Smoking status:                                   |                 |
| • Current smokers                                 | 10 (27.8)       |
| • Previous smokers                                | 8 (22.2)        |
| • Never smokers                                   | 18 (50.0)       |
| Alcohol consumption status:                       |                 |
| • Current alcohol consumers                       | 7 (19.3)        |
| • Previous consumers                              | 2 (5.6)         |
| • Never consumed alcohol                          | 27 (75.0)       |
| Family history for psoriasis                      | 5 (14.7)        |
| Diabetes                                          | 9 (25.0)        |
| Blood hypertension                                | 9 (25.0)        |
| Dyslipidaemia                                     | 4 (11.1)        |
| Previous treatment:                               |                 |
| • Topics                                          | 30 (83.3)       |
| • Systemic                                       | 16 (44.4)       |
| • Biological                                     | 4 (11.1)        |

**Table 2. DMF dosage along the observation period (mg/day).**

| Week 1 | Week 2 | Week 3 | Week 4 | Following weeks | Comment |
|--------|--------|--------|--------|-----------------|---------|
| 1      | 30     | 60     | 90     | 120             | 240 for 12 weeks and 360 for 9 weeks (continuing at data collection) |
| 2      | 30     | 60     | 90     | 120             | 120 (continuing at data collection) No further increase because lesion control was good |
| 3      | 30     | 60     | 90     | 120             | 240 (continuing at data collection) Low adherence to treatment |
| 4      | 30     | 60     | 90     | 120             | 120 (continuing at data collection) No further increase because lesion control was good |
| 5      | 30     | 60     | 90     | 120             | 240 (continuing at data collection) Itching during the first days of treatment |
| 6      | 30     | 60     | 90     | 120             | 90 (continuing at data collection) Stomachache with 120 mg |
| 7      | 30     | 60     | 90     | 120             | 90 (continuing at data collection) Itching during the first days of treatment; diarrhoea with 120 mg |
| 8      | 30     | 60     | 90     | 120             | 120 (continuing at data collection) |
| 9      | 30     | 60     | 90     | 120             | 120 (continuing at data collection) No further increase because lesion control was good |
| 10     |        |        |        |                 | NA      |
Table 2. (Continued)

| Week 1 | Week 2 | Week 3 | Week 4 | Following weeks | Comment |
|--------|--------|--------|--------|-----------------|---------|
| 11     | NA     |        |        |                 |         |
| 12     | 30     | 60     | 90     | 120 240         | (continuing at data collection) |
| 13     | 30     | 60     | 90     | 120 120         | (continuing at data collection) |
| 14     | 30     | 60     | 90     | 120 240         | (continuing at data collection) |
| 15     | 30     | 60     | 90     | 120 120         | (continuing at data collection) |
| 16     | 30     | 60     | 90     | 120 240         | (continuing at data collection) |
| 17     | NA     |        |        |                 |         |
| 18     | NA     |        |        |                 |         |
| 19     | NA     |        |        |                 |         |
| 20     | 90     | 90     | 90     | 120 120 for 3 days, 90 | (continuing at data collection) |
|        |        |        |        |                 | Abdominal cramps with 120 mg/day |
| 21     | NA     |        |        |                 |         |
| 22     | 120    | 120    | 120    | 120 120         | (continuing at data collection) |
| 23     | 120    | 240    | 360    | 360 360         | (continuing at data collection) |
| 24     | 120    | 240    | 240    | 240 240         | (continuing at data collection) |
| 25     | 120    | 120    | 120    | 120 120         | (continuing at data collection) |
| 26     | 120    | 240    | 240    | 240 240         | (continuing at data collection) |
| 27     | 90     | 90     | 90     | 90 90           | (continuing at data collection) |
|        |        |        |        |                 | Abdominal cramps |
| 28     | NA     |        |        |                 |         |
| 29     | 120    | 120    | 120    | 120 120         | (continuing at data collection) |
| 30     | 150    | 150    | 150    | 150 150         | (continuing at data collection) |
| 31     | 30     |        |        |                 | Abdominal cramps |
| 32     | 90     | 90     | 90     | 90 90           | (continuing at data collection) |
| 33     | 120    | 120    | 120    | 120 120         | (continuing at data collection) |
| 34     | 30     | 60     |        |                 | Transaminase level increase |
| 35     | 30     | 60     | 90     |                 | Stomachache |
| 36     | 30     | 60     | 90     | 90 90           | (continuing at data collection) |
|        |        |        |        |                 | Stomachache |

Disease severity

PASI score at each visit was available for 26 patients. Mean PASI was reduced from 14.9±4.9 to 7.7±3.6 after 4 months and to 3.4±2.4 after 12 months of treatment (p<0.001 versus baseline at both timepoints) (Figure 1).

As only moderate-to-severe psoriasis was treated, no patient had PASI ≤3 at baseline but this value was attained by 2/32 (6%) patients after 4 months and by 18/26 (69%) patients by 12 months (p<0.001 versus baseline).

After 4 months of treatment, 5/32 (16%) patients reached PASI 75, whilst after 12 months, 16/26 (61%) reached PASI 75 and 9/26 (35%) attained PASI 90.

Patient-reported assessment

Overall, 26 patients reported an assessment of their disease severity at all visits. The mean VAS was 5.8±2.7 at baseline and was reduced to 4.8±2.6 after 4 months and to 3.2±2.2 after 12 months (p<0.001 at both timepoints versus baseline) (Figure 2).

Quality of life

Quality of life was significantly improved after treatment with DMF. Mean DLQI (n=26) was reduced from 11±6.5 at baseline to 7.5±4.5 at 4 months and to 5±4.6 at 12 months (p<0.001 versus baseline at both visits) (Figure 3). The mean change from baseline was a 3.4±4.8-point reduction at 4 months and a 5.9±6.2-point reduction at 12 months.

Only 8/36 (22%) patients had DLQI ≤5 at baseline, and this proportion was increased to 11/32 (34%) after 4 months and to 20/26 (77%) after 12 months (p<0.001 versus baseline).

At the 12-month visit, 7 (27%) patients had their DLQI reduced by 75%.
Tolerability and effectiveness of up-titration

AEs were reported in 12 (41%) patients. Five of these patients (29%) were in the group of up-titration therapy, whilst 7 (58%) were in the group receiving the full fixed dose since the beginning of treatment. Two patients of the titration group had AEs when administered 240 mg/day DMF and were down-titrated to 90 mg/day, allowing the continuation of the therapy. One patient of the fixed-dose group received 90 mg/day; he had a mild AE and could continue the therapy. No haematological AEs were observed. AEs are reported in Table 3.

Discussion

The experiences of patients affected by moderate-to-severe plaque psoriasis with an indication for a systemic therapy and treated with DMF, either with a step-up titration or starting with a maximal fixed dose, are described in this article. We could observe that DMF treatment was effective in reducing disease severity and improving quality of life. Improvements were observed after 4 months of treatment but were more relevant and occurred in a higher proportion of patients after 12 months (Figure 4). DMF was well tolerated, as only mild, mainly gastrointestinal, AEs occurred in these patients. In addition, the up-titration schedule seemed to provide a reduced incidence of AEs compared with the fixed dose. Indeed, leukocytopenia, lymphopenia and reversible peripheral eosinophilia were not observed.

PASI 75 and absolute PASI are the mainly considered therapeutic goals in clinical practice.\(^\text{20,21}\) In our patients, after 12 months of treatment, PASI ≤3 was obtained by 69% of patients and PASI 75 by 61% of subjects.

DMF treatment improved the quality of life of our patients; nonetheless, we observed that a mean ≥5-point reduction of DLQI, which is considered as the minimal clinically relevant change, was observed after 12 months of treatment and not after 4 months, as found in the post hoc analysis of the BRIDGE study.\(^\text{22}\) A delayed effect of DMF on quality of life was reported by several previous studies. The interim analysis of the 52-week DIMESKIN trial (EudraCT: 2017-001368-40) investigating the long-term efficacy of DMF in patients with moderate-to-severe psoriasis showed a significant reduction in median DLQI at 24 weeks from baseline (median DLQI decrease from 10.5 to 1.0; \(p<0.001, n=84\)).\(^\text{23}\) In another observational study in patients treated with fumarates, an 8.9-point improvement in mean DLQI was observed after 12 months of treatment.\(^\text{4}\)

We are aware that the information we present here does not represent results from a clinical study as the common practice is described. We deem the article to be useful for clinicians who need to improve their ability to use DMF in their clinic.

Conclusion

Our experience is in accordance with previous studies and confirms that DMF is a reliable option for patients with moderate-to-severe psoriasis requiring systemic treatment;
Table 3. Adverse events during treatment with DMF, either with up-titration of the dose or with a fixed full dosage.

| Adverse events       | Up-titration (n=17), n (%) | Full dose (n=12), n (%) |
|----------------------|---------------------------|-------------------------|
| Overall              | 5 (29.4)                  | 7 (58.3)                |
| Transaminase increase| 1 (5.9)                   | –                       |
| Abdominal pain       | –                         | 1 (8.3)                 |
| Diarrhoea            | 1 (5.9)                   | 3 (25.0)                |
| Heartburn            | 3 (17.6)                  | 1 (8.3)                 |
| Flushing             | –                         | 1 (8.3)                 |
| Unknown              | –                         | 1 (8.3)                 |

Figure 4. Scalp and limb psoriasis lesions in an exemplary patient, before and after treatment with DMF. (A) and (B) baseline; (C) after 4 months; (D) and (E) after 12 months.
in addition, the recommended up-titration schedule of DMF, adjusted and personalized according to patient need and physician opinion, provided a relevant clinical benefit and was well tolerated, suggesting that correct management may extend the use of DMF to a wide proportion of suitable patients.

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