Real-world use of dimethyl fumarate in patients with plaque psoriasis: a Delphi-based expert consensus

Martina Burlando,[1] Elena Campione,[2] Aldo Cuccia,[3] Giovanna Malara,[4] Luigi Naldi,[5] Francesca Prignano,[6] Leonardo Zichichi[7]

[1]Dermatology Unit, IRCCS San Martino University Hospital, Genoa; [2]Dermatology Unit, University of Rome Tor Vergata; [3]Dermatology Unit, San Donato Hospital, Arezzo; [4]Dermatology Unit, Metropolitan Hospital Bianchi Melacrino Morelli, Reggio Calabria; [5]Dermatology Unit, San Bortolo Hospital, Vicenza; [6]Dermatology Unit, Department of Health Sciences, University of Florence; [7]Dermatology Unit, Sant'Antonio Abate Hospital, Trapani, Italy

Correspondence: Martina Burlando, Dermatology Unit, IRCCS San Martino Polyclinic Hospital, Largo Rosanna Benzi X, 16132, Genoa, Italy.
Tel.: +39.010.5555761 - Fax: +39.010.5556641.
E-mail: martinaburlando@hotmail.com

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Abstract

Dimethyl fumarate (DMF) was recently approved by the European Medicines Agency for systemic treatment of moderate-to-severe chronic plaque psoriasis. Appropriate management of DMF treatment is required to achieve optimal clinical benefits. 7 dermatology experts gathered online for 3 meetings to identify consensus on the use of DMF in patient selection, drug dosage/titration, side effects management, and follow-up, with the aim to provide guidance on the use of DMF for psoriasis in clinical dermatological practice based on literature data and expert opinion. 20 statements were discussed and voted on using a facilitator-mediated modified Delphi methodology. Strong consensus was reached for all statements (agreement level of 100%). DMF treatment is characterized by dosage flexibility, sustained efficacy, high rates of drug survival, and low potential for drug-drug interactions. It can be used in a broad range of patients, including the elderly or those with comorbidities. Side effects (mainly gastrointestinal disorders, flushing, and lymphopenia) are frequently reported but are generally mild and transient and can be minimized by dosage adjustments and a slow titration schedule. Hematologic monitoring throughout the treatment course is required to reduce the risk of lymphopenia. This consensus document provides clinical dermatologists with answers on the optimal use of DMF to treat psoriasis.

Introduction

Psoriasis is a chronic, systemic, immune-mediated disease affecting approximately 2-4% of adults in Europe and leading to a substantial physical and psychological burden.[1,2] Psoriasis pathogenesis appears to be driven by proinflammatory cytokines, and immunologic and genetic studies have identified interleukin (IL)-17 and IL-23 as key players in the disease process.[1,3] Among clinical presentations, plaque psoriasis is the most common subtype, and up to one-third of patients have moderate-to-severe psoriasis requiring systemic therapy with either conventional or biologic agents.[2] The therapeutic options for moderate-to-severe plaque psoriasis have expanded rapidly in recent years, owing to the introduction of several new drugs and physical modalities with the potential to shift traditional treatment paradigms.[4] In this rapidly evolving field, choosing the most appropriate treatment strategies based on disease characteristics and patient profiles is a challenge for both academic experts and practicing dermatologists.

Although fumaric acid esters (FAEs) have been used for decades in Germany and other European countries as a systemic therapy for psoriasis, dimethyl fumarate (DMF) is the first drug in this class to be approved by the European Medicines Agency

(EMA) for the treatment of moderate-to-severe plaque psoriasis in adult patients in need of systemic therapy.[5] After oral administration, DMF is rapidly converted to monomethyl fumarate (considered to be the active molecule), subsequently metabolized through the tricarboxylic acid cycle and excreted mainly through the respiratory system, with no known involvement of the cytochrome P450 system.[6,7] Although the mechanism of action of DMF and monomethyl fumarate in improving signs and symptoms of psoriasis has not been entirely elucidated, these molecules seem to promote the downregulation of inflammatory cytokines and an overall shift from a pro-inflammatory Th1/Th17 response to an anti-inflammatory Th2 response, and may also extend their effects on granulocytes as well as non-immune cells, such as keratinocytes and endothelial cells.[6,8] Recent findings suggest that DMF may also display an anti-inflammatory effect through the regulation of glutathione-S transferase.[6,9] In phase 3, randomized, double-blind, noninferiority BRIDGE trial, DMF was found to be significantly superior to placebo in terms of the proportion of patients achieving a ≥75% improvement from baseline in the psoriasis area and severity index (PASI 75) and a physician global assessment (PGA) score of 0 (clear) or 1 (almost clear) at week 16.[2] DMF was also proven to be non-inferior to a combination of FAEs containing DMF and monomethyl fumarate. Furthermore, DMF-treated patients reported clinically meaningful improvements in health-related quality of life.[2,10] DMF demonstrated a favorable safety profile, with most adverse events being classified as mild in severity.[2] Observational studies confirm the efficacy and safety of DMF.[11,12] Although clinical data on DMF are still scarce, several studies (including real-life observational studies) suggest that long-term treatment with FAEs is safe and beneficial (both as monotherapy and in combination with other therapies) and is characterized by high drug survival rates.[13-15] In the European S3-Guidelines, FAEs are recommended for the induction and long-term treatment of psoriasis vulgaris.[16] However, despite the overall favorable safety profile of FAEs/DMF, adverse events such as gastrointestinal (GI) disorders, flushing, and lymphopenia are common when starting treatment, requiring a careful titration schedule and hematologic monitoring.[2,17]

There is a need for guidance on the use of DMF, especially for clinicians who have not had previous experience with FAEs. In this article, we report a consensus document on real-world clinical use of DMF in moderate-to-severe psoriasis drafted by an expert panel of dermatologists using the Delphi methodology.

Methods

This consensus document was prepared by an expert panel consisting of 7 Italian dermatologists with specific experience in the use of DMF in patients with psoriasis. The Delphi technique, a structured group interaction based on a series of questionnaires, has been widely used to integrate expert opinions on various healthcare topics, mainly for the development of consensus recommendations.[18] A modified Delphi technique, consisting of 2 online meetings (*via* Zoom) and two rounds of questionnaires, was used to reach a consensus on DMF use by drafting and commenting on a series of statements in four main areas: i) patient selection; ii) drug dosage and titration; iii) side effects management; iv) follow-up. Panel members were asked to rate each statement on a Likert scale ranging from 0 (absolutely not approved) to 9 (strongly approved). Consensus for each statement was defined as a median score ≥8. The statements were based on both literature data and expert opinion. Selected literature articles on patient profile, dosing, management of side effects, and follow-up methods included DMF-related clinical studies (randomized and observational) as well as relevant reviews and previous consensus documents. Supporting evidence for DMF use was also obtained from studies on FAEs, in particular the largest real-world observational studies and registry data-based reviews.

The modified Delphi process is outlined in Figure 1. Briefly, in the first meeting, the participants discussed and modified a preliminary list of statements previously drafted by the Delphi facilitator with the help of members of the expert panel. The amended set of statements was then sent by email to each participant for voting in the first questionnaire round. Panel members were asked to vote on each statement, making comments if desired. The results of the first questionnaire and the anonymized comments were sent back to the panel members by the facilitator. During the second online meeting, the expert panel discussed each statement and voted again (second questionnaire round). A third meeting was dedicated to a final discussion about the main issues related to DMF use and to the drafting of the first outline of the manuscript, which was written, revised, and finalized over the following month.

Results

The guidance on the clinical use of DMF consisted of 20 statements. Consensus among panelists was reached for all statements, with a level of agreement of 100% (median score of 9). Statements and clinical queries are summarized in Table 1.

Discussion

Patient selection

DMF is one of the first-line options available for systemic treatment of mild-to-moderate plaque psoriasis (Table 2). The European approval of DMF for this indication (in 2017) was based

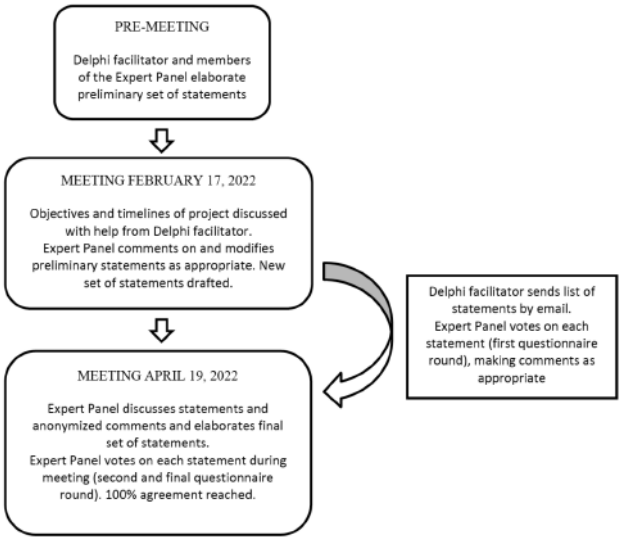

Figure 1. Modified Delphi process.

on the results of the phase 3 BRIDGE trial, as well as supportive evidence on the long-term efficacy and tolerability of FAE preparations containing DMF and other salts.[5] In the BRIDGE trial, 671 patients with moderate-to-severe chronic plaque psoriasis (defined as a PASI score >10, body surface area (BSA) involvement >10%, and a PGA score ≥3 on a 6-point scale) were randomized 2:2:1 to receive DMF, a combination of DMF and monomethyl fumarate, or placebo for 16 weeks.[2] DMF was

Table 1. Summary of statements.

Patient selection	
Which patients are potential candidates for DMF therapy?	1. DMF is one of the first-choice treatments to be considered in adult patients with mild-to-moderate plaque psoriasis for whom local therapy is ineffective or not applicable. 2. DMF is not indicated in patients with non-stable or rapidly progressing disease, or those with psoriatic arthritis. 3. DMF can be used in patients with comorbidities, elderly patients, and those with mild-to-moderate renal or hepatic impairment (provided renal/hepatic function is monitored). 4. DMF is a valid systemic option in young patients who refuse immunosuppressant therapies and/or in patients who prefer an oral treatment to an injectable one. 5. DMF is a valid treatment option in patients with psoriasis involving areas that are difficult to treat with topical therapy (*i.e.* scalp, genitals and palmoplantar areas). 6. DMF is not contraindicated in: • patients with metabolic syndrome • patients with a cancer history • patients with latent tuberculosis • women of childbearing potential, provided they are using adequate contraception 7. DMF is a slow-acting drug that requires time to induce a clinical response. It is therefore not a first-line option in patients with expectations of an immediate response.
Dosage and titration	
What is the dosage of DMF and how should it be titrated?	8. DMF treatment allows for dosage flexibility and dosage individualization based on patient characteristics and clinical response. 9. To improve tolerability, a slow titration of DMF is recommended. DMF is usually started at 30 mg/day, with gradual increases up to a maximum dose of 720 mg/day. 10. When the optimal therapeutic dose has been reached for each patient (clinical response → PASI <3), a gradual reduction of the daily dose should be considered until a maintenance dose is identified, which should be personalized based on clinical assessment and the patient's individual requirements.
How long after starting treatment is it reasonable to wait for a response?	11. The onset of clinical response varies among patients. If response is still unsatisfactory after 3 months of treatment, a change of therapy is recommended.
Is it possible to use DMF in association with other treatments?	12. DMF can be associated with other treatments (*e.g.* phototherapy or local therapies) at various stages of treatment, based on clinical opinion.
Is it possible to discontinue DMF treatment?	13. DMF treatment can be discontinued, for whatever reasons, and rebound effects are not observed. 14. DMF treatment can be resumed after a withdrawal period, at a dosage that depends on the cause of discontinuation: if due to the patient's requirements, treatment can be resumed at the same dosage used before discontinuation; if due to side effects, it is recommended to restart treatment at the last tolerated dosage, followed by gradual uptitration.
Side effects management	
What is the side effect profile of DMF? Do side effects jeopardize efficacy?	15. DMF side effects (mainly flushing and GI disorders) are often mild, usually occur at the beginning of treatment and during the titration phase and tend to improve or resolve during the course of treatment. Side effects do not jeopardize the efficacy of DMF, but may require dosage adjustments or treatment discontinuation if clinically important or not tolerated by the patient.
How should dose-dependent side effects be managed?	16. With dose-dependent side effects, the recommended option is to go back to the maximum tolerated dose. Subsequent dosage adjustments may be considered after clinical reassessment of the patient.
How should leukopenia /lymphopenia be managed?	17. Leukopenia and lymphopenia may occur in the course of treatment. These white blood cell abnormalities are usually mild and transient. Hematologic screening is recommended pre-treatment (therapy should not be initiated with leukocyte counts <3.0×10^9/L or lymphocyte counts <1.0×10^9/L) and during treatment at 3-month intervals. 18. If leukocyte counts fall to <3.0×10^9/L, or lymphocyte counts fall to <1.0×10^9/L but remain ≥0.7×10^9/L during treatment, monthly hematologic monitoring is suggested until lymphocyte levels return to normal (≥1.0×10^9/L) for two consecutive tests, at which point routine monitoring at 3-month intervals can be resumed. With leukocyte counts <3.0×10^9/L or lymphocyte counts <0.7×10^9/L, testing should be repeated after 1 month and treatment promptly discontinued if there is no improvement. Hematologic monitoring should be continued after stopping DMF until lymphocyte counts return to the normal range. Extreme caution is advised about considering the option of resuming DMF treatment once lymphocyte levels are back to normal.
Follow-up	
How frequently should follow-up visits be planned and how long should DMF therapy last?	19. Follow-up visits can be planned at 3-month intervals, at the same time as the hematology tests. 20. Once the clinical response has been reached and the minimum maintenance dosage identified, therapy with DMF can continue indefinitely based on the maintenance of clinical response.

DMF, dimethyl fumarate; PASI, psoriasis area and severity index; GI, gastrointestinal.

proven to be superior to placebo and non-inferior to the FAE preparation in reducing the severity and extent of the disease. At the end of the study, 37.5% of DMF-treated patients achieved a PASI 75 response compared with 15.3% of placebo recipients (P<0.001), and 33% *vs* 13.0% (P<0.001), respectively, had a PGA score of 0 (clear) or 1 (almost clear), co-primary endpoints of the study. DMF was also found to be superior to placebo on most secondary endpoints (including improvement in BSA score and PASI 90 response at week 16) and dermatology life quality index-related outcomes, as documented in a *post-hoc* analysis.[10] The efficacy and safety of DMF have also been investigated in real-world settings. In a prospective, single-blind study from the Netherlands, a cohort of 176 patients with moderate-to-severe psoriasis, who were treated with high-dose DMF for a median duration of 28 months, demonstrated a decrease from baseline in mean PGA scores by 1.7 points (as assessed blindly from digital photographs of the lesions), and 34% of patients had a score of clear or minimal when reaching the maintenance phase.[11] A recently published interim analysis of the prospective, real-world SKILarence in Long-term treatment (SKILL) study, examining data from 257 patients after 52 weeks of DMF treatment, shows a mean reduction in PASI scores of 79.5% in the observed cases (OC) population and 65.7% in the last-observation-carried-forward (LOCF) population, while PASI 75 response rates were 63.3% (95% confidence interval [CI] 56.9-69.3) and 51.0% (95% CI 46.3-55.6) in the OC and LOCF populations, respectively.[12] The treatment was well tolerated, with no unexpected safety concerns. Regarding treatment satisfaction, DMF treatment was rated as good or very good by 94.6% of patients and 95.5% of physicians for effectiveness, and by 87.7% and 92.6%, respectively, for tolerability. Although information from large clinical studies with DMF is still scarce, much data has been collected over time from studies of FAE preparations, supporting the evidence for the long-term efficacy of DMF.[5] As reviewed by Blair,[7] the efficacy and tolerability of FAEs have been investigated in randomized, placebo- or active-controlled trials as well as observational studies. The retrospective FUTURE study from Germany included data from 984 patients who had been treated with FAEs for a mean duration of 44 months, and the percentage of patients classified as clear or markedly improved according to PGA score was 67% after 6 months of therapy, 78% after 24 months and 82% after 36 months.[13] In the retrospective study by Dickel *et al,*[14] which included records from 859 patients treated with FAEs as monotherapy (n=626) or with concomitant therapies (n=233) for a mean duration of 3.6 years, 50% of patients experienced considerable improvement (≥2-point reduction from baseline in PGA score) after 1 year of treatment. Notably, in this study all patients were included in the data analysis, irrespective of treatment discontinuation. The efficacy of DMF or FAEs has also been documented in patients with psoriasis involving body areas that are difficult to treat with topical therapy, such as the scalp, nails, genitals, palms, or soles.[12,13,17,19] In the interim analysis of the SKILL study, improvements from baseline in nail-PGA and palmoplantar-PGA were observed in 70.2% and 57.3% of patients, respectively, after 52 weeks of DMF therapy.[12] When difficult-to-treat areas are involved, patients with mild-to-moderate psoriasis should also be considered candidates for DMF therapy.

Nearly all clinical studies of DMF or FAEs include patients with moderate-to-severe psoriasis, generally defined as a PASI score ≥10 (despite FAEs having been originally approved for severe disease only), which is reflected in the approved indications for DMF use in Europe and in the S3-Guidelines recommendations regarding FAE treatment.[5,16] Overall, information is limited in the literature about the clinical response to DMF (or FAEs) according to disease severity at baseline. In the FUTURE study, where efficacy data were stratified into three groups according to PGA-rated severity at baseline (severe and very severe; moderate-to-severe; and moderate), the improvement of skin signs and symptoms over time was found to be independent of disease severity before initiation of FAE treatment.[13] As for disease dynamics and characteristics, there is general agreement in the literature that DMF should not be used in patients with non-stable or rapidly progressing disease or those with psoriatic arthritis.[20]

Unlike other systemic treatments for psoriasis, DMF can be used in a broad population of patients, including those who are elderly or have comorbidities, and those with mild-to-moderate renal or hepatic impairment (all conditions where the safety of anti-psoriatic treatment needs to be evaluated carefully). Management of elderly patients can be challenging due to various factors, including functional impairment of vital organs, comorbidities, and consequently polypharmacy.[21] Because of its favorable pharmacokinetics, DMF has advantages over other systemic treatments. Since FAEs are not metabolized by common pathways such as the cytochrome P450 system, the potential for drug-drug interactions is low, making DMF a safe option in patients with co-medication.[18,22,23] In the FUTURE study, the efficacy of FAEs was

Table 2. Patient selection.

Statement	Based on
1. DMF is one of the first-choice treatments to be considered in adult patients with mild-to-moderate plaque psoriasis for whom local therapy is ineffective or not applicable.	Literature data
2. DMF is not indicated in patients with non-stable or rapidly progressing disease, or those with psoriatic arthritis.	Literature data
3. DMF can be used in patients with comorbidities, elderly patients, and those with mild-to-moderate renal or hepatic impairment (provided renal/hepatic function is monitored).	Literature data
4. DMF is a valid systemic option in young patients who refuse immunosuppressant therapies and/or in patients who prefer an oral treatment to an injectable one.	Expert opinion
5. DMF is a valid treatment option in patients with psoriasis involving areas that are difficult to treat with topical therapy (*i.e.* scalp, genitals, and palmoplantar areas).	Literature data
6. DMF is not contraindicated in: patients with metabolic syndrome; patients with a cancer history; patients with latent tuberculosis; women of childbearing potential, provided they are using adequate contraception.	Literature data
7. DMF is a slow-acting drug that requires time to induce a clinical response. It is therefore not a first-line option in patients with expectations of an immediate response.	Expert opinion

DMF, dimethyl fumarate.

similar in patients with or without comorbidities.[13] As documented in a retrospective study that analyzed data from 81 elderly psoriatic patients treated with DMF for up to 24 weeks, DMF seems to be effective and well tolerated irrespective of age.[24] Since the primary route of excretion of FAE metabolites is *via* exhalation of carbon dioxide (with only small amounts being excreted in the urine or feces), DMF can be used safely in patients with mild-to-moderate hepatic or renal impairment (provided hepatic or renal function is monitored throughout the treatment course) and no dose adjustment is needed.[5,6]

DMF is not contraindicated in patients with metabolic syndrome or a history of cancer, although efficacy and safety data in these patient groups are scarce. The prevalence of metabolic syndrome in patients with psoriasis is estimated to be in the range of 20-50% and there is increasing evidence that psoriasis and metabolic syndrome share multiple metabolic risk factors, as well as genetic background and pathogenic pathways.[25] Preliminary investigations suggest that the anti-inflammatory activity of DMF and its effects on the reduction of oxidative stress through the regulation of glutathione-S transferase may also have a role in ameliorating metabolic disturbances.[9] In a small prospective, randomized study that evaluated the effects of 6 months' treatment with FAEs *vs* adalimumab on cardiovascular disease parameters in patients with moderate-to-severe psoriasis, FAE treatment was associated with a significant reduction of total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein B levels, whereas adalimumab did not affect lipid markers but significantly improved flow-mediated dilation.[26] Although there are no specific clinical studies of FAEs in patients with a history of malignancies, small numbers of such patients were included in real-world observational studies. A retrospective study in a population with a high prevalence of comorbidities (103 patients) found no evidence of recurrence of malignancy during DMF treatment in the group with a cancer history (18% of the total population).[23] Overall, DMF treatment was found to be effective in this study, with almost 80% of the patients who were still on treatment achieving a PASI 75 response at 26 weeks. However, discontinuation rates due to side effects were high (51%). Given the scarcity of anti-psoriatic treatments that can be used in patients with malignancies, DMF should definitely be considered an option for oncology patients in hospital settings.

Treatment with FAEs is not associated with an increased risk of infection (except for a few isolated cases of opportunistic infections reported in patients with prolonged and severe lymphopenia), and screening for latent tuberculosis is not needed when starting DMF treatment.[5,20] In patients with pre-existing clinically relevant infections, the physician should decide whether to initiate DMF therapy once the infection has resolved.[5] In patients who develop an infection during DMF treatment, suspension of treatment should be considered and the risk-benefit ratio should be reassessed before re-initiation of therapy.[5] DMF is not contraindicated in women of childbearing potential who are using adequate contraception. Although data on the outcome of pregnancies of women exposed to DMF are limited, no increased risk of fetal abnormalities or adverse pregnancy outcomes has been reported in post-marketing studies for women with multiple sclerosis treated with DMF.[27]

Individual patient preferences and expectations are important factors in selecting long-term therapy for psoriasis. DMF offers the advantage of being an oral treatment, thus offering a valid systemic option for patients who prefer to avoid injectable therapy. Similarly, DMF is suitable for young patients wanting to avoid immunosuppressant therapies. Since DMF is a slow-acting drug, it should not be offered as a first-line option in patients with expectations of an immediate clinical response.

Dosage and titration

The DMF dosage is flexible and can be individualized according to the patient's clinical response and tolerability (Table 3). A slow and individualized titration schedule is essential for optimal patient management since it helps prevent the occurrence of side effects, which are often experienced during treatment initiation, or minimize their intensity. DMF is available as 30 mg and 120 mg gastro-resistant tablets. The recommended starting dosage is 30 mg/day, with subsequent gradual increases over the following 9 weeks up to a maximum of 720 mg/day. If treatment success is achieved before reaching the maximum allowed dosage, no further uptitration is necessary. If during the titration period, a particular dose increase is not tolerated (or abnormalities in laboratory parameters are observed), the dosage of DMF should be temporarily reduced to the last tolerated dosage.[5] The recommended uptitration schedule of DMF can be adjusted, especially during the first three weeks, to personalize the treatment according to patient need and physician's opinion.[17] After clinically relevant improvement has been obtained (usually measured by a PASI score <3), a gradual dosage reduction to each patient's maintenance effective dose should be considered.[5]

Once the individual maintenance dose has been achieved, DMF offers the advantage of a long-term therapy characterized by sustained efficacy, an acceptable safety profile, and excellent drug survival.[13-15,20] Based on clinical experience and the results of observational studies, most patients require daily maintenance doses of DMF in the range of 240-480 mg.[11,12] In the prospective interim analysis of the SKILL study, the DMF maintenance dose at week 52 was in the range of 120-480 mg in 75% of the study population and <120 mg in 10%.[12]

DMF is a slow-acting drug that may require several weeks before a meaningful clinical effect is experienced, and side effects are common during the first period of drug exposure. These facts need to be clearly communicated to the patient before treatment initiation. The onset of response after starting DMF or FAEs varies among patients, while full effectiveness of therapy is usually reached after 24 weeks of therapy.[20] In the BRIDGE trial (where assessments were scheduled at 3, 8, and 16 weeks after treatment initiation), a decrease in BSA involvement was first observed after 3 weeks of DMF therapy and became significantly different from placebo after 8 weeks.[2] In the retrospective FUTURE study, 30.8% of patients were classified as markedly improved or clear after 3 months of FAE therapy, increasing to 67% after 6 months and 76% after 1 year.[13] Based on clinical experience, if a patient fails to show a meaningful improvement after 3 months of treatment, DMF should be discontinued and replaced with another therapy.

DMF can be associated with other treatments for psoriasis, such as topical therapies or phototherapy, at various stages during the treatment course, according to the physician's opinion. Combined use of FAEs and phototherapy during the induction phase is a common practice, as it may induce a faster therapeutic response compared with DMF monotherapy.[14,28,29] Data are limited on DMF safety and efficacy when used concomitantly with other immunosuppressive or immunomodulating therapies, conventional or biologic.[5,20] DMF should be used cautiously with other systemic anti-psoriatic treatments. In particular, concurrent use with nephrotoxic drugs (*e.g.* methotrexate or ciclosporin) may increase the risk of renal adverse reactions.[5] However, off-label concomitant use of FAEs and methotrexate, though not recommended, is quite common in clinical practice. In a single-center, retrospective study, co-treatment with methotrexate was associated with a favorable safety profile and satisfactory efficacy, as demonstrated

by analysis of the digital records of 110 patients with psoriasis treated with FAEs plus methotrexate for a mean duration of 2.2 years.[14]

Once the maintenance dosage has been established, patients should continue taking DMF without interruptions (as long as efficacy and tolerability are maintained). However, DMF therapy can be temporarily discontinued, according to the patient's needs. No rebound effects are expected on treatment discontinuation.[2] After a period of withdrawal, DMF therapy can be resumed at a dosage that depends on the reason for treatment discontinuation. If treatment was discontinued for patient requirements not related to tolerability issues, it can be restarted at the same dosage administered before discontinuation, whereas a lower dose (followed by uptitration) should be considered if the patient stopped DMF because of side effects. Discontinuing DMF therapy is not needed in patients undergoing minor surgical procedures (*e.g.* dental procedures or ophthalmic surgery in outpatient settings).

Side effects management

FAEs have a well-characterized side effect profile, with GI disorders, flushing, and white blood cell count abnormalities being the most frequently reported adverse events in studies of DMF or FAEs.[5,30,31] Although side effects are experienced by up to 86% of treated patients, they are generally mild, tend to occur at the onset of therapy, and often resolve or become more tolerable once the patient is established on treatment.[11,20,30,31]

Side effects do not have an impact on DMF efficacy but often require dosage adjustments (Table 4). Treatment discontinuation should only be considered if side effects are clinically important (*e.g.* severe lymphopenia) or not tolerated by patients even after lowering DMF dosage. Literature data indicate that side effects are often the cause of treatment discontinuation, especially during the first weeks of therapy. In the BRIDGE trial, adverse events leading to treatment discontinuation (mostly GI disorders) were reported in 23% of DMF-treated patients and 25% of those receiving FAEs (*vs* 4% in placebo recipients).[2] Long-term observational studies of DMF or FAEs report discontinuation rates due to side

Table 3. Dosage and titration.

Statement	Based on
8. DMF treatment allows for dosage flexibility and dosage individualization based on patient characteristics and clinical response.	Literature data
9. To improve tolerability, a slow titration of DMF is recommended. DMF is usually started at 30 mg/day, with gradual increases up to a maximum dose of 720 mg/day.	Literature data
10. When the optimal therapeutic dose has been reached for each patient (clinical response → PASI <3), a gradual reduction of the daily dose should be considered until a maintenance dose is identified, which should be personalized based on clinical assessment and the patient's individual requirements.	Literature data/ expert opinion
11. The onset of clinical response varies among patients. If response is still unsatisfactory after 3 months of treatment, a change of therapy is recommended.	Expert opinion
12. DMF can be associated with other treatments (e.g. phototherapy or local therapies) at various stages of treatment, based on clinical opinion.	Literature data/ expert opinion
13. DMF treatment can be discontinued, for whatever reasons, and rebound effects are not observed.	Literature data
14. DMF treatment can be resumed after a withdrawal period, at a dosage that depends on the cause of discontinuation: if due to the patient's requirements, treatment can be resumed at the same dosage used before discontinuation; if due to side effects, it is recommended to restart treatment at the last tolerated dosage, followed by gradual uptitration.	Literature data/ expert opinion

DMF, dimethyl fumarate.

Table 4. Side effects management.

Statement	Based on
15. DMF side effects (mainly flushing and GI disorders) are often mild, usually occur at the beginning of treatment and during the titration phase and tend to improve or resolve during the course of treatment. Side effects do not jeopardize the efficacy of DMF, but may require dosage adjustments, or treatment discontinuation if clinically important or not tolerated by the patient.	Literature data
16. With dose-dependent side effects, the recommended option is to go back to the maximum tolerated dose. Subsequent dosage adjustments may be considered after clinical reassessment of the patient.	Literature data/ expert opinion
17. Leukopenia and lymphopenia may occur in the course of treatment. These white blood cell abnormalities are usually mild and transient. Hematologic screening is recommended pre-treatment (therapy should not be initiated with leukocyte counts $<3.0\times10^9$/L or lymphocyte counts $<1.0\times10^9$/L) and during treatment at 3-month intervals.	Literature data
18. If leukocyte counts fall to $<3.0\times10^9$/L, or lymphocyte counts fall to $<1.0\times10^9$/L but remain $\geq0.7\times10^9$/L during treatment, monthly hematologic monitoring is suggested until lymphocyte levels return to normal ($\geq1.0\times10^9$/L) for two consecutive tests, at which point routine monitoring at 3-month intervals can be resumed. With leukocyte counts $<3.0\times10^9$/L or lymphocyte counts $<0.7\times10^9$/L, testing should be repeated after 1 month and treatment promptly discontinued if there is no improvement. Hematologic monitoring should be continued after stopping DMF until lymphocyte counts return to the normal range. Extreme caution is advised about considering the option of resuming DMF treatment once lymphocyte levels are back to normal.	Literature data

DMF, dimethyl fumarate.

effects ranging from 13% to 25%.[11,14,15] With dose-dependent adverse events, dosage adjustments are often sufficient to improve tolerability. The recommended practice is to go back to the last tolerated dose and reassess the patient's clinical condition before restarting uptitration. In general, especially in the first weeks of treatment, a slow uptitration schedule is the best way to minimize the burden of side effects. Good doctor-patient communication is also critical in ensuring treatment adherence during the initial phases of DMF therapy.[20]

GI disorders (most commonly diarrhea, abdominal pain, abdominal distension, and nausea) are reported in approximately 30-63% of patients treated with DMF or FAEs.[2,11,14] They are most likely to occur during the first 2-3 months of therapy.[5] Some authors suggest that the intensity of GI disorders peaks at 3-6 weeks after starting treatment and tends to stabilize by weeks 8-9.[20] It is recommended that DMF be taken with food to improve GI tolerability.[5] The use of specific drugs to ameliorate GI symptoms is not recommended, although mebeverine may be helpful because of its antispasmodic properties.[20] Another commonly reported adverse event is flushing, experienced by approximately 14-65% of patients on DMF or FAE treatment.[2,11,14,30] Episodes of flushing usually start shortly after drug intake and resolve within a few hours. Similarly to GI disorders, flushing is most likely to occur during the first weeks of treatment and tends to decrease in intensity over time.[5] In patients experiencing severe episodes, pre-treatment with aspirin may decrease the incidence and intensity of flushing, although continuous use of aspirin is not recommended.[20] White blood cell count abnormalities, particularly lymphopenia, may occur during treatment with DMF or FAEs. Lymphopenia is most likely to be observed during the first 3 months of treatment, is generally mild, and in most cases can be managed with dose adjustments. However, treatment discontinuation is required if dose adjustments fail to restore normal lymphocyte levels.[5,20] In the randomized BRIDGE trial, 10% of DMF-treated patients experienced lymphopenia, which was considered severe ($<0.5\times10^9$/L lymphocytes) in 1.1%. Hematologic monitoring throughout the study showed that the decrease in lymphocyte levels reached a maximum at 12 weeks after initiation of treatment when approximately one-third of the patient population had lymphocyte counts $<1.0\times10^9$/L.[2,5] In the observational FUTURE study on long-term treatment with FAEs, leukopenia, and lymphopenia were reported after 24 months of therapy in up to 12% and 41% of patients, respectively.[13] In a retrospective, long-term study that analyzed data from 859 patients treated with FAEs (as monotherapy or associated with other treatments), 4.3% of patients experienced leukopenia and 16.3% severe lymphopenia ($<0.5\times10^9$/L lymphocytes) at some point during treatment.[14] Dickel *et al*. also evaluated the effects of long-term FAE treatment on specific lymphocyte subpopulations in a large subcohort (n=371) of the population of their study and found that FAEs significantly reduced the number of CD4+ and CD8+ T cells, as well as CD19+ B and CD56+ natural killer cells, compared with baseline.[32] The mean percentage reduction was highest for CD8+ T cells after 2 years of therapy. The risk of T-cell lymphopenia was found to be significantly increased with the older age of patients at initiation of treatment and significantly decreased with methotrexate co-treatment and folic acid supplementation. A tendency towards faster improvement in symptom severity in patients with decreased CD4+ and CD8+ T-cell counts was also observed, supporting evidence for a link between FAE efficacy and lymphopenia. Since persistent moderate or severe lymphopenia is considered a risk factor for opportunistic infections, such as progressive multifocal leukoencephalopathy, the EMA has issued recommendations for pre-treatment hematologic screening and regular hematologic monitoring (a complete blood count including differential) at 3-month intervals, in patients undergoing DMF treatment.[5] Treatment should not be initiated if leukocyte counts are $<3.0\times10^9$/L or lymphocyte counts are $<1.0\times10^9$/L. Cut-off values for drug discontinuation during DMF treatment are a leukocyte count $<3.0\times10^9$/L or a lymphocyte count $<0.7\times10^9$/L on 2 consecutive tests 1 month apart. With lymphocyte counts $<1.0\times10^9$/L but $\geq0.7\times10^9$/L, monitoring should be performed monthly until levels return to $\geq1.0\times10^9$/L for 2 consecutive tests, at which point monitoring every 3 months can be resumed. Patients who discontinued treatment because of lymphopenia should be monitored until their lymphocyte count has returned to normal. Extreme caution is advised about the option of restarting DMF treatment in these patients once hematologic parameters are back to normal. Regarding lymphocyte monitoring, we would like to clarify that only absolute lymphocyte counts are included in the EMA recommendations. Some authors suggest that periodic monitoring of CD4+ and CD8+ counts may be warranted, especially in older patients.[32] However, more information is required before lymphocyte subpopulation monitoring can be recommended.

Transient increases in eosinophil counts may also be observed in some patients at the start of FAE treatment. However, eosinophilia is usually self-limiting without dose adjustments and rarely leads to treatment discontinuation.[20,30] Increases in liver enzymes and serum creatinine levels in up to 40% and 19% of patients, respectively, have been reported in long-term studies on FAEs, but were usually mild and very rarely necessitated treatment discontinuation.[13,14]

Follow-up

Once the desired clinical effect has been achieved and the maintenance dosage identified, DMF treatment should be continued indefinitely, as long as efficacy and tolerability are maintained. Since hematologic parameters need to be monitored every 3 months, follow-up visits for clinical assessment can be scheduled at the same time (Table 5).

Although data on long-term treatment with DMF are limited, the sustained efficacy and long-term safety of FAEs in real-world settings are well-documented. In the FUTURE study, which collected data from 984 patients with psoriasis who had been treated with FAEs for ≥2 years, clinical efficacy actually improved over the course of treatment, with 83.6% of patients classified as markedly improved or clear (according to PGA) after >36 months of therapy compared with 67% after 6 months. In addition, >80% of patients were still being treated with FAEs at the time of documentation.[13] Cumulative improvements over time in PGA and

Table 5. Follow-up.

Statement	Based on
19. Follow-up visits can be planned at 3-month intervals, at the same time as the hematology tests.	Expert opinion
20. Once the clinical response has been reached and the minimum maintenance dosage identified, therapy with DMF can continue indefinitely based on the maintenance of clinical response.	Literature data

DMF, dimethyl fumarate.

PASI responses were also observed in the retrospective study by Dickel *et al*.,[14] which included 859 patients who had been continuously treated with FAEs for a mean of 3.6 years. Considerations about safety with long-term therapy also support the protracted use of FAEs. Data from the German Psoriasis Registry PsoBest regarding 2444 patients treated with conventional or biologic systemic drugs (including 981 patients treated with FAEs for a total exposure time of 807.8 years) show that FAEs did not increase the risk of infections, major adverse cardiac events, or other severe cardiovascular events, or malignancies compared with other systemic treatments for psoriasis.[33] In particular, FAE treatment was associated with the lowest risk for non-severe infections and non-melanoma skin cancer among all anti-psoriatic agents. Drug survival analyses are another important source of information documenting the long-term therapeutic benefits of DMF or FAEs. Drug survival is an indicator of therapeutic success, reflecting a combination of efficacy, safety, and treatment satisfaction. In a retrospective analysis of 373 patients who had been treated for psoriasis in a university hospital in the period 2003-2014, cumulative 1-year survival rates for FAEs (46%) were higher than those observed for the other systemic non-biologic anti-psoriatic agents (43% for methotrexate, 37% for acitretin, and 16% for ciclosporin); 3-year survival rates were 35% for FAEs, 20% for methotrexate, and 23% for acitretin.[34] In another retrospective study, the 4-year survival rate of FAEs was 60%.[15]

Conclusions

Despite the introduction of newer highly efficacious biologic agents, we think that DMF still plays an important role as a first-line treatment option for moderate-to-severe psoriasis, since it offers some advantages over other treatments and displays pharmacokinetic characteristics that may be highly appreciated in selected patient populations. In particular cases, DMF may indeed be the only option (or one of the very few options) available for systemic therapy. Several clinically meaningful factors characterize treatment with DMF:

i. dosage flexibility allows for personalized dosing tailored to the patient's clinical response and individual requirements;
ii. DMF is not metabolized by common pathways such as the cytochrome P450 system, and consequently, the drug-drug interaction potential is very low. Therefore, DMF can be used in patients with comorbidities receiving co-medication (unlike other systemic anti-psoriatic agents, which have known interactions with commonly used drugs);
iii. the metabolic pathway and route of elimination of DMF (mainly via exhalation of carbon dioxide) enable safe use in patients with mild or moderate hepatic or renal impairment (such as many elderly patients) without dose adjustments;
iv. DMF has an excellent long-term safety profile in terms of risks of infection, cardiovascular events, or malignancies, which has been established over a long history of experience with FAE-based products;
v. once the maintenance dose has been reached, DMF demonstrates sustained clinical efficacy, with drug survival rates that compare favorably with those of other systemic treatments;
vi. DMF has proven efficacy also in the treatment of impactful areas, such as the scalp, nails, genitals, palms, and soles.

DMF is a slow-acting drug, often requiring months or even years before reaching maximum effectiveness. Side effects (especially GI disorders and flushing) are common when starting therapy and may be burdensome but are generally mild and transient and can often be managed successfully with a careful titration schedule based on gradual dosage increases, particularly during the first few weeks. Lymphopenia (another frequently reported side effect of DMF) can also be corrected with dose adjustments in most cases, and regular hematologic monitoring should be performed throughout the treatment course. When properly managed, DMF treatment can provide meaningful clinical benefits to many patients with moderate-to-severe psoriasis, especially those with treatment needs that, for various reasons (*e.g.* age, comorbidities, polypharmacy), are still unmet.

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