ORIGINAL ARTICLE

Quality of life outcomes in adults with moderate-to-severe plaque psoriasis treated with dimethylfumarate (DMF): a post hoc analysis of the BRIDGE study

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Abstract

Background Psoriasis is a chronic inflammatory skin disease associated with quality of life (QoL) impairment. BRIDGE was a randomized, double-blind, phase III study comparing the efficacy and safety of dimethylfumarate (DMF) with a fixed combination of fumaric acid esters (FAE) or placebo for the treatment of moderate-to-severe psoriasis.

Objectives This post hoc analysis investigated treatment effect on QoL overall and by patient subgroups categorized by disease severity. Week 8 efficacy responses were also investigated as possible predictors of Week 16 Dermatology Life Quality Index (DLQI) outcomes.

Methods Patients were randomized to receive a maximum daily dose of 720 mg of DMF, FAE (gradual up-titration) or placebo for 16 weeks. Psoriasis Area Severity Index, Body Surface Area, Physician's Global Assessment and DLQI were assessed at baseline, Weeks 8 and 16. DLQI 0-1 indicated 'no effect on patient life'. Associations between baseline severity, Week 16 DLQI and Week 8 efficacy (as observed cases) were also examined.

Results At baseline, 671 patients were included in the full analysis set (267 randomized to DMF, 273 to FAE and 131 to placebo). DMF was superior to placebo ($P < 0.001$) and not significantly different to FAE regarding Week 16 DLQI outcomes ($P > 0.05$). Baseline disease severity did not impact DLQI outcomes at Week 16. In DMF- and FAE-treated patients, Week 8 PASI 50/75 responders reported better DLQI responses at Week 16 vs non-responders ($P < 0.05$). Week 8 PASI ≤ 3 and/or PGA 0-1 responders were also more likely to report DLQI 0-1 at Week 16 vs non-responders ($P < 0.05$).

Conclusion Dimethylfumarate significantly improved DLQI outcomes vs. placebo and was not affected by baseline disease severity. Efficacy responses (PASI 50/75, PASI ≤ 3 and PGA 0-1) as early as Week 8 were predictive of QoL outcomes at Week 16 in DMF- and FAE-treated patients.

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Introduction

Psoriasis is a chronic inflammatory skin disease with systemic manifestations that affects between ~2% and 4% of the Western population.[1–4] Psoriasis may also be accompanied by substantial comorbidity, including metabolic and cardiovascular complications, inflammatory bowel disease and psoriatic arthritis. Consequently, patients commonly experience psychological and social burden associated with their disease.[5,6]

Treatment selection for psoriasis patients depends on clinical need and disease severity. Patients with moderate-to-severe psoriasis are commonly treated with different types of therapy (topical agents, phototherapy, oral systemic small molecule non-biologicals and systemic biologicals); however, some may receive early intervention with systemic therapies, depending on their disease severity.[7] Recent updates to the European S3 psoriasis treatment, guidelines recommend that involvement of visible areas of the body, scalp, genitals and/or fingernails, and scratching due to itch, are criteria for the upgrade of mild to moderate-to-severe psoriasis, supporting the need for earlier treatment with systemic agents in some patients.[8]

Commonly prescribed systemic agents historically included methotrexate, ciclosporin and acitretin.[9] A fixed combination of fumaric acid esters (FAE); Fumaderm® (Biogen, Idec GmbH, Germany), of which dimethylfumarate (DMF) is the main active ingredient, has also been shown to display good efficacy and safety long-term and is currently one of the most commonly used psoriasis treatments in Germany.[10]

The BRIDGE study investigated the efficacy and safety of a new oral formulation of DMF as monotherapy, compared with FAE (Fumaderm®) and placebo, in patients with moderate-to-severe psoriasis.[11] DMF demonstrated superiority over placebo ($P < 0.001$) and non-inferiority vs. the FAE combination ($P < 0.001$) in the percentage of patients who achieved a ≥75% improvement in the Psoriasis Area and Severity Index (PASI 75) at Week 16. DMF also demonstrated a favourable safety profile.[11] DMF (Skilarence®) as monotherapy received marketing authorization for the treatment of moderate-to-severe psoriasis throughout the European Union in June 2017 and is the only FAE to be licensed throughout Europe.[12]

PASI, Body Surface Area (BSA) and Physician's Global Assessment (PGA) are commonly used to assess psoriasis treatment effectiveness.[13,14] However, quality of life (QoL) outcomes are also important when establishing patient benefit. Psoriasis can affect patients physically and emotionally, leading to anxiety, depression, reduced work productivity and higher financial burden associated with absenteeism.[5,15] Thus, the need for treatments to demonstrate a real-world impact on QoL is growing. BRIDGE investigated the effect of DMF on patient QoL using the Dermatology Quality of Life Index (DLQI).[11]

Here, we report a post hoc analysis of the impact of DMF treatment on QoL outcomes as assessed during BRIDGE, with emphasis on subgroups categorized by baseline disease severity. This study also investigated the BRIDGE efficacy measures at Week 8 (≥50% reduction in PASI [PASI 50], PASI 75, PASI ≤3, PGA of 'clear' or 'almost clear' [PGA 0-1], BSA 10–20% or >20%) as predictors of DLQI outcomes at Week 16.

Materials and methods

The BRIDGE trial (NCT01726933; EudraCT 2012-000055-13) was a multi-centre, randomized, double-blind, three-arm, 16 week, adaptive phase III study as previously described.[11] This trial was conducted in Austria, Germany, the Netherlands and Poland in patients recruited from January 2013.

Patients and treatment

Patients ≥18 years with moderate-to-severe plaque psoriasis (PASI > 10; BSA > 10%; PGA ≥ 3), with a diagnosis of ≥12 months were randomized 2:2:1 to receive DMF (Skilarence®), FAE (Fumaderm®) or placebo. Pre-treated patients underwent a washout period prior to treatment initiation. Concomitant treatment with topical and/or additional systemic therapies was not permitted.

Pregnant or breastfeeding patients, patients who failed to respond to previous FAE treatment due to lack of efficacy or tolerability and patients with baseline leucocyte counts $<3 \times 10^9$ cells/L and/or lymphocyte counts $<1 \times 10^9$ cells/L were excluded from the study.

Study drugs were up-titrated over a 9-week period, to a maximum daily dose of 720 mg. All patients underwent 16 weeks of treatment and an off-treatment follow-up period of 12 months to assess safety, rebound and persistence of response.

Assessments

The BRIDGE study assessed the percentage of patients who achieved PASI 75 and PGA 0-1 at Week 16 as co-primary endpoints. Secondary endpoints included PASI 75 at Weeks 3 and 8, total PASI, PASI 50/90 at Weeks 3, 8 and 16, PGA 0-1 at Weeks 3 and 8, and BSA at Weeks 3, 8 and 16. QoL was assessed using the DLQI and was measured at baseline and Week 16.

The DLQI comprises 10 questions relating to symptoms, feelings, daily activities, leisure, work, school, personal relationships and treatment and ranges from 0 to 30. An index of 0-1 indicates

no effects at all on patient life; 2–5 a small effect; 6–10 a moderate effect; 11–20 a very large effect; and 21–30 an extremely large effect on patient life.[16] This post hoc analysis evaluated associations between baseline disease severity parameters and DLQI response at Week 16. Efficacy responses at Week 8 (PASI 50, PASI 75, PGA 0-1, PASI ≤ 3 and BSA ≤ 3) were also examined as predictors of a DLQI 0-1 or a ≥5-point reduction in DLQI at Week 16.

Statistical analyses

Dermatology Life Quality Index responses were evaluated for the comparison between treatments using an analysis of covariance model with treatment and centre as factors and were based on the full analysis set (FAS): all patients with at least one measurement of the primary efficacy variables after Week 0. Statistical comparisons between treatment groups were performed using the Cochran–Mantel–Haenszel test for categorical data.

Post hoc analyses were also performed on the FAS population. A chi-squared test between disease severity at baseline (as a categorical variable) and DLQI 0-1 at Week 16 was carried out. A t-test was used when considering baseline disease severity as a continuous variable. Efficacy responses at Week 8 (binary variables: PASI 50/75, PASI ≤3, PGA 0-1) were also analysed as possible predictors of DLQI 0-1 at Week 16 using chi-squared testing. Results at Week 16/end of treatment were analysed using a prospectively defined observed case approach with adjustment for centre. Thus, no imputation technique was applied for missing observations, although the use of end-of-trial visit scores as Week 16 values for patients who discontinued before Week 16 allowed for simulation of a last observation carried forward approach.

Results

At baseline, 671 patients were included in the FAS. Of these, 267 were randomized to DMF, 273 to FAE and 131 to placebo. Mean (SD) DLQI at baseline in the DMF, FAE combination and placebo cohorts was 11.3 (6.26), 12.0 (7.04) and 10.9 (6.49), respectively (Fig. 1).

At Week 16, mean (SD) DLQI in DMF-treated patients was significantly lower vs placebo-treated patients, with scores of 5.4 (6.07) and 8.5 (6.88), respectively ($P < 0.0001$). Significantly more patients in the DMF cohort (36.0%) reported a DLQI 0-1 response at Week 16, compared with placebo (15.3%; $P < 0.001$). No significant differences were reported between DLQI responses in DMF and FAE-treated patients at Week 16 ($P > 0.05$; Fig. 1). Additionally, mean (SD) % change from baseline in DLQI score at Week 16 was −46.36 (54.56), −34.46 (101.22) and −4.53 (86.59) for the DMF ($n = 252$), FAE combination ($n = 254$) and placebo ($n = 117$) groups, respectively.

QoL measures at baseline by disease severity

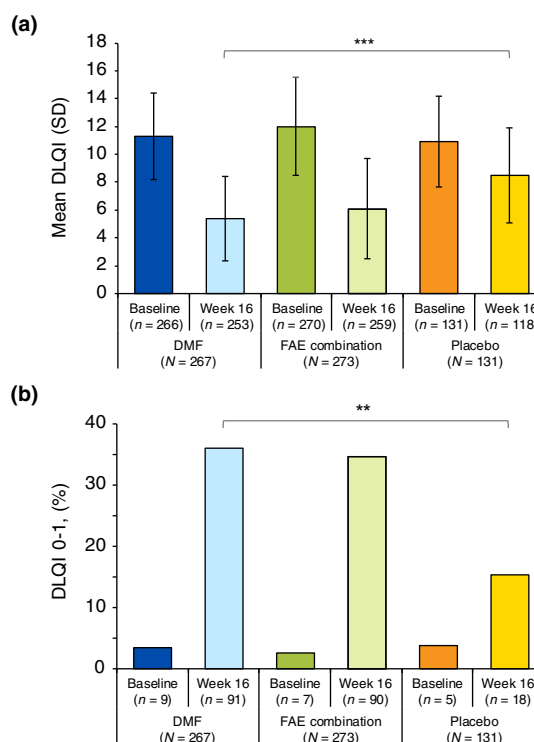In the DMF cohort, 223 (83.5%) and 43 (16.1%) patients reported a baseline PASI of 10-20 and >20, respectively

Figure 1 (a) Mean (SD) DLQI and (b) percentage of patients who reported a DLQI 0-1 response at baseline and Week 16 treated with DMF, FAE combination or placebo. **$P < 0.001$; ***$P < 0.0001$. DLQI, Dermatology Life Quality Index; DMF, dimethylfumarate; FAE, fumaric acid ester; SD, standard deviation.

(Table 1). Mean (SD) baseline DLQI was 10.89 (5.81) in the PASI 10-20 subgroup and 13.51 (7.94) in the PASI >20 subgroup.

Baseline disease severity was similar in the FAE cohort, with 221 (81.0%) and 49 (17.9%) patients reporting PASI 10-20 and PASI >20, respectively (Table 1). Mean (SD) DLQI at baseline was 11.58 (7.02) in the PASI 10-20 subgroup and 13.78 (6.90) in the PASI >20 subgroup. In the placebo cohort, 108 (82.4%) and 23 (17.6%) patients reported a PASI of 10-20 and PASI >20, respectively, with mean (SD) DLQI at baseline of 10.20 (6.54) and 14.35 (5.15), respectively (Table 1).

QoL measures at Week 16 by baseline disease severity

Mean DLQI at Week 16 by baseline PASI severity At Week 16, QoL outcomes for DMF-treated patients were similar across baseline severity subgroups with mean (SD) DLQI of 5.57 (6.18) and 4.42 (5.47) in the PASI 10-20 and PASI >20 subgroups, respectively. Similarly, in the FAE cohort, mean (SD) DLQI at Week 16 was 5.96 (7.13) and 6.64 (7.50) in the PASI 10-20 and PASI >20 subgroups, respectively, indicating that QoL outcomes

Table 1 Baseline patient demographics by disease severity

	DMF (*n* = 267)	FAE combination (*n* = 273)	Placebo (*n* = 131)
PASI at baseline			
Mean (SD) PASI	16.0 (5.17)	16.1 (6.84)	15.5 (4.60)
PASI 10-20, *n* (%)	223 (83.52)	221 (80.95)	108 (82.44)
PASI >20, *n* (%)	43 (16.10)	49 (17.95)	23 (17.56)
PGA at baseline			
Mean (SD) PGA	3.44 (0.58)	3.45 (0.60)	3.42 (0.54)
PGA 3, *n* (%)	162 (60.67)	162 (59.34)	79 (60.31)
PGA 4-5, *n* (%)	104 (38.95)	108 (39.56)	52 (39.69)
BSA at baseline			
Mean % (SD) BSA affected	21.93 (11.61)	21.27 (12.45)	21.90 (12.25)
BSA 10–20%, *n* (%)	167 (62.55)	181 (66.30)	83 (63.36)
BSA >20%, *n* (%)	99 (37.08)	89 (32.60)	48 (36.64)
DLQI at baseline			
Mean (SD) DLQI	11.3 (6.26)	12.0 (7.04)	10.9 (6.49)
DLQI 1-10, *n* (%)	126 (47.19)	126 (46.15)	68 (51.91)
DLQI >10, *n* (%)	140 (52.43)	144 (52.75)	63 (48.09)

BSA, Body Surface Area; DMF, dimethylfumarate; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment.

with DMF and FAE are not impacted by baseline disease severity. These findings are corroborated by the high percentage DLQI changes from baseline compared to placebo, in both severity groups (Table S1).

DLQI 0-1 and ≥5-point reduction responses at Week 16 by baseline severity

No significant difference was observed between the number of DMF-treated patients with a baseline PASI of 10-20 (34.8%) and >20 (41.9%) who reported DLQI 0-1 at Week 16 ($P = 0.3769$; Fig. 2).

This was also true for PGA: 38.3% and 32.3% of DMF-treated patients with baseline PGA of 3 and 4-5 reported DLQI 0-1 at Week 16, respectively ($P = 0.3327$; Fig. 2). Moreover, 35.3% of patients with a baseline BSA of 10–20% and 37.1% of patients with a baseline BSA of >20% reported DLQI 0-1 at Week 16 following treatment with DMF ($P = 0.7647$; Fig. 2).

Similarly, achievement of a ≥5-point reduction in DLQI at Week 16 was not affected by baseline disease severity in the DMF cohort: 46.7% of patients with less (PASI 10-20) and 59.5% of patients with more (PASI >20) severe disease at baseline reported a ≥5-point reduction in DLQI at Week 16 ($P = 0.1281$; Fig. 2).

As with PASI, 47.4% and 51.0% of DMF-treated patients with baseline PGA of 3 and 4-5 reported DLQI 0-1 at Week 16, respectively ($P = 0.5754$). Likewise, baseline BSA severity did not affect Week 16 DLQI 0-1 responses ($P = 0.4147$; Fig. 1). DLQI outcomes by baseline disease severity like those described for the DMF cohort were also reported in the FAE and placebo cohorts (Fig. 2).

DLQI 0-1 response at Week 16 by corresponding absolute PASI outcome

For patients who achieved DLQI 0-1 at Week 16, their corresponding absolute PASI was also evaluated. In total, 70 DMF-treated patients (80.5%) who reported DLQI 0-1 at Week 16 reported a corresponding absolute PASI of ≤5. Moreover, 59 (67.8%) and 33 (37.9%) of these patients who reported DLQI 0-1 at Week 16 also reported a PASI of ≤3 and ≤1, respectively. A similar PASI profile was observed in FAE-treated Week 16 DLQI 0-1 responders, with 73 (88.0%), 62 (74.7%) and 34 (41.0%) patients reporting a corresponding absolute PASI of ≤5, ≤3 or ≤1, respectively (Fig. 3). Finally, in the placebo cohort, 11 (64.7%) Week 16 DLQI 0-1 responders reported an absolute PASI of ≤5, 9 (52.9%) a PASI of ≤3 and 3 (17.6%) a PASI of ≤1.

Baseline severity and DLQI 0-1 response at Week 16

Baseline disease severity parameters PASI ($P = 0.7129$), BSA ($P = 0.9849$) and PGA ($P = 0.6276$) were not related to DLQI 0-1 response in DMF-treated patients at Week 16. This was also true of Week 16 responses in patients treated with FAE or placebo.

Efficacy response at Week 8 and subsequent DLQI outcomes at Week 16

PASI at Week 8 In the DMF cohort, significantly more Week 8 PASI 75 responders went on to report DLQI 0-1 at Week 16 vs. PASI 75 non-responders who reported DLQI 0-1 at Week 16 (65.0% vs 33.5%; $P = 0.0048$). A ≥5-point reduction in DLQI at Week 16 was also more frequent in Week 8 PASI 75 responders
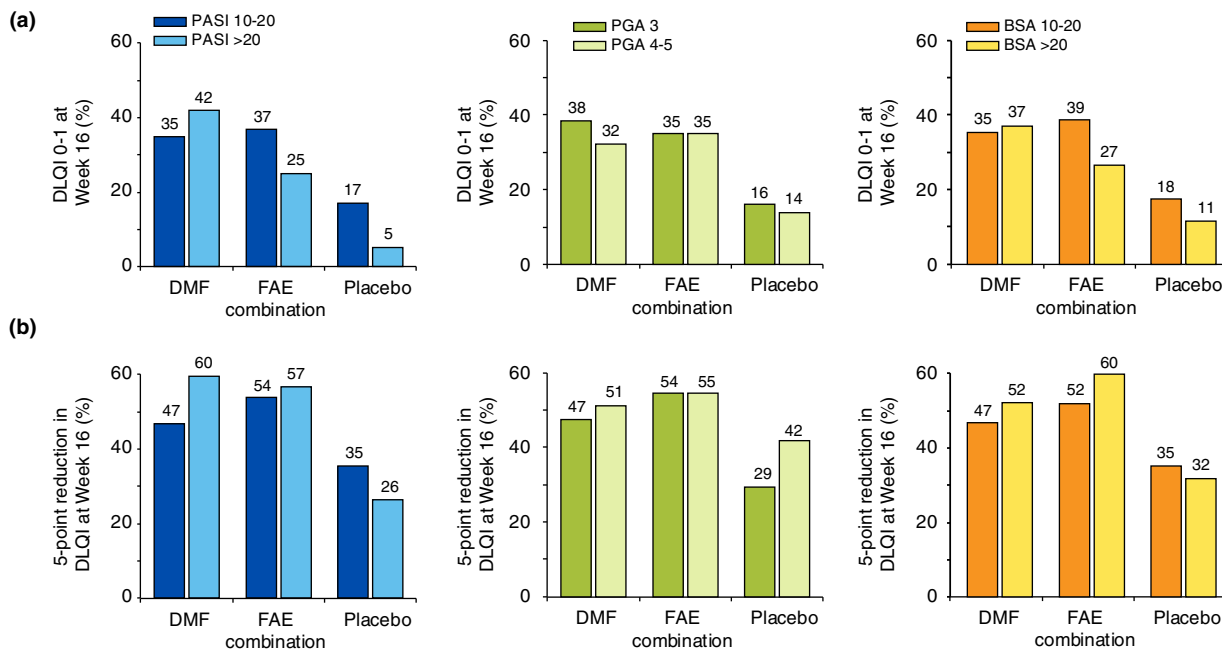
Figure 2 Percentage of patients who reported (a) DLQI 0-1 and (b) ≥5-point reduction responses at Week 16 by baseline disease severity, in patients treated with DMF, FAE combination and placebo. No significant differences were observed between disease severity subgroups (*P* > 0.05). Chi-square tests. BSA, Body Surface Area; DLQI, Dermatology Life Quality Index; DMF, dimethylfumarate; FAE, fumaric acid ester; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment.
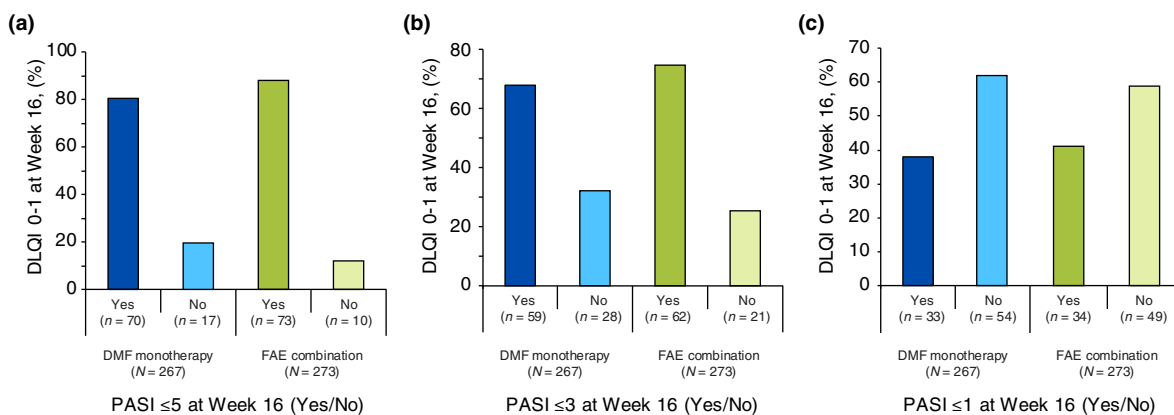

Figure 3 Percentage of patients who reported DLQI 0-1 at Week 16 and their corresponding absolute PASI score at Week 16; (a) PASI ≤5, (b) PASI ≤3 and (c) PASI ≤1. DLQI, Dermatology Life Quality Index; DMF, dimethylfumarate; FAE, fumaric acid ester; PASI, Psoriasis Area and Severity Index.

compared with non-responders (70.0% vs 47.0%; *P* = 0.0482). In the FAE cohort, similar trends were observed: significantly more Week 8 PASI 75 responders went on to achieve DLQI 0-1 (*P* = 0.0059) and ≥5-point reduction (*P* = 0.0010) responses at

Week 16 compared with Week 8 PASI 75 non-responders (Fig. 4).

As with PASI 75, significantly more DMF- and FAE-treated patients achieved DLQI 0-1 at Week 16, after achieving PASI 50
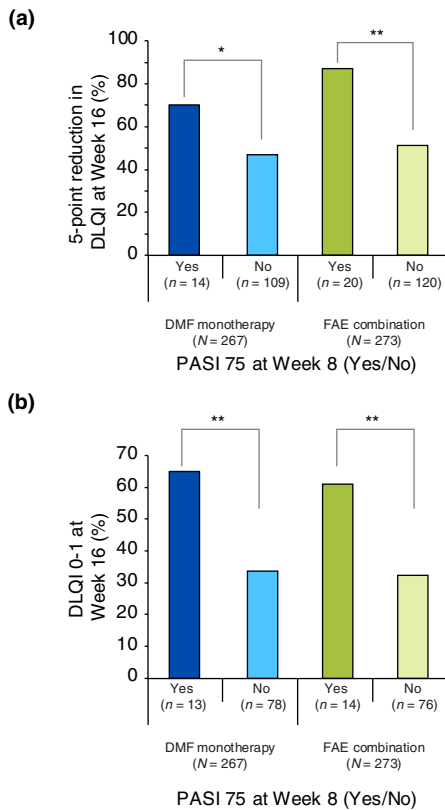
Figure 4 (a) PASI 75 at Week 8 as a predictor of a ≥5-point reduction in DLQI at Week 16 (percentage of responding patients). (b) PASI75 response at Week 8 as a predictor of DLQI 0-1 at Week 16 (percentage of responding patients). *P < 0.05; **P < 0.01. Chi-square tests. DLQI, Dermatology Life Quality Index; DMF, dimethylfumarate; FAE, fumaric acid ester; PASI, Psoriasis Area and Severity Index; PASI 75, 75% reduction in PASI.
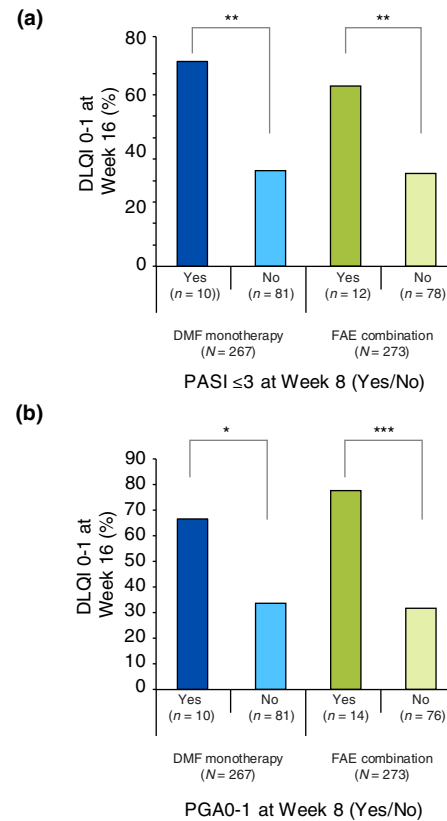
Figure 5 (a) PASI ≤3 and (b) PGA 0-1 at Week 8 as predictors of a DLQI 0-1 response at Week 16 (percentage of responding patients). *P < 0.05, **P < 0.01, ***P < 0.001 Chi-square tests. DLQI, Dermatology Life Quality Index; DMF, dimethylfumarate; FAE, fumaric acid ester; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment.

at Week 8 vs PASI 50 non-responders ($P < 0.0001$ and $P = 0.0004$ for DMF and FAE, respectively). The same was also true of a ≥5-point reduction in DLQI at Week 16 in DMF- and FAE-treated patients ($P = 0.0015$ and $P = 0.0011$ for DMF and FAE, respectively).

Achievement of absolute PASI ≤3 was also investigated. Significantly more DMF-treated patients reported DLQI 0-1 at Week 16, after achieving PASI ≤3 at Week 8 vs Week 8 PASI ≤3 non-responders who reported DLQI 0-1 at Week 16 ($P = 0.0044$). Likewise, more FAE-treated Week 8 PASI ≤3 responders also went on to achieve DLQI 0-1 at Week 16 ($P = 0.0069$; Fig. 5).

No significant difference in DLQI ≥5-point reduction responses at Week 16 was observed between Week 8 PASI ≤3 responders and non-responders treated with DMF ($P = 0.0815$). Conversely, more FAE-treated Week 8 PASI ≤3 responders went on to achieve a ≥5-point reduction in DLQI at Week 16

compared with Week 8 PASI ≤3 non-responders ($P = 0.0015$; Fig. S1).

PGA at Week 8 PGA 0-1 at Week 8 correlated with a higher likelihood of DLQI 0-1 at Week 16. In DMF-treated patients, significantly more Week 8 PGA 0-1 responders went on to report DLQI 0-1 at Week 16 compared with Week 8 PGA 0-1 non-responders ($P = 0.0106$). In FAE-treated patients, PGA 0-1 at Week 8 also correlated with a higher incidence of DLQI 0-1 responses at Week 16 ($P < 0.0001$; Fig. 5).

No significant difference in DLQI ≥5-point reduction responses at Week 16 was observed between Week 8 PGA responders and non-responders treated with DMF ($P = 0.0501$). Conversely, more FAE-treated Week 8 PGA 0-1 responders went on to achieve a ≥5-point reduction in DLQI at Week 16 compared with Week 8 PGA 0-1 non-responders ($P = 0.0108$; Fig. S1).

BSA at Week 8 No significant correlations were observed between BSA responses at Week 8 and DLQI responses at Week 16 (data not shown).

Discussion

Dimethylfumarate was superior to placebo and not significantly different to FAE regarding DLQI outcomes at Week 16. DMF-treated patients reported a mean 5.9-point reduction in DLQI following 16 weeks of treatment. This post hoc analysis also further investigated the impact on QoL in DMF- and FAE-treated patients, with a focus on subgroups as categorized by disease severity. DLQI responses at Week 16 were not impacted by baseline disease severity. No significant differences in DLQI outcomes were reported between patients with more, or less severe baseline disease, as assessed with PASI, BSA or PGA. These benefits of DMF and FAE are encouraging when considering patient suitability for treatment; baseline disease severity may not be a limiting factor.

PASI 50 and 75 at Week 8 were predictors of DLQI 0-1 and ≥5-point reduction at Week 16 in both the DMF and FAE cohorts. Our findings are in line with other studies that have reported an association between clinical response and QoL outcomes.[17–21] Mattei and colleagues reported that a PASI 75 response translated into a significant improvement in QoL, supporting its use as a tool to predict patient benefit.[22] A ≥5-point reduction in DLQI has also been shown to indicate a minimal clinically important difference (MCID) in QoL and may be a useful tool to assess treatment success.[23]

According to a European consensus on psoriasis treatment goals, an absolute DLQI of ≤5 or >5 may be used in conjunction with PASI to determine whether a patient should continue or terminate treatment.[24] This consensus recommends that while treatment failure may be indicated by a 50% or less improvement in PASI, any PASI improvement greater than 50% but less than 75% may be evaluated in conjunction with DLQI to determine the need for treatment modification (PASI ≥50% <75% and absolute DLQI >5, treatment should be modified; PASI ≥50% <75% and absolute DLQI ≤5, treatment should be continued).[24] While there may not yet be full consensus on how best to define treatment goals, efficacy responses at Week 8 as predictors of DLQI outcomes may prove to be useful monitors of treatment success. Moreover, DLQI 0-1 and a ≥5-point reduction in DLQI are both clinically relevant means by which to assess treatment efficacy.

An absolute PASI of ≤3 at Week 8 was also a predictor of DLQI 0-1 at Week 16; however, it was not predictive of a ≥5-point reduction. While PASI 50/75[24,25] and even PASI 90/100[26] responses are widely regarded as therapeutic goals, absolute PASI might also be relevant. A Spanish consensus on psoriasis treatment concluded that absolute PASI should be considered a goal and may show better correlation with DLQI than relative PASI.[27] In addition, good QoL is more commonly achieved in patients who report low absolute PASI.[28] Our findings are in line with this and also suggest that absolute PASI has predictive value for determining subsequent DLQI responses and treatment success.

PGA 0-1 at Week 8 was predictive of DLQI responses at Week 16 in both the DMF and FAE groups. Like PASI, PGA outcomes have been shown to correlate with improved QoL outcomes; thus, this result may be expected. In a multi-centre cross-sectional study, Takeshita and colleagues found that psoriasis patients treated with systemic therapy or phototherapy who reported PGA 0-1 were more likely to report that psoriasis had no effect on their QoL.[29] PGA responses may thus also be useful measures of treatment success. Low patient numbers as observed here may reflect the early time point at which efficacy was recorded. Studies investigating the efficacy of FAE have reported that maximum clinical effect may not be reached until Week 24.[30]

Up to 20% of DMF- and FAE-treated patients who did not achieve PASI 75 at Week 16 achieved DLQI 0-1 (vs. 8% with placebo), suggesting that in a subgroup of patients DLQI may not be completely dependent upon efficacy outcomes. This was also shown upon evaluation of absolute PASI at Week 16 of DLQI 0-1 responders in the DMF cohort. Only approximately one third (37.9%) of patients who reported DLQI 0-1 at Week 16 also achieved a PASI ≤1. The remaining two thirds (62.1%) of DLQI 0-1 responders reported good QoL outcomes while not achieving fully cleared skin (PASI >1). Treatment goals to achieve clear skin may thus not guarantee 'happy' patients, and by the same token, patient satisfaction may not be wholly dependent upon clear skin.

While several studies have confirmed a correlation between PASI and DLQI, there is no evidence for redundancy between the two measures. As reported here, patients may achieve improved QoL outcomes despite not reaching target efficacy. Kimball and colleagues reported that 50% of etanercept-treated patients who did not reach PASI 50 still reported at least a 50% improvement in DLQI.[31] These measures evaluate different aspects of psoriasis and can provide valuable information about patient response to therapy. The correlation between the two measures may rather be used to inform mid-treatment evaluation and to predict treatment success in the future.

Finally, the impact of DMF as reported at Week 16 in this study is in contrast to some studies with FAE that have demonstrated that full clinical efficacy may not be reached until up to 24 weeks.[30] Interim analysis of data collected during the ongoing 52-week DIMESKIN trial (EudraCT: 2017-001368-40) investigating the long-term efficacy of DMF in patients with moderate-to-severe psoriasis revealed a significant reduction in median DLQI scores between baseline (10.5) and following 24 weeks of treatment (1.0; $P < 0.001$ [$n = 84$]).[32] In another observational study investigating DLQI outcomes in FAE-treated patients, mean DLQI in patients demonstrated an 8.9-point improvement following 12 months of treatment.[33] This post hoc analysis to

examine the effects of DMF on QoL outcomes according to baseline severity has further demonstrated that DMF has significant impact on patient QoL and that efficacy responses as early as Week 8 may serve as predictors of QoL outcomes and treatment success.

References

1 Parisi R, Symmons DP, Griffiths CE et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* 2013; **133**: 377–385.

2 Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. *J Investig Dermatol Symp Proc* 2004; **9**: 136–139.

3 Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch Dermatol* 2005; **141**: 1537–1541.

4 Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003–2004. *J Am Acad Dermatol* 2009; **60**: 218–224.

5 Bhosle MJ, Kulkarni A, Feldman SR, Balkrishnan R. Quality of life in patients with psoriasis. *Health Qual Life Outcomes* 2006; **4**: 35.

6 Oliveira Mde F, Rocha Bde O, Duarte GV. Psoriasis: classical and emerging comorbidities. *An Bras Dermatol* 2015; **90**: 9–20.

7 American Academy of Dermatology Work G, Menter A, Korman NJ et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. *J Am Acad Dermatol* 2011; **65**: 137–174.

8 Nast A, Gisondi P, Ormerod AD et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris–Update 2015–Short version–EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol* 2015; **29**: 2277–2294.

9 Menter A, Korman NJ, Elmets CA et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol* 2009; **61**: 451–485.

10 Mrowietz U, Barker J, Boehncke WH et al. Clinical use of dimethyl fumarate in moderate-to-severe plaque-type psoriasis: a European expert consensus. *J Eur Acad Dermatol Venereol* 2018; **32**(Suppl 3): 3–14.

11 Mrowietz U, Szepietowski JC, Loewe R et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm(R) - and placebo-controlled trial (BRIDGE). *Br J Dermatol* 2017; **176**: 615–623.

12 European Medicines Agency (EMA). EPAR summary for the public: Skilarence, dimethyl fumarate. URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002157/WC500231110.pdf (last accessed: 2017 July 2018).

13 Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. *Ann Rheum Dis* 2005; **64**(Suppl 2): ii65–ii68; discussion ii69-73.

14 Oji V, Luger TA. The skin in psoriasis: assessment and challenges. *Clin Exp Rheumatol* 2015; **33**: S14–S19.

15 Feldman SR, Fleischer AB Jr, Reboussin DM et al. The economic impact of psoriasis increases with psoriasis severity. *J Am Acad Dermatol* 1997; **37**: 564–569.

16 Finlay AY. Quality of life measurement in dermatology: a practical guide. *Br J Dermatol* 1997; **136**: 305–314.

17 Reich K, Griffiths CE. The relationship between quality of life and skin clearance in moderate-to-severe psoriasis: lessons learnt from clinical trials with infliximab. *Arch Dermatol Res* 2008; **300**: 537–544.

18 Revicki DA, Willian MK, Menter A, Saurat JH, Harnam N, Kaul M. Relationship between clinical response to therapy and health-related quality of life outcomes in patients with moderate to severe plaque psoriasis. *Dermatology* 2008; **216**: 260–270.

19 Mazzotti E, Picardi A, Sampogna F et al. Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis. *Br J Dermatol* 2003; **149**: 318–322.

20 Gelfand JM, Feldman SR, Stern RS, Thomas J, Rolstad T, Margolis DJ. Determinants of quality of life in patients with psoriasis: a study from the US population. *J Am Acad Dermatol* 2004; **51**: 704–708.

21 Rakhesh SV, D'Souza M, Sahai A. Quality of life in psoriasis: a study from south India. *Indian J Dermatol Venereol Leprol* 2008; **74**: 600–606.

22 Mattei PL, Corey KC, Kimball AB. Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. *J Eur Acad Dermatol Venereol* 2014; **28**: 333–337.

23 Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology* 2015; **230**: 27–33.

24 Mrowietz U, Kragballe K, Reich K et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res* 2011; **303**: 1–10.

25 National Institute of Clinical Excellence (NICE). Clinical Guideline (CG153). Psoriasis: assessment and management. 2017. URL https://www.nice.org.uk/guidance/cg153/chapter/1-guidance (last accessed October 2018).

26 Manalo IF, Gilbert KE, Wu JJ. Time to raise the bar to psoriasis area severity index 90 and 100. *J Drugs Dermatol* 2015; **14**: 1086–1088.

27 Carretero G, Puig L, Carrascosa JM et al. Redefining the therapeutic objective in psoriatic patients candidates for biological therapy. *J Dermatolog Treat* 2018; **29**: 334–346.

28 Zheng J. Absolute Psoriasis Area and Severity Index: an additional evaluation for clinical practice. *Br J Dermatol* 2017; **176**: 576.

29 Takeshita J, Callis Duffin K, Shin DB et al. Patient-reported outcomes for psoriasis patients with clear versus almost clear skin in the clinical setting. *J Am Acad Dermatol* 2014; **71**: 633–641.

30 Smith D. Fumaric acid esters for psoriasis: a systematic review. *Ir J Med Sci* 2017; **186**: 161–177.

31 Kimball AB, Krueger GG, Woolley JM. The dermatology life quality index (DLQI) provides qualitatively different information from the PASI. *J Am Acad Dermatol* 2004; **50**(Suppl 3):156.

32 Dauden E, Carrascosa JM, De la Cueva P, Pau-Charles I, Fernandez-Soriano FJ. Efficacy of dimethylfumarate after 24 weeks of treatment according to clinical practice in patients with moderate-to-severe psoriasis. National Congress of Psoriasis: 4th meeting of the Psoriasis Group (GPs) of the AEDV; 2019; Madrid, Spain.

33 Walker F, Adamczyk A, Kellerer C et al. Fumaderm(R) in daily practice for psoriasis: dosing, efficacy and quality of life. *Br J Dermatol* 2014; **171**: 1197–1205.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. (A) PASI $\leq$ 3 and (B) PGA 0-1 at Week 8 as predictors of a $\geq$5-point reduction in DLQI at Week 16 (percentage of responding patients). *$P < 0.05$, **$P < 0.01$ Chi-square tests.

Table S1. Percentage change from baseline in DLQI score at Week 16 stratified by baseline disease severity based on PASI score.