



Dimethyl Fumarate's Effectiveness and Safety in Psoriasis: A Real-Life Experience During the COVID-19 Pandemic

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Received: October 21, 2021 / Accepted: January 17, 2022
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ABSTRACT

Introduction: Dimethyl fumarate (DMF) is approved as oral systemic treatment for moderate-to-severe psoriasis. Scarce evidence is available for DMF treatment in psoriatic patients at the time of COVID-19 pandemic. The objective of this study was to assess the long-term effectiveness and safety of DMF monotherapy in moderate-to-severe psoriasis during the COVID-19 pandemic period.

Methods: This multicenter, retrospective study included patients with moderate-to-severe psoriasis who had received a 48-week DMF treatment during the COVID-19 pandemic. Selected outcomes were: variation of mean PASI, proportion of patients achieving PASI50 and PASI75, variation of mean PGA and face PGA,

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genital PGA, scalp PGA, mean itch VAS and mean DLQI.

Results: Forty-four patients were enrolled, and four patients became COVID-19 positive during the observation period but did not discontinue DMF therapy. DMF produced a significant improvement of signs and symptoms of psoriasis as expressed by mean PASI variation from 13.07 at baseline to 6.11 at week 48 ($p < 0.0001$), itch VAS from 3.22 at baseline to 1.18 at week 48 ($p < 0.001$), PGA from 2.84 at baseline to 1.30 at week 48 ($p < 0.0001$) and DLQI from 13.09 at baseline to 6.07 at week 48 ($p < 0.0001$). The percentage of patients who achieved PASI50 and PASI75 was 4.55% at week 4 and 59.09% at week 48 and 0% at week 4 and 22.73% at week 48, respectively. A clinically important decrease of mean PGA score was observed in all subgroups, face psoriasis, genital psoriasis and scalp psoriasis. Adverse events were predictable and manageable.

Conclusions: DMF monotherapy is an effective and safe treatment option in moderate-to-severe psoriasis also in patients who develop SARS-CoV-2 infection.

Keywords: Dimethyl fumarate; COVID-19 pandemic; Psoriasis; Quality of life

Key Summary Points

Why carry out this study?

Among first-line treatments for psoriasis, dimethyl fumarate (DMF) demonstrated a favorable efficacy and safety profile in short- and long-term observation; however, scarce evidence is available for DMF treatment in real-life practice at the time of the COVID-19 pandemic

It has been suggested that the immunomodulatory, anti-oxidative and anti-inflammatory properties of DMF could reduce the cytokine storm caused by severe COVID-19

We aimed to assess the long-term effectiveness and safety of DMF monotherapy in moderate-to-severe psoriasis patients during the COVID-19 pandemic period

What was learned from the study?

DMF monotherapy significantly improved all disease activity indexes showing a good safety profile and an optimal drug survival rate

DMF monotherapy was an effective and safe treatment option in moderate-to-severe psoriasis also in four patients who developed SARS-CoV-2 infection

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease with systemic manifestations that affects between ~ 2% and 4% of the Western population. Psoriasis is usually accompanied by substantial quality of life (QoL) impairment [1–5].

Dimethyl fumarate (DMF) is a methyl ester of fumaric acid (chemical formula $C_6H_8O_4$) that is hydrolyzed in the small intestine to the active metabolite monomethyl fumarate, approved for the treatment of moderate-to-severe plaque

psoriasis [6, 7]. DMF is known to exert anti-inflammatory, anti-oxidative and immunomodulatory effects primarily through three molecular pathways: (1) activation of nuclear factor erythroid 2-related factor 2 (Nrf2), which binds to the antioxidant response element in the nucleus to stimulate transcription of phase II enzymes [superoxide dismutase, NAD(P)H quinone oxidoreductase-1 and heme oxygenase-1]; (2) inhibition of nuclear factor kappa B (NF- κ B), which prevents the translocation of NF- κ B into the nucleus, the release of pro-inflammatory cytokines and subsequent inflammation and damage; (3) immunomodulatory effects through hydroxycarboxylic acid receptor 2 [2, 6, 8, 9].

Several clinical randomized and observational studies have demonstrated that DMF, among oral traditional systemic agents, presents clinical long-term efficacy and favorable safety profile [1–3, 5]. A recent European Expert Consensus proposed DMF as a first-line therapeutic option to achieve sustained disease control for patients with moderate-to-severe plaque psoriasis when psoriasis cannot be adequately controlled with topical treatments and phototherapy [3, 10–15].

Scarce evidence is available for DMF treatment in psoriatic patients in real-life practice, in particular at the time of the COVID-19 pandemic. Therefore, the aim of this study was to assess the long-term effectiveness and safety profile of DMF monotherapy in patients with moderate-to-severe psoriasis during the COVID-19 pandemic.

METHODS

Study Design

Multicenter, retrospective, real-life study conducted at the Departments of Dermatology of the University of L'Aquila and Ancona, Italy.

Patients

Consecutive adult patients with moderate-to-severe psoriasis unresponsive to topical

treatment, phototherapy and/or conventional treatments for psoriasis, undergoing DMF treatment according to the National and International Guidelines [15], starting treatment from January to September 2020, were included in the study. Patients had to be treated with DMF as monotherapy, as reported in the summary of product characteristics (SPCs), and followed for an observation period of 48 weeks [16]. The investigation was conducted in accordance with the Helsinki Declaration, and patients signed a declaration allowing the use of clinical records for scientific purposes. Ethics committee approval for retrospective studies was not required.

Assessments, Endpoints and Follow-Up Procedures

Prior to DMF therapy, demographic characteristics, previous anti-psoriatic treatments, comorbidities, clinical characteristics including Psoriasis Area Severity Index (PASI) [17] [range 0 (no disease) to 72 (maximal disease)], Physician Global Assessment (PGA) [18], face PGA, genital PGA, scalp PGA [PGA range 0 (no symptom) to 5 (severe symptoms)], itch VAS (visual analog scale) [range 0 (no symptom) to 10 (severe symptoms)], Dermatology Life Quality Index (DLQI) [19] [range 0 (no effect at all on patient's quality of life) to 30 (extremely large effect on patient's quality of life)]. Routine laboratory assessments including lymphocyte and neutrophil count, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), were obtained for all participants. All patients underwent a COVID-19 rapid nasopharyngeal swab test from September 2020 to December 2020 and were asked to communicate the results to the referring specialist. Effectiveness was assessed as improvement vs. baseline in PASI, PGA, itch VAS and DLQI and by evaluating the proportion of patients achieving PASI50 ($\geq 50\%$ improvement of PASI from baseline) and PASI75 ($\geq 75\%$ improvement of PASI from baseline). Safety profile and treatment survival rate were monitored at each visit.

Patients starting DMF monotherapy were routinely followed for 4, 12, 24 and 48 months.

DMF Treatment Protocol

DMF, as gastro-resistant tablets, was prescribed as routine clinical practice, in accordance with the SPCs. During the first week, DMF 30 mg was taken once a day (1 tablet in the evening), from the second week, DMF 30 mg was taken twice a day (1 tablet in the morning and 1 tablet in the evening), and from the third week, DMF 30 mg was taken three times a day (1 tablet in the morning, 1 at noon and 1 in the evening). From the fourth week onwards, treatment switched to one tablet of DMF 120 mg in the evening. This dose was then increased by one tablet of DMF 120 mg per week at different times of the day for the next 5 weeks. The maximum permitted daily dose was 720 mg (2 tablets of DMF 120 mg 3 times a day) [16].

Data Analysis

Statistical analysis was performed using a software (GraphPad, San Diego, CA, USA). Imputation of missing data (IMD) was performed by last observation carried forward (LOCF) analysis. Paired Student *t*-test comparing baseline values to each time point (weeks 4, 12, 24 and 48) was used. Data are presented as percentage change vs. baseline for PASI, PGA, itch VAS, DLQI; mean \pm standard deviation (SD) for PGA score in the subgroups: face psoriasis, genital psoriasis and scalp psoriasis; proportion of patients achieving $\geq 50\%$ improvement of PASI or $\geq 75\%$ (PASI 50, PASI 75).

RESULTS

Study Population

A total of 44 patients satisfied the inclusion criteria and were enrolled in the study. The mean age at the start of DMF monotherapy was 50.48 years (range 22–75); 65.91% of the patients were male. The mean body mass index (BMI) was 25.44 (range 20.24–31.46) kg/m². All

patients had plaque-type psoriasis. Concerning previous anti-psoriatic therapy, 70.45% received topical treatment, 11.36% phototherapy and 43.18% systemic agents such as ciclosporin (22.73%), acitretin (15.91%), methotrexate (11.36%), adalimumab, etanercept and apremilast (2.27%). Difficult-to-treat psoriasis localizations were involved as follows: scalp (56.82%), nails (20.45%), face (13.64%), genitals and palmoplantar area (9.09%).

The most common comorbidities were hypertension (29.55%), hypercholesterolemia (22.73%) and type 2 diabetes (13.64%). Clinical characteristics and peripheral blood hematological parameters are reported in Table 1.

Table 1 Patients' clinical and hematological characteristics at baseline

Mean clinical characteristics, <i>n</i> (range)	
PASI (0–72)	13.07 (6.8–56.2)
PGA (0–5)	2.84 (1–5)
Itch VAS (0–10)	3.22 (0–10)
DLQI (0–30)	13.09 (2–23)
PGA-face (0–5)	2 (1–5)
PGA-genital (0–5)	3.5 (3–4)
PGA-scalp (0–5)	2.84 (1–5)
Mean peripheral blood hematological parameters, <i>n</i> (range)	
Lymphocytes ($\times 10^3/\mu\text{l}$)	2.83 (1.3–4.92)
Neutrophils ($\times 10^3/\mu\text{l}$)	5.78 (2.63–8.2)
NLR, <i>n</i>	2,20 (0.86–5.15)
CRP (mg/dl)	2.98 (0.1–78)
ESR (mm/h)	15.11 (2–57)

PASI Psoriasis Area Severity Index, *PGA* Physician Global Assessment, *VAS* visual analog scale, *DLQI* Dermatology Life Quality Index, *NLR* neutrophil-to-lymphocyte ratio, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

DMF Usage

Single maximum dosages, corresponding to the minimum effective dose or the maximum tolerated dose maintained by each patient, were 90 mg for 2 patients, 120 mg for 9 patients, 240 mg for 3 patients, 360 mg for 20 patients, 480 mg for 8 patients, 600 mg for 1 patient and 720 mg for 1 patient.

Effectiveness

DMF produced a significant improvement of mean PASI from baseline starting from week 12 and maintained until week 48 ($p < 0.0001$) (Fig. 1). The mean PASI value (mean \pm SD) varied from 13.07 ± 7.35 at baseline to 10.26 ± 4.37 at week 4, to 8.07 ± 3.74 at week 12, to 6.58 ± 5.12 at week 24 and 6.11 ± 5.22 at week 48. The percentage of patients who achieved PASI50 was 4.55% at week 4, 20.45% at week 12, 54.55% at week 24 and 59.09% at the end of observation period (week 48) (Fig. 2). The percentage of patients who achieved PASI75 was 0% at week 4, 6.82% at week 12, 18.18% at week 24 and 22.73% at the end of the observation period (week 48) (Fig. 2). Similar results were observed for mean PGA with a mean reduction from baseline of -20.07% , -33.45% , -49.64% and -54.22% at week 4, 12, 24 and 48, respectively ($p < 0.0001$) (Fig. 1). Furthermore, DMF treatment significantly reduced mean itch VAS, which varied from 3.22 ± 3.02 (SD) at baseline to 2.34 ± 2.57 (SD) at week 4, 1.52 ± 2.28 (SD) at week 12, 1.19 ± 2.30 at week 24 and 1.18 ± 2.32 (week 48) (-63.25% ; $p < 0.001$) (Fig. 1). Regarding quality of life, as measured by mean DLQI, a significant improvement was already seen at week 4 with a score reduction of 20.85% ($p < 0.0001$). An increase in improvement in mean DLQI was observed at the different visits, week 4, 12, 24 and 48 (Fig. 1). More specifically, the mean DLQI decreased from 13.09 ± 5.96 (SD) at baseline to 10.36 ± 4.85 (SD) at week 4, to 7.86 ± 4.82 (SD) at week 12, to 6.36 ± 5.95 (SD) at week 24 and to 6.07 ± 5.97 at week 48 ($p < 0.0001$). A clinically significant benefit was

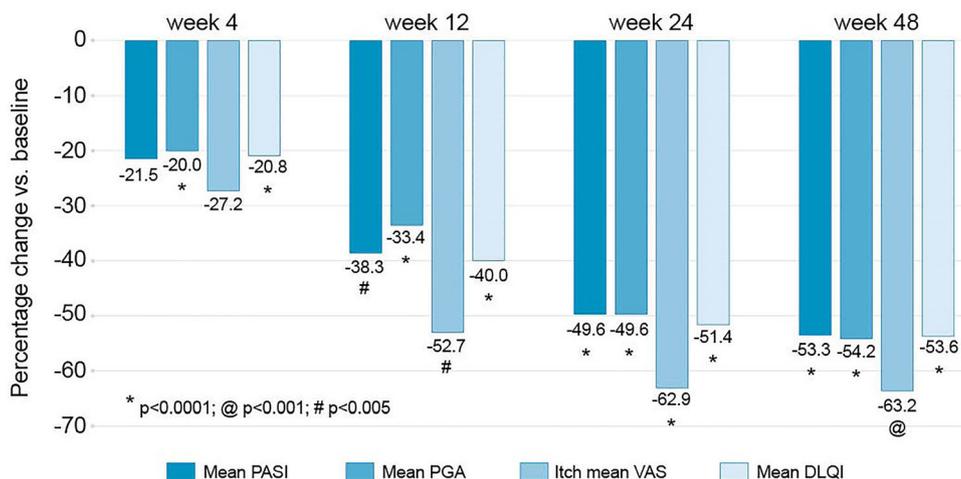


Fig. 1 Variation of clinical and DLQI scores during DMF treatment expressed as percentage change vs. baseline of PASI, PGA, itch VAS, DLQI. *PASI* Psoriasis Area Severity

Index, *PGA* Physician Global Assessment, *VAS* visual analog scale, *DLQI* Dermatology Life Quality Index

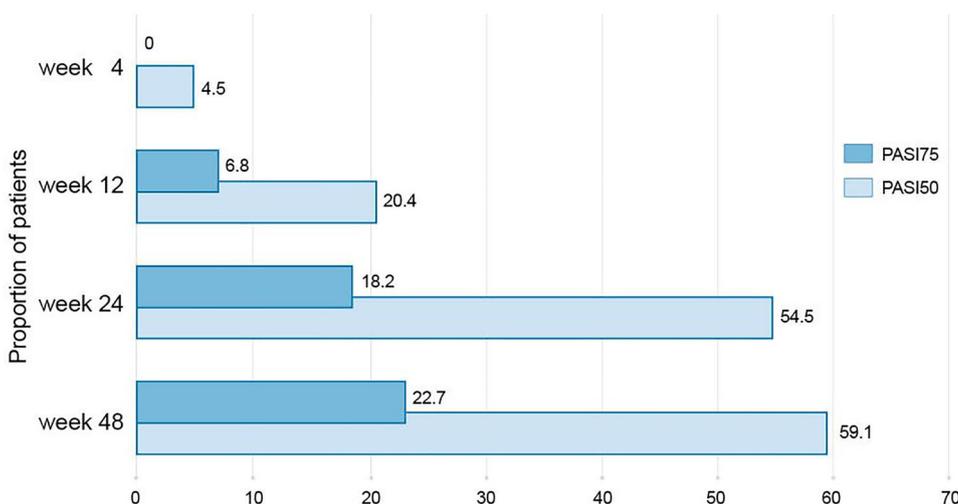


Fig. 2 Proportion of patients achieving ≥ 50% improvement in Psoriasis Area and Severity Index (PASI 50) and PASI 75 at week 4, week 12, week 24, week 48. *PASI50*

≥ 50% improvement in Psoriasis Area and Severity Index vs. baseline, *PASI75* ≥ 75% improvement in Psoriasis Area and Severity Index vs. baseline

observed at the end of the study (48 weeks) (Fig. 3).

An analysis of mean PGA improvement, depending on difficult sites, was performed. A clinical important decrease of mean PGA score was observed in all subgroups, face psoriasis, genital psoriasis and scalp psoriasis (Fig. 4).

Safety

Hematological Parameters

Neutrophil count remained stable over the course of the study; in particular, $5.78 \times 10^3/\mu\text{l}$ at the baseline visit and $5.45 \times 10^3/\mu\text{l}$ after 48 weeks ($p = 0.5058$). Similar results were observed for the NLR with a baseline value of 2.19 and 2.76 after 48 weeks ($p = 0.2713$).



Fig. 3 Clinical improvement of psoriasis with DMF treatment in a 73-year-old woman presenting baseline PASI 46 (A) reduced to PASI 0 at week 48 (B) and in a

30-year-old male patient presenting baseline PASI 12 (C) reduced to PASI 0 at week 48 (D)

Adverse Events and Dropouts

One hundred fourteen adverse events were observed with 75% of patients experiencing at least one adverse event. The most common adverse events were flushing (54.55%), diarrhea (43.18%), gastric pain (29.33%), persistent diarrhea (> 8 weeks) (15.91%), anorexia (13.64%), and nausea, hair loss and depression < 10%. Considering flushing and gastrointestinal effects, which were the most common side effects, they were mild and transient in most cases, while in a minority of cases,

corresponding to higher severity forms, a dose reduction strategy was adopted to limit the effect.

SARS-CoV-2 Infection

All patients underwent COVID-19 screening with a rapid nasopharyngeal swab test between September and December 2020 (baseline visit) with negative results. Six patients, for personal or occupational reasons, performed IgG/IgM COVID-19 tests during the study period, and the results were negative. Thereafter, only 4 of

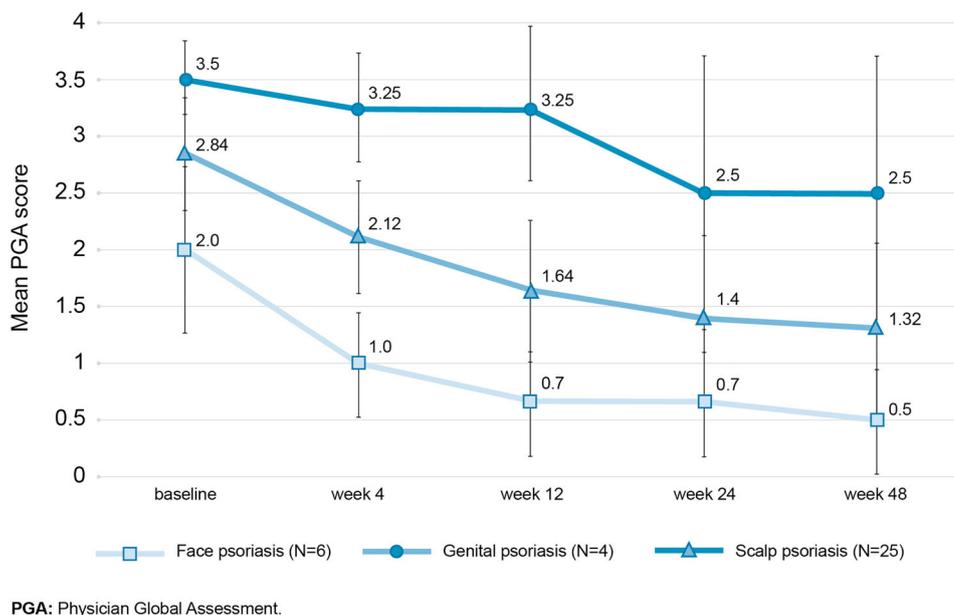


Fig. 4 Mean PGA score \pm SD over time at different psoriasis sites during DMF treatment

44 patients developed COVID-19 positivity during the study period.

All four patients were male, aged between 53 and 67 years, with a BMI between 24.8–28.4 kg/m² (Table 2). During DMF treatment, they developed a mild form of COVID-19. The presence of SARS-CoV-2 infection did not cause discontinuation of DMF treatment.

Treatment Survival Rate

At the end of the follow-up period (week 48), 70.45% remained on treatment with a dropout percentage of 29.55%.

In total, there were 13/44 dropouts: week 4: seven dropouts, four because of poor compliance, two because of nausea and gastric symptoms and one because of mood alteration and acute defluviu in the same patient; week 12: two discontinuations, one because of gastric symptoms and one because of ineffectiveness; week 24: four dropouts because of inefficacy.

DISCUSSION

This retrospective study demonstrated that DMF monotherapy significantly improved all

evaluated psoriasis disease activity indexes, e.g., PASI, PGA and itch VAS. A sub-analysis according to psoriasis sites demonstrated an important clinical reduction of mean PGA referring to face, genital and scalp psoriasis, known as difficult-to-treat areas. Moreover, > 50% of patients reached PASI50 at week 24, which was maintained until week 48, and > 20% reached PASI75 at week 48. The effectiveness in controlling and reducing psoriatic symptoms was consistent as expressed by the reduction of itch VAS and resulted in significant improvement in patients' quality of life as measured by DLQI throughout the study. Drug survival rate was elevated, demonstrating appropriate side effect management since few patients interrupted DMF because of tolerability problems.

Our results are comparable to those obtained in the Bridge study; nevertheless, there were differences in trial design and patients characteristics. Mrowietz et al., indeed, reported achievement of PASI50 in about 50% of patients and PASI75 in about 40% of patients treated with DMF for 16 weeks [11]. In our study, a subgroup analysis for face, genital and scalp locations was carried out for the first time, demonstrating a clinically significant

Table 2 Clinical characteristics of patients who developed COVID-19 positivity during the study

Age	53	57	65	67
Sex	Male	Male	Male	Male
BMI (kg/m ²)	26.0	27.5	24.8	28.4
Age of plaque psoriasis onset	32	16	62	43
Comorbidity	Hypertension and dyslipidemia	Hypertension and dyslipidemia	Hypertension and cardiac arrhythmia	Hypertension
Previous treatments	Acitretin and topical treatment	Ciclosporin and topical treatment	Topical treatment	Ciclosporin and topical treatment
Mean clinical characteristic	PASI 18.1, PGA 4, DLQI 15, nail PGA 2	PASI 9, PGA 1, DLQI 19, face and scalp PGA 2	PASI 15, PGA 4, DLQI 20, scalp PGA 3	PASI 15.7, PGA 2, DLQI 15, scalp PGA 4, nail PGA 3
Week of DMF treatment—development of SARS-Covid-2 positivity	Week 5	Week 2	Week 26	Week 12
COVID-19 symptomatology	Fever, cough and general malaise for 10 days, without complication toward interstitial pneumonitis	No specific symptoms	Transient fever with auto-resolution and coexistent dysgeusia and general malaise	Loss of taste and smell
Hospitalization	No	No	No	No
DMF treatment discontinuation	No	No	No	No

improvement in psoriatic lesions in difficult-to-treat sites, as assessed by PGA.

Adverse events, such as flushing, diarrhea and gastric pain, although frequent, were well known, predictable, manageable and similar to those reported in different clinical real-life experiences and trials [10, 20–24].

The long-term observation showed a good drug retention rate since dropouts were limited and occurred in 29.54% patients. The rates of discontinuations were lower than those reported in the Bridge trial [3], with the new formulation of DMF (LAS41008) at 37.1% and

Fumaderm® at 38.5%, respectively, demonstrating that in real life the clinician's behavior in terms of dose adjustment and management of side effects may lead to a higher retention rate.

The effectiveness, registered in this real-life experience with DMF, becomes more interesting when we consider that patients who developed SARS-CoV-2 positivity during the study did not discontinue the current therapy and had a positive disease course. Indeed, Timpani et al. suggested that the immunomodulatory, anti-oxidative and anti-inflammatory properties

of DMF could reduce the cytokine storm caused by severe COVID-19 [6]. Moreover, recent research demonstrated that the expression of Nrf2-dependent genes is suppressed in biopsies from COVID-19 patients and that treatment of cells with Nrf2-agonist 4-octyl-itaconate and DMF limits COVID-19 replication. DMF furthermore limits the release of pro-inflammatory cytokines in response to SARS-CoV-2 infection [25]. This observation is even more significant during the COVID-19 pandemic when the therapeutic choice is challenged by several concerns in terms of immunosuppression and risk of infection and the influence of traditional immunosuppressive drugs on the efficacy of vaccines [26, 27]. Interestingly, although there is still not much evidence regarding the use of SARS-CoV-2 vaccine in patients with psoriasis treated with DMF, in patients with multiple sclerosis treated with DMF the vaccine response was not changed, suggesting that the vaccination should proceed immediately and without interruption of DMF treatment [28]. The findings of this study should be seen in light of some limitations related to the small sample size and the heterogeneous clinical evaluation for the retrospective observational nature of the study carried out in a real-life setting.

CONCLUSIONS

In conclusion, this real-life experience demonstrated that DMF treatment was effective and safe in patients with moderate-to-severe chronic plaque psoriasis including patients who developed SARS-CoV-2 positivity. The small number of patients with SARS-CoV-2 positivity could be attributed to the strict Italian lockdown and social distancing measures. The findings of this study have to be seen in light of some limitations, including the general small sample size, small number of patients with COVID-19 and heterogeneous clinical evaluation following from the retrospective observational nature of the study carried out in a real-life setting. Additional real-life research is needed to further investigate the use of DMF in patients with psoriasis and in particular conditions during the COVID-19 pandemic.

ACKNOWLEDGEMENTS

Funding. This study and the journal's Rapid Service Fee were supported by Almirall S.p.A. (provider: Thenewway Srl).

Medical Writing and Editorial Assistance. Medical writing assistance was provided by Irene Scagnol, Biologist with a PhD in Clinical Pharmacology, University of Milan, supported by Almirall S.p.A.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Conceptualization: Maria Esposito, Anna Campanati, Alessandro Giunta, Anna Maria Offidani, Maria Concetta Fargnoli. Methodology: Maria Esposito, Anna Campanati, Gianluca Calianno, Federico Diotallevi. Formal analysis and investigation: Alessandro Giunta, Maria Esposito, Anna Campanati. Writing—original draft preparation: Irene Scagnol. Writing—review and editing: all authors. Supervision: Maria Concetta Fargnoli, Anna Maria Offidani, Luca Bianchi.

Disclosures. Maria Esposito has served as speaker and/or consultant for Abbvie, Almirall, Biogen, Celgene, Eli Lilly, Janssen, Leo Pharma, Novartis, Sanofi Genzyme and UCB. Anna Campanati has served as speaker and/or consultant for Abbvie, Almirall, Eli Lilly, Janssen, Leo Pharma, Novartis, Sanofi Genzyme and UCB. FD has served as speaker and/or consultant for Eli Lilly, Novartis. AO has served on advisory boards, received honoraria for lectures and research grants from Almirall, Abbvie, Galderma, Leo Pharma, Celgene, Pierre Fabre, UCB, Eli Lilly, Pfizer, Janssen, Novartis and Sanofi-Genzyme. Alessandro Giunta has served as speaker and/or consultant for Abbvie, Biogen, Eli Lilly, Pfizer and UCB. Gianluca Calianno has nothing to disclose. Luca Bianchi has served on advisory boards and received honoraria for

lectures and research grants from Almirall, Abbvie, Leo Pharma, Amgen, Biogen, UCB, Eli Lilly, Janssen, Novartis and Sanofi-Genzyme. Federico Diotallevi has served as speaker and/or consultant for Eli Lilly and Novartis. Anna Maria Offidani has served on advisory boards and received honoraria for lectures and research grants from Almirall, Abbvie, Galderma, Leo Pharma, Celgene, Pierre Fabre, UCB, Eli Lilly, Pfizer, Janssen, Novartis and Sanofi-Genzyme. Maria Concetta Fargnoli has served on advisory boards, received honoraria for lectures and research grants from Almirall, Abbvie, Galderma, Leo Pharma, Mylan, Medac Pharma, Celgene, Pierre Fabre, UCB, Eli Lilly, Pfizer, Janssen, Novartis, Sanofi-Genzyme, Roche, Sunpharma and MSD.

Compliance with Ethics Guidelines. The investigation was conducted in accordance with the Helsinki Declaration, and patients signed a declaration allowing the use of clinical records for scientific purposes. Ethics committee approval for retrospective studies was not required.

Data Availability. Data available on request from the authors.

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