*Article*

# Title: Update on effective management strategies in patients with dimethylfumarate flushing induced: real life preliminary results of an observational psoriatic patients cohort study

Sara Mazzilli[1], Annunziata Dattola[1], Tania Gaetana Costanza[2], Augusto Orlandi[1], Katia Aquilano[3], Daniele Lettieri[3], Flavia Lozzi[1], Emy Dika[4], Caterina Lanna[1], Luca Bianchi[1], Elena Campione[1].

1-Department of Dermatology University of Rome Tor Vergata, Rome, Italy

2-Anatomic Pathology Unit, Department of Biomedicine and Prevention, Tor Vergata Univeristy of Rome, Italy

3- Nutritional Biochemistry Lab. Departemtn of Molecular Biology, University of Rome Tor Vergata, Italy

3- Dermatologic Unit, Departement of Dermatology Bologna, Italy

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**Corresponding author:**

Sara Mazzilli

Department of Dermatology University of Rome "Tor Vergata", Italy

viale oxford 81

saramazzilli2@gmail.com

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**Abstract:**

**Background**: Dimethylfumarate (DMF) is an orally administered fumaric acid esters (FAE) approved for plaque psoriasis. The most represented adverse event for incidence reported in all studies regarding multiple sclerosis and psoriasis treatment was flushing followed by gastrointestinal and lymphopenia (AEs). We report our experience on effective management strategies in patients with dimethylfumarate fushing induced. **Methods:** The purpose of our study is addressed to propose feasibles strategies able to mitigate adverse events developing in order to improve therapy compliance. We report our real life experience of 20 patients affected by mild to moderate plaque psoriasis in treatement with DMF 10 male and 10 female, with 45,4 years old mean age underwent to a reducing a daily dosage regimen with DMF from 120 mg to 30 mg tablets. Patients experience flushing around 30-45 minutes after assuming the medication.per day.

**Results:** Patients achieving a good adherence and efficacious results in terms of PASI 75 reduction after 16 weeks of treatment. **Conclusion:** DMF is efficacious and has a favorable

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benefit–risk profile, thanks to the possibility of implementing posology strategies in order to optimize adherence to the therapy.

## Introduction

Dimethylfumarate (DMF) is an orally administered fumaric acid esters (FAE) approved for plaque psoriasis monotherapy treatment in case of systemic therapy needs, since June 2017 already used for other neurological disorders. The anti-inflammatory and immune-modulating mechanism exploited by DMF is addressed to NF-κB inhibition related to inflammatory cytokine reduction with consensual pro-apoptotis induction, keratinocyte proliferation blockage, expression of adhesion molecules decrease, and inflammatory infiltrate within psoriatic plaques decrease[1]. Moreover DMF is able to reduce inflammatory Th1/Th17 proliferation enhancing anti-inflammatory Th2 cells. Half-life DMF corresponds to 12 minuts, being subsequently hydrolyzed to monomethyl fumarate (MMF with 36 hours half-life)[2]. How DMF pro-active form is able to enhance IL-4 and IL-5 levels is not yet well explained. Certainly, MMF promoting effect on type 2 cytokine secretion is indirectly mediated, with a subsequent rescue of Th2 cells[3]. It is recommended to begin treatment with DMF with a low initial dose followed by subsequent gradual increases. Although there isn't a recommended dosing, it is suggested to have flexible dosage according to the individual patient's needs and susceptibility, most of the patients require between two and four 120 mg tablets of DMF per day. The most represented

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adverse event for incidence reported in all studies regarding multiple sclerosis and psoriasis treatment was flushing followed by gastrointestinal and lymphopenia (AEs)[4]. Gastrointestinals symptoms frequently included diarrhoea, abdominal pain, nausea and flatulence. Ralf Gold et Al evaluate GI-related events during the first 3 weeks of therapy and rapidly decreasing thereafter. This work group assess the severity of GI events over 12 weeks according to the Modified Overall Gastrointestinal Symptom Scale were mild to moderate in the majority of patients reporting GI-related events and taking symptomatic GI medication (53.6%). Only 10% of all patients discontinued study treatment due to AEs in general, while 6.6% discontinued due to GI-related events. The severity of GI-related events decreased using symptomatic treatment included one or more medications (e.g. acid secretion blockers, antidiarrhoeals or antiemetics). Skin flushing is experienced by approximately 30–50% of patients treated with FAEs; are usually experienced in the first few weeks assuming DMF. Flushing can be defined as a warmth sensation accompanied by erythema most commonly localized on the face occurring in episodic attacks. [6] Disease severity can vary extremely from asymptomatic to absolutely uncomfortable. Distress caused by frequent episodes lead to lack of adherence. It could be associated with non malignant conditions as fever, hyperthermia, emotions, menopause, medications, alcohol, food, hypersensitivity reactions, rosacea, hyperthyroidism, dumping syndrome, superior vena cava syndrome, and neurologic etiologies[5]. On the other hand, the following malignant conditions could also be responsible for flushing: mastocytosis, medullary thyroid carcinoma, pheochromocytoma, carcinoid tumors, gastroenteropancreatic neuroendocrine tumors, bronchogenic carcinoma, vasointestinal polypeptide secreting

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tumors, and renal cell carcinoma[6-7]. Despite the multifactorial etiopathogenesis of this disorder, emotional component is included as well in the skin in this disorder genesis. Furthermore, in susceptible individuals flushing can be a consequence of/due to topical substances application or of sistemic drugs administration.(Fig.1) Flushing related medications includes all vasodilators, calcium channel blockers, nicotinic acid, morphine,amyl nitrite and butyl nitrite, cholinergic drugs, bromocriptine, thyroid releasing hormon, and tamoxifen oppure Hormonal, non steroidal inflammatory, serotonin, antiemetics, chemoterapic agents and vasodilators can be responsible of flushing drug-induced[8].

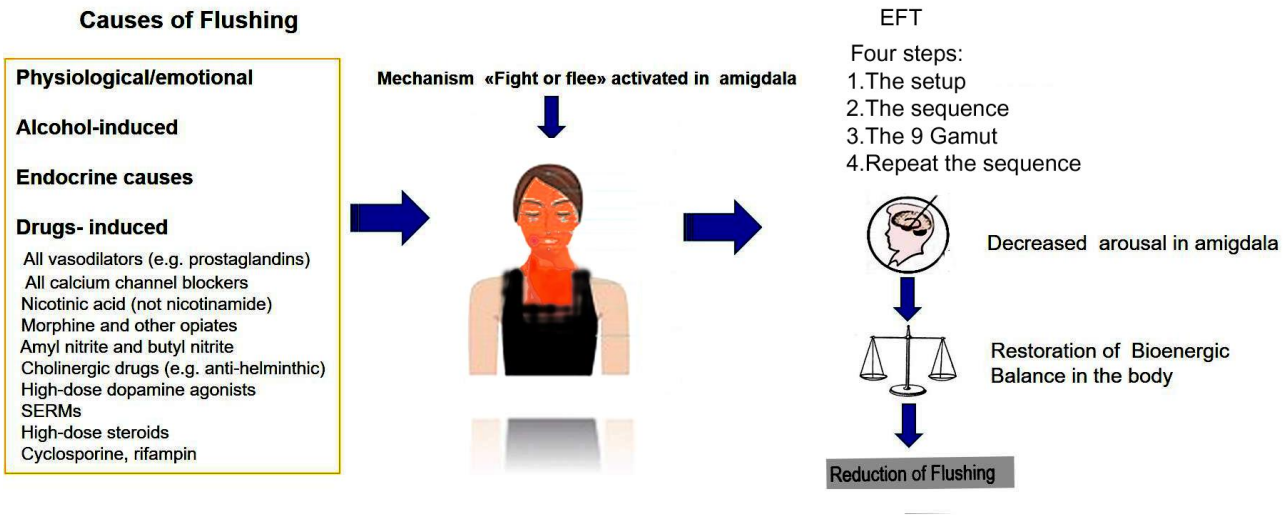


Fig.1 Flushing image. Iatrogenic and emotional component well explained. Emotional freedom tequinque (EFT) a psycological method able in our patient to reduce flushing intensity and frequence episodes, this image explained the mechanism of action of this interesting methodic

## Material and methods

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We report our real life experience of 20 patients affected by mild to moderate plaque psoriasis in treatement with DMF enrolled at the Dermatologic Department of University of Rome Tor Vergata from December 2019 to February 2020. 10 male and 10 female, with 45,4 years old mean age underwent to a reducing a daily dosage regimen with DMF from 120 mg to 30 mg tablets per day, achieving a good adherence and efficacious results in terms of PASI 75 reduction after 16 weeks. (Table 1)

Table 1. Demographic and clinic-pathological features of enrolled patients (n= 20)

| |
|---|
| **AGE (MEAN OF AGE 45.4)** |
| <45 |
| >46 |
| |
| **SEX** |
| FEMALE |
| MAN |
| |
| **BMI (MEAN OF BMI 21.1)** |
| <21.1 |
| >21.1 |
| |
| **SMOCKER STATUS** |
| NO |
| YES |
| |
| **COMORBODITIES** |
| NO |
| YES |
| |
| **NAIVE status** |
| NO |
| YES |
| |
| **FLUSHING** |
| NO |
| YES |

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**ABSENCE OF FLUSHING AFTER TREATMENT**
NO
YES

**TREATMENT**
LOW DOSAGE
HIGH DOSADE

**FAILURE**
NO
YES

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All our cohort signed the informed consent before starting the treatment according to the Helsinki declaration. Patients experience flushing around 30-45 minutes after assuming the medication occurring mostly in the evening in relation to allergenic foods. Duration flushing average induced by DMF generally corresponds to half an hour consisting of intense redness and burning sensation involving face, neck and sometimes all the body, often decreasing autonomously within a short time or using acetylsalicylic acid as preventive strategy also in prevention as suggested by many published trial guidelines [9]. In case of multiple tablets daily assumption, number of events expected could be variable and abundant, representing a relevant limitation in term of therapeutic adherence. Generally, the number of flushing events decreases with the duration of therapy, modulating drug intake dosage, anticipating medication assumption in the first hours of the morning, reducing the dosage or using single pills with higher dosages and fewer

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administrations per day. This could be crucial for adverse events decrease with a consensual therapeutic compliance improvement and reduction treatment interruption[10].

In this context we report one case of female patient experiencing multiple DMF-induced flushing episodes assuming 240 mg tablets per day in the first days of treatment. DMF was administerd for a resistant palmo-plantar psoriasis involving both palms (PPGA 8 at baseline). She reported the onset of her symptomatology an hour later having taken the pill, along with an exacerbation of the flushing in the event of adding an antihistamine assumption. The patient achieves a good adherence to the therapy in term of reducing of intensity and frequentcy of flushing episodes during the days, through the use of emotional freedom technique (EFT). (Fig.2-3)

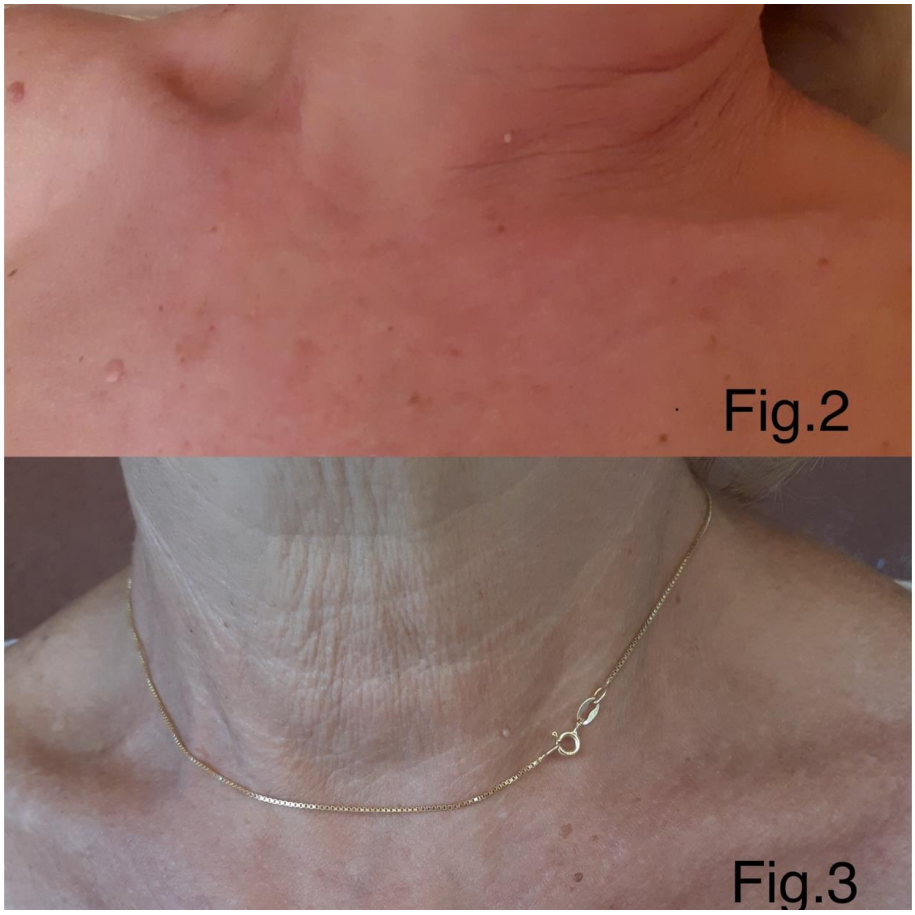

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Fig.2 Clinical picture Flushing before EFT

Fig.3 Clinical picture Flushing after EFT

EFT component is well known, already defined a "tapping" technique using the combine approach of cognitive reprocessing exposure and acceptance therapy with the energetic methods related to acupuncture or other energy therapies. To date, more data published confirm a 98% efficacy rate with the use of this procedure from psychological distress (posttraumatic stress disorder, phobias, anxiety, depression, etc.) to physical conditions (asthma, fibromyalgia, pain, seizure disorders, etc.) to performance improvement (athletic, academic). [11] Emotional flushing component is well known, but to ourknowledge no data are available regarding the therapeutic use of this technique in disorder management. [5]

**Statistical analysis**

The univariate analysis of the relationship between clinicopathological variables and the markers were performed using the Spearman's rank test. We used non parametric **McNemar's test** to analyze the absence of flushing before and after therapy at low dosage. The differences were considered statistically significant for *p-value* <0.05. All the statistical analyses performed with SSPS V20 (Stat Corp, College Station, Texas, USA).

**Results**

Ten man and 10 female, (mean age was 45.4 yrs; table 1) were analyzed in that pilot study where we reduced dosage of the daily regimen for high frequency of flushing from 120 mg to 30 mg pills per day, achieving a good adherence and efficacious results in terms of

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PASI 75 reduction after 8 weeks (PASI mean =3,5; at T0 was 7.5). Nine of enrolled patients showed comorbibietes and 17 patients evidenced flushing. We analyzed the relationship between the clinicopathological paramentrs and we evidenced a positive correlation between age and increased of BMI and the presence of comorbidities (rho=0.56 and 0.60 respectively, $p<0.05$). Inverse correlations evidenced between comorbidities presence and naïve status and between absence of flushing and failure (rho= -0.53 and -0.45 respectively, $p<0.05$). PASI reduction was correlated with absence of Flushing after treatment (rho= 0.57, $p<0.05$).

We also analyzed the efficacy of low DMF dosage on flushing reduction and evidenced by Mcnemar test that 9/12 enrolled patient showed a reduction of flushing after therapy at low Dosage ($p<0.03$).

**Discussion**

The purpose of our study is addressed to propose feasibles strategies able to mitigate adverse events developing in order to improve therapy compliance. Lori Mayer et Al. propose efficacious management strategies to facilitate optimal outcomes for patients aussminf DMF.

This work group consider some key points to ameliorate adherence therapy using, initiation dose protocol gradually increasing to maintenance dose, dietary suggestions for co-administration with food, flushing symptom management with aspirin, and temporary dose reduction.

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Using the available evidence from clinical trials and evaluations of post-marketing studies, these strategies to manage gastrointestinal and flushing symptoms can be effective and helpful to the patient when initiating delayed-release dimethyl fumarate. [11]

Considering transient flusing episodes often decreasing over time, dosage reduction strategy adoptage even temporarily allows the patient to be able to continue the therapy without an important deterioration in the quality of life.

In our experience, we assess management strategies addressed to flushing DMF induced in 20 patients affected by mild to moderate plaque psorasis, confirming the effectiveness of our protocol in term of therapy compliance improvement and reduction of lost to follow up patients. We perform stastical analysis confirming that temporary daily lower dose especially at the beginning of therapy (from more than 120 mg tablets per day to one or to 30 mg per day) as suggested by some data published[10], is able to achieve a good adherence and otpimal outcomes in terms of PASI 75 reduction after 8 weeks of treatment. Our evaluation stategies adopted included also american breakfast daily assumption before intake tablet or fatty meals in order to facilities flushing events reduction in relation to molecule absorption. Therefore, a clinician daily dosage management to establish the correct patient drug dosage regimen is mandatory. Daily dosage decrease, associated to more tablets per day assumption with lower dosage in some cases, is able to modulate dimethylfumarate flushing induced.

To date, several data published considered mitigation protocols in order to reduce flushing drug induced.[12] Symptom management should be re-evaluated after 2–3 months when symptoms normally abate. If a patient continues to experience side effects, the dose

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may be reduced from 240 mg BID to 120 mg BID until tolerance is achieved. The evening dose is then increased to 240 mg, with the ultimate goal being 240 mg B

**Conclusion**

DMF is efficacious and has a favorable benefit–risk profile, also thanks to the possibility of implementing posology strategies in order to optimize adherence to therapy. Because GI and flushing AEs typically occur only in the first days of therapy, it would be better to adopt a strenght follow-up, particularly if the patient has comorbidities that would contraindicate a high-fat diet with fewer healthy fats or aspirin uptake.

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**Figure legend:**

Table 1. Demographic table

Fig.1 Causes of Flushing

Fig.2 Clinical picture Flushing before EFT

Fig.3 Clinical picture Flushing after EFT