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ORIGINAL ARTICLE

# Dietary habits of psoriatic patients treated with dimethyl fumarate and drug-related side effects: results from an observational study

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## ABSTRACT

BACKGROUND: Despite its favorable long-term safety profile, side effects during dimethyl fumarate (DMF) treatment for psoriasis are not uncommon and may lead to treatment suspension. The association between side effects, especially gastrointestinal, and dietary habits has not yet been specifically addressed.

METHODS: This observational, cross-sectional study aimed to assess the dietary habits of patients with moderate-to-severe plaque psoriasis in treatment with DMF who attended three Italian psoriasis clinics. Demographic and clinical data, including any side effects, were collected from the patients' medical records. A self-administered questionnaire recorded and scored: 1) if meals are eaten regularly or not; 2) daily intake at meals of fatty foods, milk and dairy products, alcohol, fruit and vegetables; and 3) in the case of side effects, the time between eating and their onset.

RESULTS: We included 53 patients in treatment with DMF at a daily dose of 232.4±194.1 mg for 38±29.8 weeks. Thirty-eight (71.7%) reported side effects, namely flushing (60.5%), diarrhea (44.7%), gastralgia (29%) and nausea (15.8%). Overweight seemed associated with the occurrence of side effects. In 47.4% of subjects, side effects appeared within 2 hours of having a meal. Daily fat intake appeared to protect against side effects, albeit without statistical significance; skipping meals was correlated with their onset in subjects complaining of diarrhea.

CONCLUSIONS: Finding some correlation between dietary habits and occurrence of side effects during DMF treatment requires further investigation with the aim of developing possible strategies to improve its tolerability and retention rate.

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KEY WORDS: Dimethyl fumarate; Psoriasis; Therapy.

Dimethyl fumarate (DMF) is a valuable systemic treatment largely employed in the management of moderate to severe plaque psoriasis as first-line therapy. It has been available in Italy since 2017 and an increasing number of patients are being treated with this drug. DMF is well-known for its safety without cumulative toxicity, but side effects are not rare and include gastrointestinal symptoms, flushing and white blood cell count abnormalities. The occurrence of side effects is known to compromise treatment adherence and may lead to DMF withdrawal. These events, both described by the pivotal trial BRIDGE[1] and reported in the European Guidelines,[2] are consistent with those we observed in a previous study aiming to evaluate the effectiveness, tolerability and drug survival in a dermatological real-life setting.[3] We found that 61.16% of patients had at least one side effect during

treatment with DMF. Since most of them were gastrointestinal, namely diarrhea, nausea, gastralgia, with the present study we decided to evaluate any correlation between their occurrence and the dietary habits of the psoriatic patients treated with DMF, with particular regard to their intake of fats, milk and derivates, fruit and vegetables and alcohol. In a teleological perspective, our findings could provide useful dietary indications for predicting the incidence of side effects.

## Materials and methods

### Study design and setting

The present study was set up as an observational, cross-sectional, multi-centric study involving outpatients affected with plaque psoriasis in treatment with DMF. The eligible subjects attended the psoriasis clinic of three Italian units of dermatology for a control visit between February and April 2022. All patients took the drug during a main meal. During treatment, both clinical and laboratory assessments were regularly scheduled. To be eligible, the patients had to be in treatment with DMF for at least 4 weeks and undergo at least one control visit. Refusal to answer the questionnaire was the sole exclusion criterion. Concomitant topical treatment was not an exclusion criterion. The local Ethics Committee approved the current study (protocol 649/2020/Oss/AOUFe). For data collection and elaboration, a system of pseudo anonymization, in which the study subjects were assigned a code, was adopted. All the included subjects gave their written informed consent.

### Data collection and analysis

During the 3-month inclusion period, all consecutive eligible psoriatic patients who attended their referral clinic psoriasis were asked to participate in this study and answer a self-administered questionnaire. The following data were collected from their medical records: 1) demographics (age, sex, weight, height and Body Mass Index); 2) mean DMF daily dose at the time of study inclusion; 3) duration of treatment; 4) occurrence and type of side effects; and 5) DMF daily dose and treatment duration at their onset. The questionnaire was formulated in collaboration with a dietician to investigate some dietary habits, considered potentially relevant for DMF treatment, especially for its tolerability and safety. In particular, it recorded: 1) whether meals are eaten regularly or not; 2) daily intake of fatty foods, milk and dairy products, alcohol, fruit and vegetables; and 3) in the case of side effects, the time between the meal and their onset (≤2 hours *versus* >2 hours). In order to quantify each food intake (fatty foods, dairy products, alcohol and fruit and vegetables), it was scored on a 0-10 scale according to the meal in which it is usually taken. In particular, 5 points were given when the food is consumed for lunch, 3 points if it is consumed at dinner and 2 at breakfast. So, if a food, for example a fatty food, is normally eaten for both lunch and dinner, a cumulative score of 8 points for its daily intake was given. The same scoring was used for measuring the daily habit of skipping one or more meals (thus, skipping breakfast corresponds to a score of 2, skipping lunch to 5 points and skipping dinner to 3 points). These scores were determined in order to reflect the standard dietary habits of the Italian population[4, 5]

### Statistical analysis

Results represented by continuous variables were summarized using mean and standard deviation, while frequencies (absolute and percentage) of values were used for categorical variables. In the case of quantitative variables, comparisons between two groups of values were performed with Student's *t*-test for independent samples or Mann-Whitney's *U* Test, as appropriate, while comparisons of more than two groups were performed with ANOVA (Analysis of Variance). For categorical variables, contingency tables were made and analyzed by $\chi^2$ test or Fisher's Exact Test, as appropriate. Correlation between variables was calculated with Spearman's Rank Correlation Test. A P value <0.05 was considered statistically significant.

## Results

### Study patients

We included 37 men (69.8%) and 16 women (30.2%). The mean age±SD of the study patients was 58.2±13 years, their BMI was 27.2±4.3, including 18 (34%) patients with a normal weight, *i.e.*, BMI ≤24.99, 26 (49%) overweight, BMI 25 to 29.99, and 9 (17%) obese, BMI≥30. At the moment of filling in the questionnaire, the mean DMF daily dose among the study patients was 232.4±194.1 mg and mean treatment duration was 38±29.8 weeks. Details are reported in Table I.

### Side effects occurrence

Thirty-eight patients (71.7%) reported side effects during treatment, which occurred on average 4.3±4.6 weeks af-

TABLE I.—*Characteristics of the study population.*

| Parameters | Values |
|---|---|
| Demographics | |
| Total patients, N. | 53 |
| Males, N. (%) | 37 (69.8) |
| Females, N. (%) | 16 (30.2) |
| Mean±SD age, years | 58.2±13.0 |
| Mean±SD body weight, kg | 82.4±16.0 |
| Mean±SD BMI (Body Mass Index) | 27.2±4.3 |
| Patients per BMI class, N. (%) | |
| Normal weight | 18 (34.0) |
| Overweight | 26 (49.0) |
| Obesity | 9 (17.0) |
| Scores for dietary habits at main meals, mean±SD | |
| Skipped meals | 1.5±2.2 |
| Consumption of fatty foods | 7.5±2.2 |
| Consumption of milk and dairy products | 4.1±3.2 |
| Consumption of fruit and vegetables | 6.8±2.8 |
| Consumption of alcohol | 3.0±3.2 |
| Treatment with dimethylfumarate | |
| Mean±SD duration at enrolment, weeks | 38.0±29.8 |
| Mean±SD daily dose at enrolment, mg | 232.4±194.1 |

BMI: Body Mass Index; SD: standard deviation.

ter starting the therapy, at a mean DMF daily dosage of 146.1±141.3 mg. An association between treatment duration and the daily dose of DMF at the occurrence of side effects was found (ρ=0.37, P=0.02). Mean age of patients complaining of side effects was 57.7±12.8 years and their mean weight was 82.1±13.4 kg. The distribution of BMI classes in this group was significantly different (P=0.026) from those who had not experienced side effects; in particular, overweight subjects were 60.5% *versus* 20%. No associations with further demographic features were found (Table II). Most side effects were gastrointestinal, including diarrhea, which was reported by 17 patients (44.7%), gastralgia by 11 (28.9%) and nausea by 6 (15.8%) patients. Considering each side effect separately, the most frequent was flushing (23 patients, 60.5%).

### Dietary habits and their correlation with DMF side effects

In 18 patients (47.4%), side effects appeared within 2 hours of having a meal. The mean score regarding the habit of skip-

TABLE II.—*Overall characteristics of the side effects of dimethylfumarate in the study population.*

| Parameters | Patients with side effects | Patients with no side effects | P |
|---|---|---|---|
| Total cases, N. (% of population) | 38 (71.7) | 15 (28.3) | |
| Demographics | | | |
| Males, N. (% of total cases) | 27 (71.1) | 10 (66.7) | 0.75 |
| Females, N. (% of total cases) | 11 (28.9) | 5 (33.3) | |
| Mean±SD age, years | 57.7±12.8 | 59.3±14.1 | 0.70 |
| Mean±SD body weight, kg | 82.1±13.4 | 83.1±21.9 | 0.86 |
| Mean±SD BMI | 27.0±3.4 | 27.8±6.1 | 0.62 |
| Patients per BMI class, N. | | | |
| Normal weight | 10 | 8 | 0.026* |
| Overweight | 23 | 3 | |
| Obesity | 5 | 4 | |
| Type of side effects | | | |
| Flushing, N. (% of patients who had side effects) | 23 (60.5) | – | |
| Diarrhea, N. (% of patients who had side effects) | 17 (44.7) | – | |
| Gastralgia, N. (% of patients who had side effects) | 11 (29.0) | – | |
| Nausea, N. (% of patients who had side effects) | 6 (15.8) | – | |
| Circumstances of side effects | | | |
| Mean±SD treatment duration at the onset, weeks | 4.3 (4.6) | – | |
| Mean±SD drug dose at the onset, mg | 146.1±141.3 | – | |
| Time to occurrence after meals | | | |
| Up to two hours, N. (%) | 18 (47.4) | – | |
| More than two hours, N. (%) | 19 (50.0) | – | |
| No answer | 1 (2.6) | – | |
| Scores for dietary habits at main meals, mean±SD | | | |
| Skipped meals | 1.7±2.3 | 1.27±2.1 | 0.56 |
| Consumption of fatty foods | 7.2±2.4 | 8.3±1.3 | 0.07 |
| Consumption of milk/dairy products | 4.0±3.2 | 4.3±3.4 | 0.60 |
| Consumption of fruit/vegetables | 6.8±2.7 | 6.7±3.0 | 0.90 |
| Consumption of alcohol | 3.1±3.2 | 2.9±3.4 | 0.82 |
| Resolution of side effects | | | |
| Cases, N. (%) | 20 (52.6) | – | |
| Mean±SD time to resolution, weeks | 9.05±7.43 | – | |

*Statistically significant.
BMI: Body Mass Index; SD: standard deviation.

ping a meal per day was 1.5±2.2. This indicates that patients had no tendency to skip meals. Skipping meals was not correlated with the occurrence of side effects, considered as a whole (P=0.56). In Table II the scores of mean daily intakes of each food considered in this study are also reported. Overall, occurrence of side effects was not related to consume of milk and dairy (P=0.60), fruits and vegetables (P=0.90) and alcohol (P=0.82). Daily fat intake appeared to protect against side effects, with a P value close to statistical significance (P=0.07). Considering each side effect separately (Table III), in patients complaining of flushing, side effects' occurrence was significantly associated to their late onset with respect to meal consumption, namely after 2 hours (P=0.007), to a lower daily dose of DMF (P=0.02), namely 114.8±129.7 mg *versus* 194±149.1 mg of those who did not experience this side effect, and they tended to occur early during the treatment (P=0.06) (3.2±3 weeks *versus* 6.1±6.2 weeks). Diarrhea was significantly related to skipping meals (P=0.002), gastralgia had a significant association with lower consumption of fats (P=0.032), whereas the occurrence of nausea was statistically related to a higher DMF daily dose (265±190.1 mg *versus* 123.8±121.4 mg, P=0.021) and occurred later (8.7±8.1 weeks *versus* 3.4±3 weeks, P=0.035).

## Discussion

In the treatment of plaque psoriasis, DMF is characterized by both a favorable long-term safety profile and

TABLE III.—*Characteristics of each of the side effects of dimethylfumarate observed in the study population.*

| Parameters | Side effects | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Flushing | | | Diarrhea | | | Gastralgia | | | Nausea | | |
| | Yes | No | P | Yes | No | P | Yes | No | P | Yes | No | P |
| Total cases, N. | 23 | 15 | | 17 | 21 | | 11 | 27 | | 6 | 32 | |
| Demographics of patients | | | | | | | | | | | | |
| Males, N. | 18 | 9 | 0.23 | 14 | 13 | 0.28 | 7 | 20 | 0.70 | 3 | 24 | 0.33 |
| Females, N. | 5 | 6 | | 3 | 8 | | 4 | 7 | | 3 | 8 | |
| Mean±SD age, years | 56.9±13.8 | 58.9±11.3 | 0.62 | 58.2±13.0 | 57.3±12.8 | 0.83 | 62.2±10.0 | 55.9±13.4 | 0.12 | 59.0±7.9 | 57.4±13.6 | 0.70 |
| Mean±SD body weight, kg | 83.2±10.9 | 80.3±16.8 | 0.55 | 81.6±16.2 | 82.4±11.1 | 0.87 | 82.8±12.8 | 81.7±13.9 | 0.82 | 84.5±18.7 | 81.6±12.5 | 0.73 |
| Mean±SD BMI | 27.3±3.6 | 26.4±3.2 | 0.43 | 26.6±3.7 | 27.3±3.2 | 0.55 | 27.4±3.5 | 26.8±3.4 | 0.64 | 27.6±4.2 | 26.9±3.3 | 0.69 |
| Patients per BMI class, N. | | | | | | | | | | | | |
| Normal weight | 5 | 5 | 0.64 | 7 | 3 | 0.17 | 2 | 8 | 0.78 | 1 | 9 | 1.00 |
| Overweight | 14 | 9 | | 8 | 15 | | 7 | 16 | | 4 | 19 | |
| Obesity | 4 | 1 | | 2 | 3 | | 2 | 3 | | 1 | 4 | |
| Scores for dietary habits at main meals, mean±SD | | | | | | | | | | | | |
| Skipped meals | 1.3±1.9 | 2.1±2.8 | 0.46 | 2.9±2.5 | 0.7±1.7 | 0.002* | 2.5±3.0 | 1.3±2.0 | 0.25 | 0.3±0.8 | 1.9±2.4 | 0.13 |
| Consumption of | | | | | | | | | | | | |
| Fatty foods | 6.9±2.7 | 7.6±1.8 | 0.51 | 7.1±2.3 | 7.2±2.5 | 0.76 | 5.7±3.1 | 7.7±1.7 | 0.032* | 7.8±1.6 | 7.0±2.5 | 0.52 |
| Milk/dairy products | 6.7±2.9 | 7.1±2.6 | 0.78 | 5.0±3.7 | 3.2±2.6 | 0.15 | 4.5±3.4 | 3.8±3.2 | 0.57 | 3.8±2.9 | 4.1±3.3 | 0.73 |
| Fruit/vegetables | 4.4±3.3 | 3.4±3.0 | 0.19 | 7.4±2.6 | 6.4±2.9 | 0.30 | 6.7±3.2 | 6.9±2.6 | 0.97 | 6.8±3.5 | 6.8±2.7 | 0.98 |
| Alcohol | 3.2±3.3 | 2.9±3.2 | 0.74 | 3.2±3.0 | 3.0±3.5 | 0.69 | 1.8±2.5 | 3.6±3.4 | 0.14 | 3.7±3.6 | 3.0±3.2 | 0.64 |
| Circumstances of side effects | | | | | | | | | | | | |
| Mean±SD treatment duration at the onset, weeks | 3.2±3.0 | 6.1±6.2 | 0.06 | 4.2±3.7 | 4.3±5.3 | 0.78 | 4.3±3.8 | 4.2±4.9 | 0.83 | 8.7±8.1 | 3.4±3.0 | 0.035* |
| Mean±SD drug dose at onset, mg | 114.8±129.7 | 194.0±149.1 | 0.020* | 137.6±146.2 | 152.9±140.4 | 0.43 | 174.5±170.7 | 134.4±129.3 | 0.43 | 265.0±190.1 | 123.8±121.4 | 0.021* |
| Time to occurrence after meals | | | | | | | | | | | | |
| Up to two hours, N. (%) | 7 | 11 | 0.007* | 10 | 8 | 0.33 | 7 | 11 | 0.30 | 3 | 15 | 0.66 |
| More than two hours, N. (%) | 16 | 3 | | 7 | 12 | | 4 | 15 | | 2 | 17 | |

*Statistically significant.

absence of major contraindications. On the other hand, side effects secondary to this drug are not uncommon and can represent a cause of treatment suspension. In fact, within the first year of treatment, DMF is often switched to other conventional or biological therapies and, at month 12, the mean value of cumulative survival of DMF is around 50%.[3, 6, 7] Overall, drug suspension is reported in up to two-thirds of patients in the available published studies.[2, 3, 6-10] As stated above, the main reason for treatment discontinuation or switching to another drug is the occurrence of side effects, although usually mild and reversible. In a recent paper by Augustin, side effects, considered as a whole, and serious side effects occurred in 37% and 1.9% of the patients, respectively, after 52 weeks of DMF treatment. The most frequently reported side effects were diarrhea, lymphopenia, flushing, abdominal pain and epigastralgia.[11] A personalized titration schedule may provide a relevant, clinical benefit in terms of tolerability and quality of life improvement, without sacrificing the effectiveness of the drug, compared to full-dose schedule, as reported in a real-life experience by Malara *et al.*[12] In our previous multicentric real-life study, mean daily dose was 262.13 mg, thus much lower than the maximum allowable dose (720 mg).[3] It was observed that the extent of gastrointestinal side effects is not associated either with the time of drug intake, *i.e.*, in the morning rather than the evening, or with concurrent food intake.[2] However, this association has not yet been systematically investigated. Discovering a protective role of the diet on the onset of side effects could affect/improve the tolerability profile of DMF and adherence to treatment. In the present study, we were interested in addressing the potential correlation between occurrence of side effects and meals. More in detail, we aimed to assess whether the intake of food, and of certain categories of food, in the main meals of the day conditioned the incidence of DMF side effects. In our population, 71.7% of patients reported side effects during the treatment, with a high incidence of flushing, diarrhea, gastralgia and nausea, in line with the previous published experiences. Considering the mean daily dose recorded in our study patients (at week 38±29.8 they were treated with a mean daily dose of 232.5±194.1 mg), it can be argued that most of them underwent a dose titration. This shows that a slower gradual increase in daily dosage, when compared with the indications of the technical data sheet, or even a dose reduction, when a clinically relevant improvement has been achieved, are quite common in clinical practice for improving drug tolerability. A first noteworthy finding is that DMF-related side effects were more frequent in overweight or obese patients. Therefore, particular attention should be paid to this category of subjects undergoing treatment. The side effects observed appeared in less than 2 hours after the meal in half of the patients. This finding suggests that the food intake had neither a protective role nor favored the onset of side effects in our population. In keeping with this, flushing occurred mostly more than 2 hours after the meal, with statistical significance. Thus, a close correlation between flushing and food intake appears unlikely. Fat intake was found to tend to protect against the incidence of side effects, although without a statistical significance. Gastralgia was similarly less frequent in subjects with a fatty diet. Therefore, counseling patients to take the drug in conjunction with a fatty meal could have beneficial repercussions on the drug tolerability. On the other hand, this result does not render a fatty diet advisable, especially in the psoriatic patient who is often overweight and suffering from metabolic syndrome. Even if skipping meals was not correlated with the occurrence of side effects in general, diarrhea was reported mostly by subjects who had this habit. No significant associations emerged between DMF and daily intake of fruit and vegetables, dairy products or alcohol. In order to improve the education of patients affected with relapsing-remitting multiple sclerosis (RRMS) on potential DMF-associated side effects, a group of North American clinicians reached a survey-based consensus that a high-protein, low-starch, and high-fat meal may reduce the impact of gastrointestinal side effects.[13] Unequivocal evidence of a correlation between food and side effects did not emerge from our study. However, the lower incidence of side effects, especially gastrointestinal ones, observed in patients who usually consume fatty foods or in those who consume meals regularly are rather in line with the consensus strategies provided for improving the tolerability of DMF in patients with multiple sclerosis.[13] Conversely, the finding of the appearance of side effects more than two hours after the consumption of meals in half of our patients is less consistent.

### Limitations of the study

The study findings should be interpreted in the light of the following limitations. The number of patients included was relatively small and the period of observation short. Data on eating habits were self-reported; therefore, their veracity is not demonstrable. The questionnaire was not validated and was not administered at the same time point

for all patients; furthermore, the daily dose of DMF was different for each patient at the time of filling out the questionnaire. Since this was an observational, real-life study, although the dosing scheme adopted was rather overlapping between the participating centers, there was a certain variability that must be taken into consideration. We included patients who were undergoing treatment at the study recruitment period. Therefore, psoriatic patients who discontinued the treatment, for any reasons, prior to the inclusion phase were not eligible. This could represent a selection bias in some way. Our findings on dietary habits and DMF-related side effects indicate pure associations while a cause-effect relationship was not conclusively proven. Being an Italian study, the eating habits of the subjects included reflect the national diet, which is inevitably different from that of other countries. The scores attributed to individual meals, to quantify both the consumption of each food and the habit of skipping meals, were arbitrary and reflect the average food intake of Italians. The Mediterranean diet is quite different from the standard Western diet; for example, the prevalent habit in Italy is to have a small amount of food for breakfast compared to the other meals.[5, 6]

## Conclusions

Despite these limitations, our study, which for the first time specifically addressed the correlation between dietary habits and tolerability of DMF in psoriatic patients, suggests this aspect should not be neglected. In particular, paying more attention to the dietary habits of the patients treated with DMF could be a helpful strategy to improve treatment adherence and retention rate of this drug. Prospective testing of these strategies is needed in the development of stronger clinical practice recommendations.

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*Conflicts of interest.*—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

*Authors' contributions*.—Alessandro Borghi, Giulia Odorici, Alberto Monti, Vito Di Lernia, Fabrizio Guarneri and Monica Corazza have given substantial contributions to study conception and design, data acquisition, analysis and interpretation, Alessandro Borghi, Giulia Odorici, Alberto Monti, Federico Bardazzi, Vito Di Lernia, Fabrizio Guarneri and Monica Corazza to manuscript writing and critical revision for important intellectual content, Alessandro Borghi and Giulia Odorici equally contributed and share first authorship. All authors read and approved the final version of the manuscript.

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