# Gastrointestinal pirfenidone adverse events in idiopathic pulmonary fibrosis depending on diet: the MADIET clinical trial



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*To the Editor:*

Idiopathic pulmonary fibrosis (IPF) is a chronic and lethal interstitial lung disease (ILD) [1, 2]. Antifibrotic medications such as pirfenidone have been a turning point in the management of IPF, slowing of disease progression and improving survival [1–5].

However, mild-to-moderate gastrointestinal (GI) adverse events (AEs), including nausea and vomiting, have been reported in clinical trials and real-world practice as the most frequent challenge for drug adherence in IPF [1, 3–7]. Differences in prevalence and severity of GI AEs and drug withdrawal between north and south Europe countries could be related to different factors, including the type of diet [6–8]. The Mediterranean diet is characterised by a high ratio of monounsaturated fatty acids (MUFA) to saturated fatty acids (SFA) [9–11]. Olive oil is commonly used in MUFA diet and serves a distinct function in the GI tract, including optimal digestion [11]. Diets rich in SFA are more likely to drive gastro-oesophageal reflux events [9, 10]. This is the first study to evaluate the effect of diet (MUFA *versus* SFA) on the incidence and severity of GI AEs in patients with IPF treated with pirfenidone: a multicentre, international (UK, Germany, the Netherlands, Italy, Greece and Spain), minimal-interventional, non-randomised, open-label, phase IV trial (NCT03539289). Consecutive patients aged >40 years, anti-fibrotic treatment naïve, with IPF multidisciplinary diagnosis [2], and due to initiate pirfenidone treatment, were eligible. During the screening visit, patients completed the Food Frequency Questionnaire (FFQ), a questionnaire of usual dietary habits, focused on eliciting prevalent use of fatty acid types and method of cooking foods. An independent central committee (three experts in nutrition) evaluated the FFQ and assigned participants to MUFA or SFA arms depending on the FFQ score. Exclusion criteria included irregular or ill-defined diet type for at least 6 months prior to baseline (indeterminate for MUFA or SFA after FFQ analysis), major GI disorders at baseline (such as gastric or bowel surgery, and ulcus) and symptomatic or uncontrolled gastro-oesophageal reflux, among others (NCT03539289). Recruitment was performed between January 2018 and November 2019. Patients were instructed on: 1) following the same type of diet (food and cooking type) they were following in the previous months; 2) dosing and administration of pirfenidone according to the standard of care; and 3) the use of a patient diary to ensure there was no change in the type of diet during the study. The patient diary included daily data about food intake, any change in pirfenidone doses, and information on all AEs (according to the Common Terminology Criteria (CTC) for Adverse Events version 5.0) and their relationship with pirfenidone. All patients maintained high compliance (>80%) to the type of assigned diet. After a screening period (7–28 days), pirfenidone was initiated and patients were followed for up to 16 weeks. As per treatment standard of care protocol, alcohol consumption was not allowed. Liver function was assessed at baseline, after 1 week of pirfenidone initiation or dose increase, and after 1 and 4 months of full-dose pirfenidone (weeks 4 and 16 of the study).

The primary outcome was the difference in the rate of any GI AEs associated with pirfenidone treatment over 16 weeks according to diet. Secondary outcomes included differences in patient characteristics and functional test scores (forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide ($D_{LCO}$) and 6-min walk distance (6MWD)) at baseline and at the end of the study; severity and frequency of AEs were assessed longitudinally, and pirfenidone treatment modifications due to AEs. GI AEs were defined as a negative or undesirable reaction that occurred in the GI system digestive tract (including

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**Individuals with IPF who follow a MUFA diet report a lower incidence of pirfenidone gastrointestinal adverse events than those that follow a SFA diet, which could explain the different prevalence in GI pirfenidone AEs reported by countries in IPF cohorts** https://bit.ly/3LuzAUJ

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mouth, oesophagus, stomach, small intestine, colon, rectum or anus) as a result of pirfenidone or other external factors. Symptoms, onset, causality, severity, resolution and documentation were considered.

Descriptive analysis consisted of summary statistics as counts, mean±SD or median and quartiles 1 (Q1) and 3 (Q3) for continuous variables, and counts and percentages for categorical ones. The primary analysis was based on the full analysis set population defined as all recruited patients who signed the informed consent to participate during the entire study and per protocol for modified analysis set (subjects who presented major protocol deviations). The rate of patients reporting any GI AEs due to pirfenidone treatment over 16 weeks (nausea, diarrhoea, dyspepsia, reflux, vomiting, stomach discomfort, abdominal distension) based on CTC grading were compared by means of a Chi-square test. AEs were evaluated computing 95% confidence intervals for the risk ratio using unadjusted and adjusted by baseline characteristics log binomial regression. To account for non-random assignment to receive MUFA or SFA diets, a propensity score matching analysis was conducted. Propensity scores were estimated for each patient using a logistic regression model with diet as dependent variable and age, gender, body mass index (BMI) and food type as independent variables. The nearest matching approach was applied to identify matching pairs of patients on MUFA and SFA and this subsample was used to repeat the primary analysis. Standardised mean differences were calculated and compared before and after matching using a graphical approach. The number of GI AEs over 16 weeks was compared between diets using the Wilcoxon–Mann–Whitney test. The effect size was assessed fitting a zero-inflated Poisson regression model (due to excess of zeros, significant Vuong test). Both unadjusted and baseline characteristics adjusted models were fitted. For validating our unadjusted and adjusted analyses regarding the risk of GI AEs, a standardised mean difference (SMD) analysis was carried out. Severity, treatment discontinuation and dose reduction due to GI AEs were compared between diets by means Chi-square or Fisher's test. Pulmonary function (FVC, $D_{LCO}$ and 6MWD) were evaluated using analysis of covariance. Sample size estimation was based on comparison of two independent proportions. Accepting an error type I of 5% and a power of 90% in a two-sided test, 44 subjects were deemed necessary in each study arm to identify differences in frequency, expected to be 37% in SFA and 6% in MUFA, assuming 20% dropout.

From 95 screened patients, 86 patients were included as the final analysed population: 49 in the MUFA arm and 37 in the SFA arm. Baseline demographic characteristics (table 1) were similar between both groups, including age, BMI and hepatic metabolic markers. Details about the main differences in fatty acid intake between both groups are included in table 1.

MUFA-rich diet was associated with a lower incidence of pirfenidone related GI AEs (26.5%) compared to SFA-rich diet (64.9%) (p=0.001) (table 1), increasing the odds of not having a GI AE by more than nine-fold. In an unadjusted log binomial model, the risk ratio was 0.41 (95% CI 0.23–0.67), equivalent to a 59% (95% CI 33–77%) reduction in risk of GI AEs due to pirfenidone with MUFA *versus* SFA diet. After propensity matching, a subsample included 37 patients per group. In the adjusted model, the risk ratio was 0.42 (95% CI 0.22–0.71); a 58% reduction with a MUFA diet (95% CI 29–78%) with respect to a SFA diet. GI AEs were similar to the whole group analysis (MUFA arm 27%, SFA arm 64.9%; p=0.002) (table 1). SMD values showed minimal differences between both approaches regarding the risk of GI AEs (matched and unadjusted).

The median (Q1, Q3) number of GI events was 0 (0, 1) in MUFA diet and 1 (0, 2) in SFA diet (p=0.001). The odds ratio from the unadjusted zero-inflated Poisson regression model was 0.11 (95% CI 0.02–0.57); MUFA diet decreased the odds of having GI AEs by 89% (95% CI 43–98%). In the adjusted model, the odds ratio was 0.07 (95% CI 0.01–0.51); MUFA diet decreased the odds of having GI AEs by 93% (95% CI 49–99%).

No statistically significant differences were found between MUFA and SFA in severity of AEs (p=0.476) (grade 1, mild: 76.9% *versus* 62.5%; grade 2, moderate: 23.1% *versus* 37.5%). The proportion of drug discontinuation due to AEs was higher in the SFA diet group (7.69% MUFA diet *versus* 12.5% SFA diet). Interestingly, analysis of the different food types revealed that 50% of 16 patients reporting daily use of margarine or butter required dose reduction or drug discontinuation during the study.

Pirfenidone pharmacokinetics analysis was performed in a subgroup of 14 patients (seven MUFA diet and seven SFA diet) during the week of reaching the full dose of 2403 mg·day$^{-1}$. A previously developed and validated procedure based on ultra-high-performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS) measured mass concentrations of pirfenidone in plasma, according to European Medicines Agency and Clinical and Laboratory Standards Institute guidelines. No differences in the total serum concentration of pirfenidone and its metabolite (5-carboxy-pirfenidone) were found.

**TABLE 1** Idiopathic pulmonary fibrosis patient profile and relevant medical history at baseline, and gastrointestinal adverse events reported during the follow-up period (first 16 weeks of pirfenidone treatment)

| | SFA diet (n=37) | MUFA diet (n=49) | Subjects n |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | 74.3±6.57 | 71.8±8.58 | 86 |
| Gender | | | 86 |
| Male | 26 (70.3%) | 38 (77.6%) | |
| Female | 11 (29.7%) | 11 (22.4%) | |
| White ethnicity | 36 (97.3%) | 49 (100%) | 86 |
| **Habits** | | | |
| Smoking history | | | 86 |
| Never smoked | 10 (27.0%) | 13 (26.5%) | |
| Ex-smoker | 27 (73.0%) | 36 (73.5%) | |
| Alcoholic consumption during last year | | | 86 |
| Is a non-drinker | 22 (59.5%) | 36 (73.5%) | |
| Has an average consumption | 15 (40.5%) | 12 (24.5%) | |
| **Anthropometrics** | | | |
| Height (cm) | 166±9.28 | 167±7.84 | 86 |
| Weight (kg) | 78.9±12.0 | 81.3±13.7 | 85 |
| BMI ($kg \cdot m^{-2}$) | 28·5±3.60 | 29.2±4.48 | 85 |
| BMI WHO categories | | | 85 |
| Normal | 3 (8.11%) | 4 (8.16%) | |
| Overweight | 25 (67.6%) | 28 (57.1%) | |
| Obesity | 9 (24.3%) | 16 (32.7%) | |
| **Months since diagnosis, median (Q1; Q3)** | 2.96 (0.72; 10.8) | 2.10 (0.79; 3.98) | 86 |
| **Comorbidities** | | | |
| Cardiovascular disease | 21 (56.7%) | 25 (51%) | 86 |
| Gastrointestinal | 13 (35.2%) | 14 (28.5%) | 86 |
| Gastro-oesophageal reflux | 10 (27%) | 12 (24.5%) | 86 |
| Respiratory | 7 (19%) | 8 (16.3%) | 86 |
| **Most frequent fatty acids intake (baseline and during the study)** | Lamb, pork, beef, burger, sausages, hot dogs, bacon, whole milk, cream, cheese, butter, margarine, pastries, cakes and cookies | Salmon, sardine, trout, almonds, walnuts, olive oil, olives, avocado, chia seeds | 86 |
| **Gastrointestinal AEs** | **SFA diet (n=37)** | **MUFA diet (n=49)** | **p-value** |
| **Unadjusted model (n=86)** | | | |
| Number events/number patients | 24/37 | 13/49 | |
| Rate (95% CI) | 64.9 (47.5–79.8) | 26.5 (14.9–41.1) | 0.001[#] |
| RR MUFA *versus* SFA (95% CI) | 0.41 (0.23–0.67) | | 0.001 |
| **Adjusted model (n=74)** | | | |
| Number events/number patients | 24/37 | 10/37 | |
| Rate (95% CI) | 64.9 (47.5–79.8) | 27 (13.8–44.1) | 0.002[#] |
| RR MUFA *versus* SFA (95% CI) | 0.42 (0.22–0.71) | | 0.003 |
| **Number of events, median (Q1; Q3)** | 1 (0; 2) | 0 (0; 1) | 0.001[¶] |
| **Zero-inflated Poisson model** | | | |
| Unadjusted OR MUFA *versus* SFA (95% CI) | 0.11 (0.02–0.57) | | 0.009 |
| Adjusted OR MUFA *versus* SFA[+] (95% CI) | 0.07 (0.01–0.51) | | 0.009 |

Data are presented as mean±SD or n (%), unless otherwise indicated. SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; BMI: body mass index; WHO: World Health Organization; Q: quartile; AE: adverse event; RR: risk ratio; OR: odds ratio. [#]: Chi-square test; [¶]: Wilcoxon–Mann–Whitney test; [+]: for the adjusted analyses age, gender, BMI, food type (mixed variety, low-meat, predominantly meat), and number of daily meals were used.

However, the serum peak concentration ($C_{max}$) of both components was non-significantly higher after 1 h of pirfenidone intake in SFA diet participants (MUFA *versus* SFA: $C_{max}$ 9.95±24.5 *versus* 13.2±14.4 $mg \cdot L^{-1}$, area under the curve over the first 4 h 29.8±25.7 *versus* 33.5±21 $h \cdot mg \cdot L^{-1}$, median $t_{max}$ 2.00 (1–4) *versus* 1.00 h). No differences in end study lung function or 6MWD, after adjusting for baseline values, were found between study groups nor in interaction between baseline pulmonary function and study group.

Different factors associated with digestion and absorption could be involved in the incidence of pirfenidone GI AEs, such as the type of food and drug intake, patient age and gastro-oesophageal reflux [12–15]. Several approaches for preventing and managing potential pirfenidone-related GI AEs in patients

with IPF include: dose escalation schedules, adjusting pirfenidone dose to patient weight, and pirfenidone administration at mealtimes [13–15]. In the present study, the protocol regarding drug intake during meals and dose adjustment was the same across centres, and no significant differences were found in patient age or the prevalence of gastro-oesophageal reflux among countries. However, southern European centres had a predominant number of patients that usually follow MUFA diet, compared to centres from northern European countries (except for the Netherlands) with a clear prevalence of SFA diet. Country socio-cultural differences, such as mealtimes or the way of eating, could be also involved in the different GI AE prevalence, as could be diet-driven alterations in the gut microbiome. However, no differences in GI AEs among patients that followed SFA diet or distinct SFA clusters were present among countries (including northern *versus* southern European countries). On the other hand, a higher serum peak drug absorption in the first hour in those patients that followed SFA diet was demonstrated in the study. Therefore, the differences in GI AEs could be due to both direct effects on digestive transit but also indirect consequences of altered drug absorption and peak drug exposure. The main limitations to this study include potential confounders such as subject biology and investigator bias due to the non-randomised nature of the treatment arms. Furthermore, lack of data on the microbiome and water consumption impacted our understanding of the dietary effects. Finally, participants were predominantly of white ethnicity which may limit generalisability to other ethnicities.

In conclusion, this study demonstrates that a SFA diet is associated with worse tolerability and higher risk of GI AEs in patients with IPF taking pirfenidone. This identifies diet as an important modifiable target to reduce pirfenidone-related GI AEs. Additional studies are required to analyse the effect on GI AEs of a dietary intervention, such as reducing saturated fat intake or cooking with olive oil.

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This study was prospectively registered at ClinicalTrials.gov with registration number NCT03539289. All of the individual patient data collected during the study will be shared. The data will be made available within

12 months after publication. All available data can be obtained by contacting the corresponding author. It will be necessary to provide a detailed protocol for the proposed study, to provide the approval of an ethics committee, to supply a signed data access agreement and to have discussion with the original authors for re-analysis.

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