Electronically monitored medication adherence in idiopathic pulmonary fibrosis: prevalence, predictors and outcomes

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Shareable abstract (@ERSpublications)
This study used electronic monitoring systems for the first time in IPF patients to assess taking and timing of pirfenidone. Medication nonadherence is a prevalent issue that increases over time and is associated with patients' lung function outcomes. https://bit.ly/3wEFUlq

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Abstract

Medication adherence studies in idiopathic pulmonary fibrosis (IPF) are limited, use cross-sectional designs and report discontinuation rates.

We prospectively investigated adherence to pirfenidone in IPF patients using electronic monitoring, which provides insights on whether and when the medication was taken on a day-by-day basis. We investigated the impact of nonadherence on lung function and selected predictors for nonadherence based on the COM-B behavioural model. The longitudinal statistical analyses included generalised estimation equations and linear mixed effects models.

55 patients initiating pirfenidone were followed-up for 2 years after diagnosis (76.4% men, mean age 71.1 years (range 50–87 years), mean forced vital capacity (FVC) 88% predicted (SD 18.3), mean diffusing capacity of the lung for carbon monoxide (D_{LCO}) 58.1% predicted (SD 14.7)). Our data showed an association (p=0.03) between the proportion of days with three pirfenidone intakes (*i.e.* dosing adherence) and FVC % predicted, whereby a high dosing adherence seemed necessary to maintain stable or improving FVC % predicted values. 58.2% of the participants were able to implement at least 90% correct dosing days, yet adherence significantly decreased over time. Too short dosing intervals had negative effects on lung function outcomes. Knowledge on IPF and self-reported adherence were significantly associated with electronically measured adherence.

In conclusion, nonadherence is prevalent and might negatively affect lung function. Further research is needed on the impact of nonadherence on outcomes and its predictors, so that tailored interventions can be developed. Meanwhile, a self-report questionnaire could be used to identify adherence issues and teams should equip patients with knowledge about their treatment and how to take it.

Introduction

Idiopathic pulmonary fibrosis (IPF) progressively affects the lung parenchyma through fibrosis, causing pulmonary function impairment and respiratory failure [1, 2]. To date, two antifibrotic drugs, pirfenidone and nintedanib, slow down disease progression, reduce the risk of hospitalisations and improve the patient's prognosis [1, 3]. To reach the full benefits on patients' outcomes, medication adherence is essential. Adherence is defined as "the process by which patients take their medication as prescribed" and consists of initiation, implementation and discontinuation [4, 5]. The process starts when a patient takes the first prescribed dose of the medication (*i.e.* initiation). Implementation refers to how well a patient's actual regimen corresponds to the prescribed regimen in terms of taking and timing of intake. Discontinuation occurs when patients stop taking medication on their own initiative [5]. Nonadherence in chronic diseases is prevalent, is multi-causal and may lead to poor health outcomes and higher healthcare costs [6]. Hence,

adherence management should be a crucial part of the long-term routine care [7]. Unfortunately, evidence on adherence to antifibrotic drugs is scarce, although adherence could be challenging as both drugs have complex drug regimens. In fact, several doses per day are required, the medication has to be taken over a long period of time and there may be burdensome medication side-effects [8, 9]. Prior studies primarily evaluated discontinuation rates (ranging between 21 and 58%) cross-sectionally or retrospectively, and used adherence measures, such as self-reporting or pharmacy refill data, which are known to underestimate adherence problems [10–13]. To investigate adherence to complex pharmacological regimens one needs accurate measurement methods. Electronic monitoring is considered the gold standard adherence measure. It allows the measurement of day-to-day intake patterns continuously over time and is suitable to model the impact of nonadherence on clinical outcomes [4, 5, 14]. To our knowledge, no study investigated adherence patterns longitudinally in patients with IPF.

We conducted a prospective observational study to electronically assess the prevalence of medication nonadherence, to identify potential adherence predictors and to investigate the link between nonadherence and clinical outcomes.

Methods

We report our study according to the "Espacomp Medication Adherence Reporting Guideline" (EMERGE) (supplementary material S1) [15].

Design, setting and sample

The SUPIRIO-study ("Supporting adherence to pirfenidone in patients with IPF: the key to successful treatment outcomes") was conducted at the IPF Centre University Hospitals Leuven (UZ Leuven), Belgium and according to the principles of the Declaration of Helsinki [16]. The Ethical Committee Research UZ Leuven/KU Leuven approved the study (ref. S61427). We registered the study in the ClinicalTrials.gov database (identifier NCT03567785) and mandated written informed consent from all participants.

We included Dutch- or French-speaking adults with a confirmed IPF diagnosis, who initiated pirfenidone treatment and who were followed-up at UZ Leuven. We excluded patients who did not manage their medication regimen independently (help from informal caregivers was allowed). In 2019, the Ethical Committee approved an amendment, allowing to enrol patients who have a shared follow-up between a district hospital and UZ Leuven.

Procedure

Inclusion took place between July 2018 and March 2020. Figure 1 shows the timing of study visits and collected variables, whereby visit 1 marks pirfenidone initiation and the timepoint of face-to-face patient enrolment. At our centre, about five newly diagnosed patients initiate treatment with pirfenidone each month. Study visits took place after scheduled outpatient visits at UZ Leuven.

Medication adherence was continuously measured from pirfenidone initiation to up to 2 years, using the Medication Event Monitoring System (MEMS, AARDEX Group, Belgium). The MEMS Cap is a special cap holding a microchip and a pressure-release system that records the date and time patients open and close their pill bottle. Medication intake is presumed when opening the bottle.

Participants received oral and written information on the MEMS Caps and were asked to fill the bottle with pirfenidone after visit 1 and each time the bottle was empty. Also, we asked participants to keep a diary in which they could note abnormalities related to the MEMS Caps (*e.g.* accidental bottle openings without drug intake). These events were not considered as nonadherence and thus excluded during MEMS Cap data analysis. Medication intake patterns were not disclosed to patients, nor to their healthcare professional. A researcher read the MEMS Cap using the MEMS Adherence Software platform at each study visit and participants received a bundle with questionnaires (see supplementary material S2 for more information on the content and scoring of questionnaires used at every study visit). If a planned study visit was not possible due to the COVID-19 pandemic or because the patient was being followed-up by a district hospital, the questionnaires were sent by post to the participants' homes and the MEMS Cap was read at a subsequent visit at UZ Leuven. The study ended in February 2021, hence not all participants completed the 2-year follow-up period.

Variables and measurements

Supplementary material S2 contains detailed information on the outcome and predictors variables.

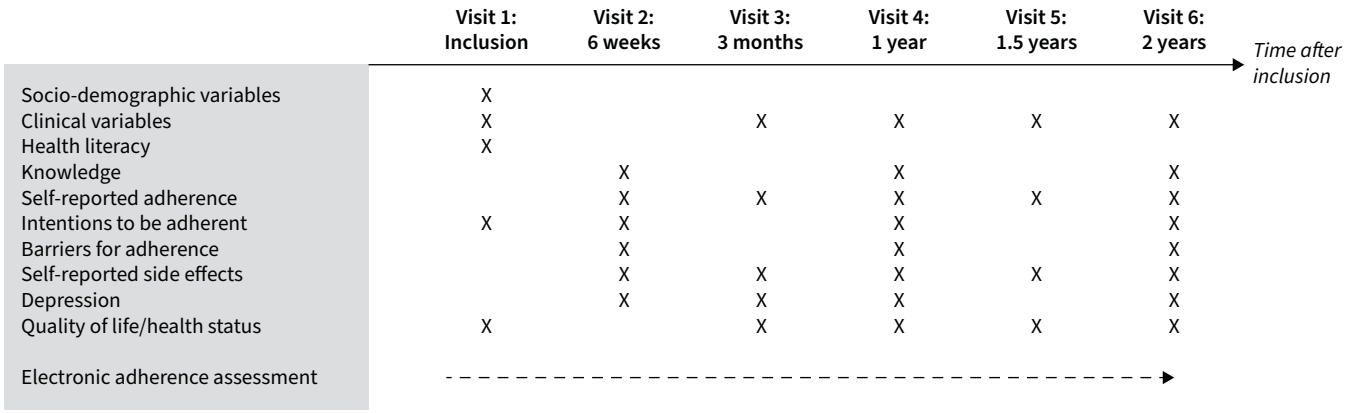

FIGURE 1 Study visits and variables.

Sociodemographic variables

We documented sex, age, ethnicity, marital status and education level using a self-report interview developed for the purpose of this study.

Operational definitions of pirfenidone adherence

The electronically compiled MEMS data metrics were computed from the first to the last available data point to assess adherence in view of implementation. For pirfenidone, three intakes a day with a dose of 801 mg were required and patients at UZ Leuven are instructed to leave at least 3 h between each intake. We used the following four implementation metrics:

- Taking adherence: the proportion of prescribed drug that is taken
- Dosing adherence: the proportion of days where the correct number of doses are taken (three doses a day, unless otherwise prescribed)
- The proportion of drug holidays: defined as at least 3 days without intake
- Timing nonadherence: the proportion of inter-dose intervals shorter than 3 h

The initiation component was not a part of this research as having started treatment was an eligibility criterion. We documented patient-initiated discontinuations. Temporary interruptions to pirfenidone (*e.g.* due to side-effects), but with a later re-initiation of medication, were not considered as nonadherence if instructed by the treating pulmonologist.

Predictors of implementation

To select the variables that might favour adequate implementation, we used the COM-B model as a theoretical framework, which states that (medication taking) behaviour is the result of capability, opportunity and motivation [17]. Capability refers to the individual's psychological and physical capacity to engage in the specific behaviour. Opportunity encompasses the environmental and social factors that facilitate or hinder adherence. Motivation refers to reflective or automated processes that direct behaviour [17]. We also selected additional variables known to predict medication adherence based on evidence in other diseases. Additionally, we investigated whether self-reported taking adherence as measured with the adapted BAASIS questionnaire was associated with electronically assessed adherence [18].

The following variables and questionnaire were assessed as predictors (supplementary material S2): health literacy (Subjective Health Literacy Screener [19]); intentions to adherence (based on the manual for health services researchers and the stages-of-change theory [20]); adherence barriers (IMAB); depression (PHQ9 [21]); knowledge on IPF and pirfenidone (investigator-developed) and self-reported side-effects (investigator-developed).

Outcomes of implementation

We investigated the outcomes: FVC % predicted, D_{LCO} % predicted and health-related quality of life (HRQoL)/health status (The King's Brief Interstitial Lung Disease questionnaire (K-BILD), EQ-Health Index), for which the operational definition is explained as part of the statistical analysis section [22, 23].

Statistical data analysis

The median values, range and interquartile ranges of the implementation metrics were calculated.

We studied the link between the implementation metrics and the outcomes using linear mixed effects models, relating the outcome measured at visit *d* and implementation metrics computed between visits *d-1* and *d*. These models included a random intercept varying across subjects and a constant slope linking implementation and outcome. FVC and D_{LCO} values for every timepoint were expressed relatively to their baseline value, while for quality of life (QoL) we used baseline QoL as a covariate [24].

We investigated if a threshold of adherence can be linked to stable or improving FVC-values, using a receiver operating characteristic (ROC) curve. The outcome for the analysis was the distinction between a stable/improving FVC *versus* a deteriorating FVC (*i.e.* $\geqslant$10% reduction compared to baseline). We searched for the optimal adherence threshold based on the maximised sum of sensitivity and specificity.

With a logistic regression, we investigated the link between the proportion of days with the correct number of intakes to predictors measured only at baseline. For the predictors measured at several timepoints, we investigated the link with implementation longitudinally by using a logistic regression where dependence among observations from a participant over time was considered through a generalised estimation equations (GEE) approach with a first-order autoregressive covariance structure [25]. Implementation was represented as a sequence of binary data points (*i.e.* Z_{ij}), whereby each point described whether participant *i* took their medication correctly on day *j*. Z_{ij}=1 in case the participant took exactly three doses on day *j*, Z_{ij}=0 otherwise. Periods where patients had to temporarily discontinue their drug regimen in concertation with their doctor were censored and not included in the analyses.

We applied a backward stepwise feature selection process to reduce the risk of overfitting. First, all possible models relating all predictors but one to Z_{ij} were fitted, and the corresponding values of the quasi-likelihood under the independence model information criterion (QIC_u) were stored [25]. The first removed predictor was the one corresponding to the model with the lowest QIC_u. As a second step, all possible models relating all predictors except two (the previously removed one and a second one) to Z_{ij} were fitted. The second removed predictor was the one corresponding to the model with the lowest QIC_u. This process was continued until the removal of no additional predictor could decrease the QIC_u.

Moreover, using the same methods, we conducted univariate analyses to study the influence of each individual predictor on the quality of implementation. Note that for the GEE models, time was also included as covariate.

All predictors were re-scaled to range between 0 and 1 to facilitate the fitting process. The fitting was limited to the first 600 days of follow-up, because only eight subjects had data for a longer duration. The significance level was taken at p=0.05. IBM SPSS statistics version 28 and Python 3 were used, and a statistician with specific expertise on adherence data analysis (AP) not affiliated to the IPF team conducted the analyses.

Results

Participants' characteristics

66 out of 104 eligible patients consented yet in this paper, we report data of 55 out of 66 participants. Three participants declined the use of the MEMS Cap, three caps were lost by patients during follow-up and for five participants no more caps were available.

Figure 2 shows the study flowchart. The sociodemographic characteristics of the participants included in the analyses are described in table 1. Data from the follow-up visits (n=55) are described in supplementary material S3.

Prevalence of nonadherence to pirfenidone

In figure 3 we show individual adherence patterns as visualised by samples of four chronology plots, and in figure 4 we provide the "lasagna plot" containing data of the daily medication history of all participants until the end of the study follow-up or discontinuation. 30.9% (n=17) had at least 95% correct dosing days and 58.2% (n=32) at least 90%. In table 2, we report the summary statistics of the four implementation metrics at group level. Two participants discontinued all treatment on their own initiative (3%), one participant early after treatment initiation (persistence of 8 days) and one participant after 577 days.

Link with outcomes, threshold for optimal adherence and predictors of adherence

In table 3, we present the link between the outcomes and the four implementation metrics, showing that the proportion of dosing intervals shorter than 3 h negatively impacts FVC % (p=0.00) and D_{LCO} % predicted (p=0.01) values. Furthermore, the proportion of days with the correct number of doses taken

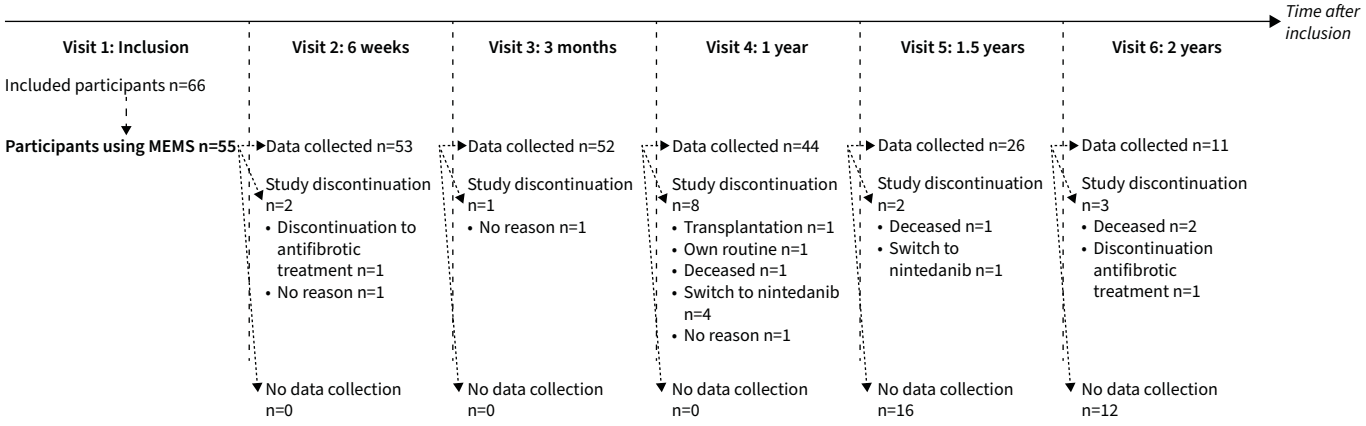

FIGURE 2 Study flowchart (n=55). "Study discontinuation" refers to the patients who had a data collection point planned but discontinued the study (*e.g.* deceased, medication switch)."No data collection" refers to the patients who did not have a new data collection point planned and thus ended the study as anticipated (*e.g.* due to the prospective inclusion and design of the study).

positively and significantly impacts FVC % (p=0.03), but not D_{LCO} % predicted values. No clear effect was shown between adherence and HRQoL. Having >93% of correct days was the threshold linked to stable or improving FVC % predicted, *i.e.* FVC above 90% of its baseline value (sensitivity: 62%, specificity: 70%) with the area under the curve (AUC) being 0.63.

Table 4 indicates that no predictor measured at baseline is related to dosing adherence. The longitudinal analysis shows that dosing adherence significantly decreases over time. Also, self-reported taking nonadherence is significantly associated with a poorer electronically measured dosing adherence in both the univariable and multivariable models (p=0.02 in both cases). In the univariable analyses, knowledge

TABLE 1 Sociodemographic and clinical characteristics (n=55)

	Baseline (Visit 1)
Sex n (%)	
Male	42 (76.4)
Female	13 (23.6)
Age years	
Mean±SD	71.1±8.2
Range	50–87
Median (IQR)	72 (10)
Ethnicity Caucasian n (%)	55 (100)
Marital status n (%)	
Partner	47 (85.5)
No partner	8 (14.5)
Education level n (%)	
Lower education	13 (23.6)
Moderate education	28 (50.9)
Higher education	14 (25.5)
D_{LCO} % predicted n	54
Mean±SD	58.1±14.7
Range	24.2–111
Median (IQR)	58.5 (18.3)
FVC % predicted n	54
Mean±SD	88±18.3
Range	50–126
Median (IQR)	88 (29)

IQR: interquartile range; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity.

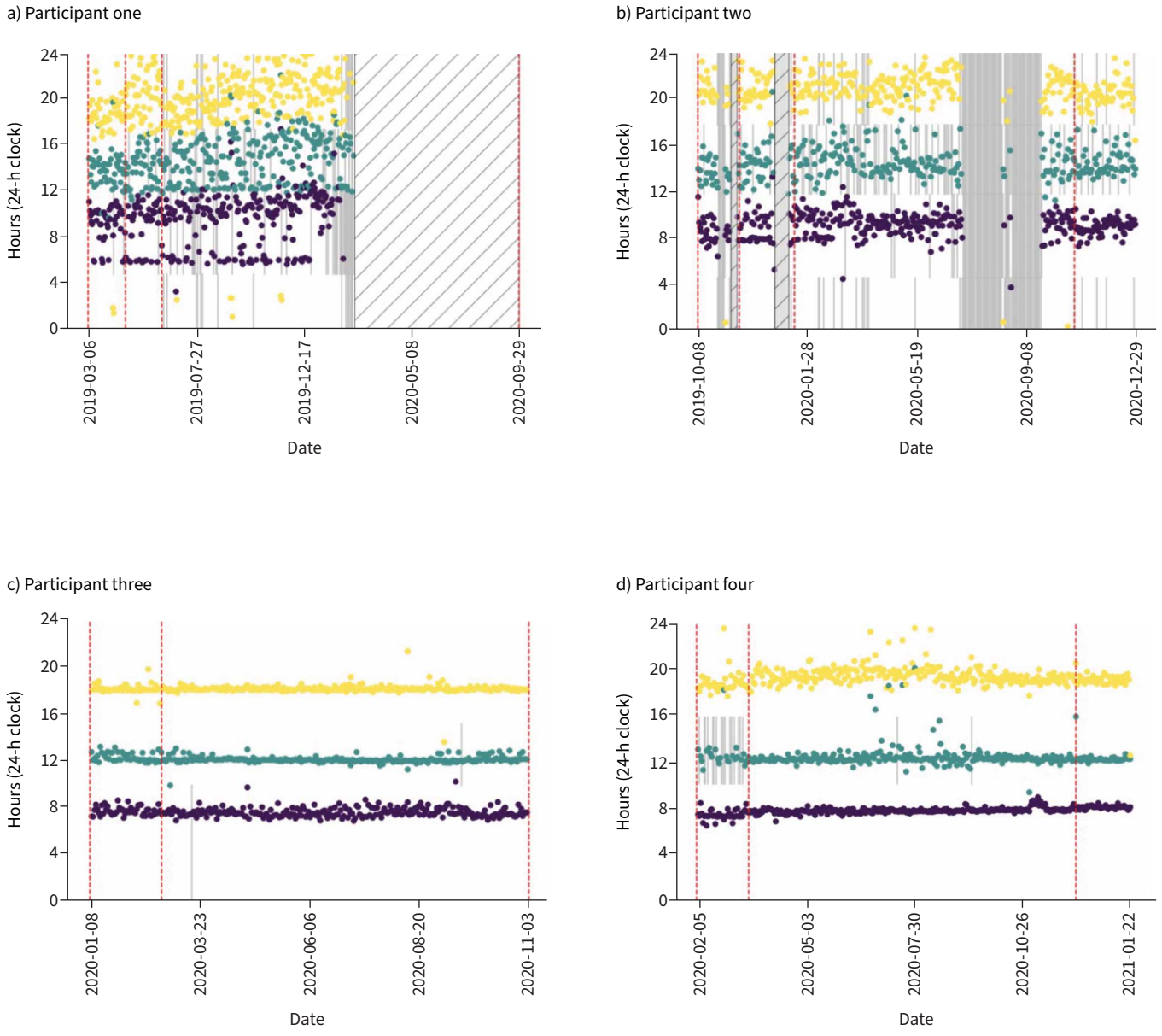

FIGURE 3 Chronology plots of four participants. Chronology plots allow us to visualize any missing or extra drug intake, drug holidays, timing of intake, consistency in timing and taking and discontinuation. Dates are shown on the x-axis (calendar) and time (24-h clock) is shown on the y-axis. Three daily pirfenidone doses at mealtime are recommended for idiopathic pulmonary fibrosis patients: coloured dots are bottle openings (i.e. presuming medication intake): purple (morning dose), green (midday dose) and yellow (evening dose). The grey bars are points where no medication intake (i.e. opening bottle) are monitored and the red lines refer to study visits. a) Participant one took pirfenidone at times that varied greatly and missed several doses, especially at the end of the monitoring. The patient had 78.2% of days with correct dosing of pirfenidone. This reflects a poor implementation pattern. The patient stopped using the bottle without discontinuing the treatment. b) Patient two had two registered non-monitoring periods at the beginning of treatment, yet the plot shows two additional periods for which no reason was provided (i.e. considered as long drug holidays). Also, multiple intakes were missed, including short drug holidays. During the monitored period, the patient only had 59.4% of correct dosing days. c) Patient three had a regular timing adherence and only missed two doses during the monitoring period of 10 months. More specifically, the patient had 99.3% of correct dosing days. d) Patient four had similar adherence pattern as patient three but showed issues in taking adherence early after treatment initiation and especially for the timing point at the midday meal. During the monitored period, the patient had 94.8% of correct dosing days.

about disease and treatment was significantly associated with better dosing adherence. Further analyses using a logistic regression reveal that knowledge about pirfenidone is also significantly negatively related to self-reported omission of pirfenidone (p=0.00).

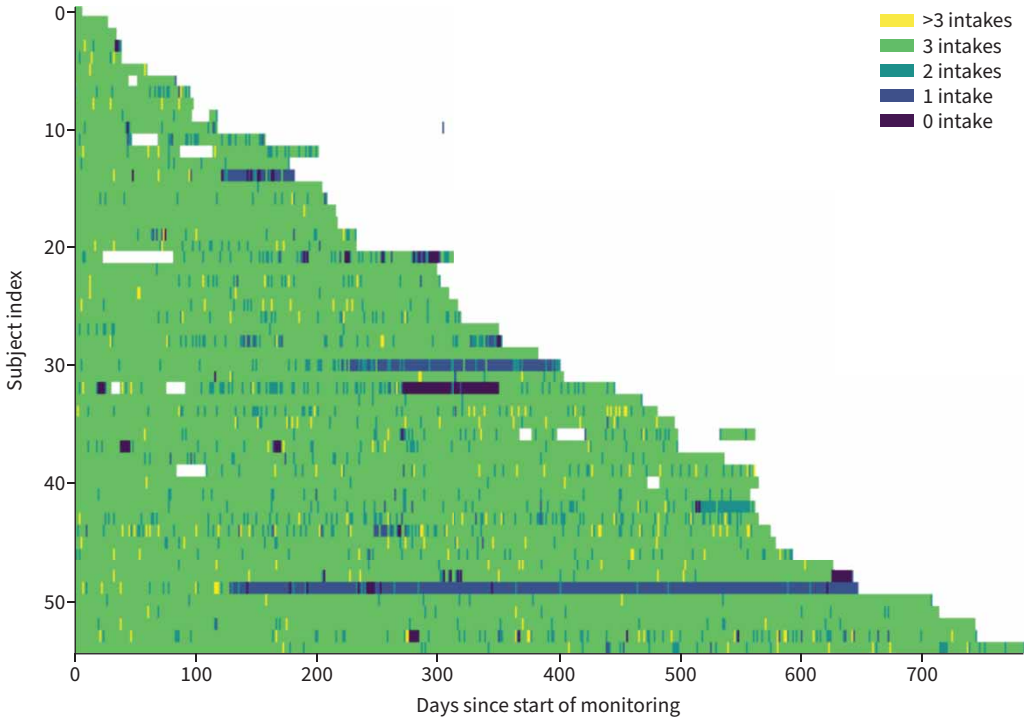

FIGURE 4 Lasagna plot of the study cohort. The rows represent the individual participants, and the columns indicate the days. Each white rectangle represents a non-monitored day, each purple rectangle represents a day with no intake, and each colored rectangle represents a day with 1, 2, 3 or more than 3 intakes. The binary variable Z_{ij} is equal to 1 for days depicted in green and 0 for days depicted in purple, blue, turquoise and yellow. It is undefined for days depicted in white.

Discussion

This is the first study that used electronic monitoring to prospectively measure adherence patterns, their impact on outcome and its predictors in IPF. Noteworthily, we found that the proportion of days with three-daily pirfenidone dosing (*i.e.* correct dosing) was significantly associated with FVC % predicted values for which high adherence seems to be required. Also, timing nonadherence was associated with FVC and D_{LCO} % predicted values. Overall, dosing adherence decreased over time. We also found an association between electronically measured adherence and self-reported adherence, and adherence was also associated with disease and treatment-related knowledge.

Our observations suggest that taking the correct number of doses and sufficiently spacing the intakes is important for clinical effectiveness, as measured with lung function parameters. Moreover, we calculated that having <93% of correct dosing days is associated with deteriorating FVC% predicted values. These data should be interpreted cautiously, as the AUC is 0.63, and we did not take variability in timing intervals, reductions in daily dose or physician-initiated treatment interruptions into account. Nonetheless, our exploratory observations prudently suggest that almost perfect adherence is needed to ensure optimal FVC, which is in line with the 90–95% thresholds used in, for instance, transplantation or HIV, whereby minor deviations of the drug regimen might impact outcomes [26, 27]. In our study, 54.5% of the participants did not reach the 93% threshold. This rate seems higher than the 20–30% nonadherence often

TABLE 2 Overview of the summary statistics of the implementation metrics

Implementation metric	Range %	Median % (IQR)
Proportion of prescribed drug taken (taking adherence)	47–101	98 (5)
Proportion of days with the correct number of doses taken (correct dosing)	18–100	92 (10)
Proportion of drug holidays	0–2.4	0 (0)
Proportion of too short dosing intervals (timing adherence)	0–7.9	1.5 (2.1)

TABLE 3 Link between implementation and outcomes

Implementation metric	Outcome						
	FVC (p-value)	D_{LCO} (p-value)	EQ-Health Index (p-value)	K-BILD breathlessness (p-value)	K-BILD psychological (p-value)	K-BILD symptoms (p-value)	K-BILD total (p-value)
Proportion of prescribed drug taken (taking adherence)	0.126 (0.53)	0.161 (0.53)	−0.073 (0.77)	25.1 (0.30)	31.6 (0.21)	44.9 (0.13)	17.7 (0.24)
Proportion of days with the correct number of doses taken (correct dosing)	0.304 (0.03#)	0.223 (0.22)	0.106 (0.59)	33.2 (0.09)	7.89 (0.66)	27.5 (0.20)	17.1 (0.13)
Proportion of too short dosing intervals	−1.621 (0.00#)	−1.531 (0.01#)	−0.596 (0.28)	−73.5 (0.11)	16.3 (0.70)	−97.2 (0.05)	−28.8 (0.29)
Proportion of drug holidays	−0.626 (0.87)	−0.903 (0.85)	1.329 (0.79)	71.8 (0.86)	108 (0.78)	305 (0.50)	54.8 (0.82)

The table contains the slopes of the random intercept models linking implementation to outcomes. The slopes are dimensionless. FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K-BILD: The King's Brief Interstitial Lung Disease questionnaire. #: significance at the 0.05 level.

mentioned in systematic reviews in other diseases, although it is difficult to compare numbers, as often other less stringent definitions or less reliable methods might have been used, which might underestimate the true nonadherence rate [28]. However, pirfenidone needs to be taken three times a day, and adherence becomes more challenging when the number of daily doses increases [29].

Interestingly, we also observed that regularity of intake may play a role in predicting lung function outcomes, as the proportion of doses taken too closely together (*i.e.* <3 h apart) had a negative impact on D_{LCO} and FVC predicted values. To our knowledge, medication leaflets or published drug testing trials in IPF do not mention a recommended time interval between doses. Only the Food and Drug Administration prescribing information highlights the regularity of intake, but does not provide further specification [30, 31]. Given the lack of guidance on timing adherence, we used our hospitals' recommendation of leaving at least 3 h between each dose. Further prospective studies are needed to determine which dosing interval is optimal to ensure the maximal therapeutic benefit of antifibrotic drugs.

We also need to understand the predictors of adherence to implement person-tailored adherence-supporting strategies in IPF care. Surprisingly, although we selected *a priori* theory- and evidence-based predictors known to be associated to adherence behaviour, except for disease and treatment-related knowledge, we did not observe an effect on adherence in our prediction model. Ensuring that patients with IPF understand why and how they should take the medication hence seems to be an important avenue to ensure adherence. Further fully powered studies are needed to understand the drivers of nonadherence in IPF. Meanwhile, problems with, *e.g.* side-effects, mental health issues or poor health literacy call for action, as these factors were highly prevalent in our sample, and even though they did not impact adherence, they might affect patients' HRQoL.

Moreover, we noted an association between self-reported adherence and electronically measured adherence. This finding implies that integrating an easy-to-use self-reported adherence questionnaire in routine care may already provide insights about future adherence. However, one should keep in mind that self-report typically overestimates adherence compared to electronically monitored adherence, as we also observed in our study (data not shown) [14].

Our prospective study is novel, but there are some limitations to be mentioned. Firstly, this is an exploratory study whereby a power calculation was not performed, and the analyses are performed on a small sample size (especially at visit 5 and visit 6, which is due to the study design).There are also missing data for instance due to the COVID-19 pandemic, which were not included in the analysis. Secondly, the generalisability of our findings can be attained by selection bias, and we only included patients initiating pirfenidone, so further studies should assess medication adherence in patients on nintedanib or other drug components in the pipeline. Thirdly, we argue that sufficiently powered studies are needed to further investigate how much adherence is sufficient to maximise the effect of antifibrotic drugs [32]. Lastly, we used MEMS as it is considered the gold standard adherence measure, yet one may wonder whether patients will not change their medication behaviour because they know they are being monitored. However, this Hawthorne effect disappears after about 5–6 weeks, and we monitored our patients for a

TABLE 4 Predictors of taking adherence

Predictor of dosing adherence	Coefficient (dimensionless)	p-value
Univariate analyses		
Individual predictors measured only at baseline		
Age	0.88	0.63
Marital status	−0.23	0.85
Health literacy	0.00	1
Individual predictors measured longitudinally with time as covariate		
Time	−1.23	0.01
Intention to be adherent	−1.89	0.52
Time	−0.97	0.04
Number of side-effects reported	−0.55	0.57
Time	−0.96	0.04
Self-reported omission of pirfenidone	−1.41	0.02*
Time	Not converged	
Depression		
Time	−1.02	0.04
Barriers to adherence	−0.43	0.43
Time	−1.05	0.11
Knowledge about pirfenidone	2.12	0.03*
Prediction models (multivariate analyses)		
Model with predictors measured only at baseline		
Age	1.12	0.57
Marital status	−0.37	0.78
Health literacy	0.01	0.99
Model with predictors measured longitudinally		
Time	−1.21	0.04*
Intention to be adherent	Not selected	
Number of side-effects reported	Not selected	
Self-reported omission of pirfenidone	−1.60	0.02*
Depression	0.04	0.98
Barriers to adherence	Not selected	
Knowledge about pirfenidone	Not selected	

The variables which were not selected did not sufficiently improve the quality of the model. *: significance at the 0.05 level.

median of 384 days [33]. One may also question the feasibility of using adherence monitoring devices, but only five participants stopped using the MEMS Cap during study follow-up. Also, the participants had to fill the bottle themselves, but none of our participants found this inconvenient. By using the MEMS, we were able to see day-to-day patterns including drug intakes and particularly whether doses were taken too close to each other, which is not measurable with self-report, pill counting or pharmacy refills. This led us to evaluate the important impact of adherence behaviour on outcomes [34].

In conclusion, we presented unique insights on adherence patterns in IPF. We showed that nonadherence to pirfenidone is a problem that increases over time and may result in a negative impact on lung function outcomes. However, more research is needed to confirm our findings and to further investigate the prevalence and predictors of nonadherence, as well as its impact on outcomes. We recommend measuring adherence as part of routine IPF follow-up and to tackle gaps in treatment knowledge.

Provenance: Submitted article, peer reviewed.

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