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Choice of antifibrotic medication and disease severity predict weight loss in idiopathic pulmonary fibrosis

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Abstract

Purpose: Although safety and tolerability of approved antifibrotics has been reported extensively, little is known about their effects on weight. We analyzed predictors of weight change after one year of uninterrupted antifibrotic therapy in patients followed at our institution's interstitial lung disease clinic.

Methods/ Results: We identified 80 patients on antifibrotic therapy (44 pirfenidone/ 36 nintedanib) with at least one year of follow-up and no therapy interruptions. Thirty-five patients (44%) lost more than 5% of their baseline body weight, and 11 (19%) lost more than 10%. A higher proportion of patients of nintedanib experienced a clinically significant weight loss (>5%) versus pirfenidone (61% vs 30%, $p=0.005$). Univariate and multivariate analyses identified nintedanib therapy and a higher composite physiologic index (CPI) as predictors of weight loss.

Conclusions: Weight loss is common among IPF patients on antifibrotic therapy. Nintedanib therapy and more advanced disease were identified as predictors of weight loss in this population.

Keywords

idiopathic pulmonary fibrosis; nintedanib; pirfenidone; weight loss; body mass index

1. Introduction

The treatment of idiopathic pulmonary fibrosis (IPF) has been revolutionized by the introduction of antifibrotic therapy, but medication intolerance is common and often necessitates dose reduction or discontinuation [1, 2]. Both the ASCEND and the INPULSIS trials demonstrated that nausea and diarrhea are common during treatment with pirfenidone and nintedanib, respectively, affecting 30-63% of the participants [1, 2]. These side effects

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may interfere with nutrient intake and absorption and thus can result in weight loss, an effect that can be particularly concerning in such a frail population [3]. Moreover, recent data demonstrated that a >5% weight loss can be seen in up to 20% of IPF patients, even in the absence of therapy [4]. In our practice, we have observed a number of patients with striking weight loss despite minimal or no gastrointestinal side-effects. Thus, the aim of this study was to investigate the changes in body weight after the initiation of antifibrotic therapy among patients who were able to tolerate the medications and to determine predictors of weight loss.

2. Materials and Methods

2.1 Patient population

We analyzed the trends in body weight over a 12 month period in all patients initiated on antifibrotic therapy (nintedanib or pirfenidone) between 1/1/2015 and 12/31/2016 at the Cleveland Clinic, a quaternary referral center. Patients who were unable to tolerate 12 months of therapy, including those who switched agents, were excluded; other exclusion criteria included new cancer, inadequate follow up (less than 12 months or not returning for longitudinal care), missing data, death or transplant within the first year of therapy. This project was approved by the Cleveland Clinic IRB (#17-1600). The choice of antifibrotic therapy was left to the discretion of the practicing physician. Weights are routinely obtained on the same scale at all visits.

Patient demographics, comorbidities, pulmonary function tests and body mass index (BMI) at baseline, at 6 months and at 12 months of therapy were extracted from the medical records. The gender-age-physiology (GAP) and the composite physiologic index (CPI) scores were calculated at the time of therapy initiation [5, 6]. These scores were selected because of their ability to predict mortality in patients with IPF.

2.2 Statistical analysis.

ANOVA test was used to compare normally-distributed continuous variables. The % difference in the body weight was calculated as (weight at 12 months- weight at baseline)/ weight at baseline. The threshold for minimal clinically significant weight loss was set at 5% in concordance with the American Heart Association and Obesity Society Guidelines [7]. Linear regression models were used to predict the percentage change in weight at 12 months. The variables significant at $p < 0.15$ on univariate analysis were identified as potential predictor variables and entered into a multivariate linear regression model. Stepwise method was used for variable selections. All analyses were performed by using the SAS 9.4 for Linux (SAS, Cary, North Carolina). The level of statistical significance was set at $p < 0.05$ (two tailed).

3. Results

During the study period 80 out of the 228 patients started on antifibrotic therapy fulfilled the inclusion criteria (44 treated with pirfenidone and 36 with nintedanib) and were included in the analysis. Demographic and clinical data for the study population are depicted in Table 1.

Our cohort consisted mostly of elderly, Caucasian males with a history of smoking. Most patients were overweight or obese at baseline, with a mean BMI of 31.1 kg/m². The average % absolute weight loss was 4.5% (Table 2). No differences were seen in the baseline characteristics between patients receiving nintedanib or pirfenidone (Table 3). Thirty-five patients (44%) lost more than 5% of their baseline body weight and 15 (19%) more than 10%. Average weight loss was more profound among patients treated with nintedanib (Table 2) and more patients on nintedanib had clinically significant weight loss (61% vs 30%, $p=0.005$). Secondary analysis did not reveal evidence of weight loss reversal or slowing down during the first year of therapy (Figure 1). The weight loss seemed to be more pronounced among patients with a FVC (%) of less than 60% (data not shown).

Univariate analysis identified therapy type and CPI, but not age, gender or baseline BMI as predictors of weight loss. The same predictors remained significant in multivariate regression analysis taking into account age, BMI, CPI and treatment selection (CPI, $p=0.012$ / choice of therapy, $p=0.004$). Subgroup analysis identified that females, patients with a BMI<30 and patients with more severe disease experienced a greater weight loss on nintedanib compared to pirfenidone (Table 4).

4. Discussion

We herein demonstrate that a clinically significant weight loss is common during the first year of treatment with antifibrotics. Although some reduction in body weight can be expected as a consequence of the disease, the proportion of patients achieving a significant weight loss in our cohort is much higher than that reported in the literature in patients off therapy, suggesting a specific medication effect [4]. This is more pronounced among patients on nintedanib and in those with more severe disease.

In the INPULSIS and ASCEND trials weight loss was reported in 9.7% and 12.6% of participants, respectively, but there was no attempt to quantify its magnitude [1, 2]. Our data, along with those from the German compassionate use program for nintedanib demonstrate that weight loss on antifibrotics is more prevalent than initially reported [8]. The exact mechanisms underlying these effects are unknown, although it may be related to reduction of food intake due to nausea or malabsorption due to diarrhea. Moreover, *in vitro* data also show that tyrosine kinase inhibitors inhibit lipogenesis in isolated adipocytes, suggesting a fat storage defect that may be contributing to weight loss [9]. Our data may be consistent with the latter, since none of the patients included in the analysis discontinued the medication because of intolerable side effects.

The implications of the observed weight trends are unclear. Our population consisted of predominately overweight and obese individuals with comorbidities (e.g. hypertension, diabetes mellitus and obstructive sleep apnea) who may actually benefit from weight loss [10]. Moreover, with the implementation of strict BMI cut-offs by many lung transplant programs, antifibrotic-related BMI reduction may help patients qualify for transplantation, whereas weight loss before transplant in obese individuals has been associated with improved outcomes [11]. On the other hand, weight loss may worsen the functional capacity of a frail individual.

To our knowledge this is the first attempt to address the effects of antifibrotic therapy on the body weight of individuals with IPF. Although our data look intriguing, our study has some limitations. There was no systematic documentation of the severity and/or frequency of medication side effects. However, it is common practice in our institution to discontinue and/or switch therapy in patients with significant side effects, thus those individuals were excluded from our analysis. Moreover, a larger patient population and a prospective study design would have allowed for a more in- depth assessment of factors associated with weight loss. However, our results can be the basis for further research to identify the extent and severity of metabolic alterations associated with antifibrotic use.

5. Conclusions

Weight loss is common among IPF patients on antifibrotic therapy, especially among those on nintedanib therapy or with more advanced disease.

Acknowledgments:

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Abbreviations:

IPF	Idiopathic Pulmonary Fibrosis
GAP	gender-age-physiology
CPI	composite physiologic index

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Figure 1:
Body weight trajectory at 6 and 12 months

Table 1:

Baseline Cohort Characteristics

Factor	Statistics
Age (years)	68.4±8.4
Male	62 (77.5)
Caucasian	77 (96.3)
Smoking history	52 (65.0)
Diabetes mellitus	18 (22.5)
Hypertension	46 (57.5)
Gastroesophageal reflux	41 (51.3)
Obstructive Sleep Apnea	20 (25.0)
BMI	31.1± 5.7
FVC (% predicted)	71.5 ± 17.3
FEV1 (% predicted)	77.9 ± 18.9
DLCO (% predicted)	50.1 ± 15.4
CPI	47.3 ± 12.2
GAP	3.7 ± 1.3

Parameters presented as Mean ± SD or N (% of analyzed patients).

Table 2:

% Body Weight Change in 12 Months

Factor	N	% Weight change in one year	p-value
Change in weight at 12 months%	80	-4.5±5.6	
Gender			
Males	62	-4.1±5.5	0.21
Females	18	-6.0±6.0	
Age			
65	30	-3.3±5.6	0.157
>65	50	-5.2±5.6	
BMI			
Non- obese (<30)	41	-3.7±5.0	0.17
Obese (≥ 30)	39	-5.4±6.2	
CPI			
CPI< 40	24	-1.9±5.7	0.008
CPI> 40	54	-5.4±5.2	
GAP			
GAP ≤ 3	37	-3.3±6.3	0.041
GAP>3	41	-5.3±4.8	
Treatment			
Pirfenidone	44	-3.3+/-4.5	0.03
Nintedanib	36	-6.0+/-6.6	

Parameters presented as Mean ± SD. p-values determined by ANOVA

Table 3:

Baseline patients characteristics according to treatment allocation.

Factor	Nintedanib	Pirfenidone	p-value
Age	68.6±7.4	68.3±9.2	0.86
BMI	31.4±6.2	30.9±5.4	0.73
FEV1 (%)	79±18	77±19.7	0.64
FVC (%)	72±16	70.7±18.4	0.66
DCLO (%)	53.9±16.1	47±14.3	0.06
CPI	45.25±13.14	49.07±11.24	0.17

Parameters presented as Mean ± SD. p-values determined by ANOVA

Table 4:

Subgroup Analysis

		<u>% Body Weight change in 12 months</u>		p-value
Factor	N	Pirfenidone	Nintedanib	
Gender				
Males	62	-3.3±4.6	-4.9±6.3	0.27
Females	18	-3.0±4.1	-10.6±5.9	0.006
Age				
65	30	-2.4±4.1	-4.8±7.3	0.25
>65	50	-3.9±4.7	-6.6±6.2	0.088
BMI				
Non- obese (<30)	41	-2.0±3.7	-5.8±5.7	0.014
Obese (30)	39	-4.7±4.9	-6.2±7.5	0.44
CPI				
CPI< 40	24	-0.38±3.2	-3.3±7.3	0.22
CPI> 40	54	-3.9±4.1	-7.3±5.8	0.015
GAP				
GAP 3	37	-2.4±4.5	-4.5±8.0	0.30
GAP>3	41	-3.5±3.8	-7.2±5.0	0.011

Parameters presented as Mean ± SD. p-values determined by ANOVA