Patient Preference and Adherence

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ORIGINAL RESEARCH

I-PreFer Study: A Discrete Choice Experiment to Explore Patient, Caregiver and Pulmonologist Preferences of Idiopathic Pulmonary Fibrosis Pharmacological Treatment Options

Maria Hollmen[1], Marlies Wijsenbeek[2], Tom Bromilow[3], Adam B Smith[3], Stuart Mealing[3], Damian Lewis[3], Liam Galvin[4], Steve Jones[4], Guus Asijee[5], Stéphane Soulard[5], Antoine Froidure[6,7]

[1]Faculty of Medicine, University of Helsinki, Helsinki, Finland; [2]Centre of Excellence for Interstitial Lung Diseases and Sarcoidosis, Department of Respiratory Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands; [3]York Health Economics Consortium (YHEC), York, UK; [4]European Pulmonary Fibrosis & Related Disorders Federation, Overijse, Belgium; [5]Boehringer Ingelheim, Amsterdam, the Netherlands; [6]Service de Pneumologie, Cliniques Universitaires Saint-Luc, Brussels, Belgium; [7]Institut de Recherche Expérimentale et Clinique, UCLouvain, Belgium

Correspondence: Maria Hollmen, Faculty of Medicine, University of Helsinki, Haartmaninkatu 8 P.O. Box 63, Helsinki, 00014, Uusimaa, Finland, Email maria.hollmen@hus.fi

Purpose: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and ultimately fatal lung disease that, while rare, has seen incidence rise over time. There is no cure for IPF other than a lung transplant, though two antifibrotic (AF) drugs do exist to slow disease progression. While these drugs are efficacious, they are both associated with differing profiles of adverse events. This study aimed to elicit patient, caregiver and pulmonologist preferences on the treatment profiles of AFs via a discrete choice experiment (DCE).

Patients and Methods: The DCE and associated survey were distributed across 7 European countries, and bespoke DCEs were developed for patients/caregivers and pulmonologists. After collaboration with European Pulmonary Fibrosis & Related Disorders Federation (EU-PFF) and expert pulmonologists, respectively, a patient/caregiver DCE with 5 attributes and a pulmonologist DCE with 6 attributes were finalized. The DCEs had a blocked approach to reduce participant burden and were distributed on an online survey platform. Preferences were estimated through conditional multinomial logit regression analysis.

Results: Ninety-five patients, 22 caregivers and 115 pulmonologists fully completed their respective DCEs. Overall, patients and caregivers preferred management of treatment-related adverse events over both survival benefits and disease progression. Nearly all preference levels were found to be significantly different from their reference level. In contrast, pulmonologists showed a greater preference for control of lung function and exacerbations over adverse events. Although there were relative differences between the univariate subgroups in terms of the preference weights, most of these were not statistically significant.

Conclusion: The outcomes from this study suggest that while patients and caregivers had similar preferences for characteristics of IPF treatments, pulmonologists did not share those same preferences. Patients and caregivers preferred safety, while pulmonologists preferred efficacy. These differences should be considered by clinicians to better involve the patient in treatment decision-making for IPF.

Keywords: treatment preferences, online survey, outcomes research, lung disease

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common form of pulmonary fibrosis. It is a chronic, progressive, and ultimately fatal lung disease. Whilst considered rare, the incidence of IPF has risen over time.[1,2] There is currently no cure for IPF, except for lung transplantation in a small minority of patients. Without treatment, the median survival from diagnosis is three to five years.[3,4] There are two main antifibrotic pharmacotherapies currently available for IPF: pirfenidone and nintedanib. Both treatments aim to slow the process of scarring, thereby delaying lung degeneration

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and are recommended by the latest clinical practice guidelines on IPF.[5–7] Whilst efficacious, both pharmacotherapies are associated with frequent adverse events, such as diarrhea and sun sensitivity (nintedanib and pirfenidone respectively).[8,9] Therefore, in daily practice, treatment choices should, preferably, be jointly decided between healthcare professionals and patients to ensure that the chosen treatment is appropriate for the patient's preferences, lifestyle and values.

Although treatment options are limited, different stakeholders may have different preferences regarding treatment. Preferences in treatment options may be elicited directly (ie, directly asking the preference between existing treatment options), however this opens up the possibility of potential bias towards certain treatments. One way to elicit stakeholder preferences on treatment options whilst avoiding this bias is through discrete choice experiments (DCE). DCEs are a method to indirectly elicit preferences from participants. Instead of directly asking participants whether they would prefer one real-life treatment or another, a DCE asks participants to decide between numerous hypothetical scenarios where the levels of different factors (attributes) are varied. These decisions are analyzed to understand which attributes (and levels within each attribute) most significantly affect patient choice.[10]

IPF treatment preferences have previously only been collected from a patient perspective in the United States.[11] The aim of this study was to use discrete choice experiments to collect a broader range of preferences (patient, caregiver and pulmonologist) across seven European countries where preferences had not been collected before. Collecting preferences from different stakeholders allows us to compare them and identify areas of discord. In addition, the study aimed to examine the effect of patient characteristics on preferences. This information can then be used to improve the patient experience in the management of IPF by informing pulmonologists on the issues patients and caregivers value.

Materials and Methods

The study entitled "I-PreFer" (Preferences for Treatment Options in Idiopathic Pulmonary Fibrosis) covered seven countries: Belgium, Finland, France, Greece (pulmonologists only), the Netherlands, the Republic of Ireland (ROI) and the United Kingdom (UK). Three surveys were developed (one for patients, caregivers and pulmonologists) and each survey contained a DCE, and a questionnaire identifying patient characteristics. In this manuscript, we describe the development of the DCEs and their results after international administration. The results from the questionnaire portion of the surveys can be found in Hollmen et al.[12] The DCEs were developed in English and translated using a medical translation firm (TransPerfect Translations). The organization running the study, York Health Economics Consortium, is wholly owned by the University of York and seeks ethical approval for studies involving human subjects from the University. As such, the I-PreFer study and associated surveys were granted ethical approval by the University of York Health Sciences Research Governance Committee (HSRGC/2021/448/D: I-PreFer, letter dated 14 April 2021) and conformed to all relevant pharmacovigilance rules and reporting standards. A study information page was included at the start of the survey to inform stakeholders of the aims of the research, any potential risks of participation, the anonymous nature of the study and where the data would be stored. This was followed by a question asking for their voluntary consent to participate. If consent was given, the survey continued. Otherwise, the survey ended. This study was conducted in accordance with, and complies with, the principles laid out by the 18th World Medical Assembly in the Declaration of Helsinki (Helsinki, 1964) and all subsequent amendments.

DCE Design

Two DCEs were developed, one for patients and caregivers, and one for pulmonologists. In the initial stage of the study, the aim was to identify the key treatment benefits and adverse effects that would influence decision-making and treatment preferences, hereafter referred to as "attributes". An initial list of 19 potential attributes was generated via a desk-based literature review that identified a previous DCE in IPF (Hollin et al)[11] and the summary of product characteristic documents (SmPC) for pirfenidone[13] and nintedanib.[14]

Three advisory boards were organized to review and refine the potential list of attributes into the final attributes for each DCE. The patient/caregiver board was attended by a patient and caregiver who were both representatives from the European Pulmonary Fibrosis & Related Disorders Federation (EU-PFF). The pulmonologist boards were attended by three external clinicians with experience in managing IPF. Due to sample size considerations, the patient/caregiver was planned to have six attributes while the pulmonologist DCE was planned to have five attributes.

Participants of the advisory boards were first asked to review the initial list of 19 attributes, then add any potential attributes that were missed in the literature review and finally, remove any attributes that they considered irrelevant to the DCE. Then, the participants were asked to rank the remaining attributes in terms of those which were most important in treatment decision-making. The top six (five for the pulmonologist DCE) were then taken as the final attributes for the DCEs. The participants were then asked to develop the levels for each of the final attributes using their experience of the attribute. It was planned for most attributes to have three levels, however the participants reached a consensus for two and four levels on certain attributes. These collaborative steps led to the systematic creation of a patient/caregiver DCE and a pulmonologist DCE which comprised six and five attributes, respectively. The final designs of the two DCEs are shown in Table 1 and 2. A list of the original 19 attributes and their final ranking for each DCE and an example choice set for each DCE are included in Tables S1–S3.

Table 1 Patient and Caregiver DCE

Attribute	Levels
Slowdown of disease How well the treatment slows down the progression of IPF	Disease progression unchanged
	Disease progression slower
	Disease progression stopped
	Disease progression reversed
Survival Whether the treatment has an impact on life expectancy	No survival benefit
	Up to one year longer life
	More than one year longer life
Number of exacerbations Whether the treatment has an impact on the number of IPF exacerbations experienced	No effect on number of exacerbations
	Reduction in number of exacerbations
Adverse event: diarrhea Whether the treatment causes diarrhea, and, if so, the impact of diarrhea on daily life	Severe diarrhea, or hard to manage in daily life
	Mild or moderate diarrhea, but manageable in daily life
	No diarrhea
Adverse event: sun sensitivity Whether the treatment causes sun sensitivity, and, if so, the impact of sun sensitivity on daily life	Sun sensitivity that restricts outside activities by time-of-day despite sun cream and clothing
	Sun sensitivity that is manageable with sun cream and/or clothing
	No sun sensitivity
Adverse event: nausea Whether the treatment causes nausea, and, if so, the impact of nausea reaction on daily life	Severe nausea, or hard to manage in daily life
	Mild or moderate nausea, but manageable in daily life
	No nausea

Abbreviations: DCE, discrete choice experiment; IPF, idiopathic pulmonary fibrosis.

Table 2 Pulmonologist DCE

Attribute	Levels
Slowdown of disease How well the treatment slows down the progression of IPF	Large decline, despite the treatment, in lung function
	Small decline, despite the treatment, in lung function
	Stabilization of lung function
	Improvement of lung function

(*Continued*)

Table 2 (Continued).

Attribute	Levels
Number of exacerbations Whether the treatment has an impact on the number of IPF exacerbations experienced	No exacerbations
	Exacerbation(s) despite treatment
Adverse event: gastro-intestinal effects Whether the treatment causes diarrhea and nausea, and, if so, the impact of diarrhea and nausea on daily life	GI effects causing a large impact on quality of life and discontinuation of medication
	GI effects causing a large impact on quality of life, but patient feels better with reduced dose
	GI effects causing a low impact on quality of life. Medication is continued
	No gastro-intestinal effects
Adverse event: sun sensitivity reaction Whether the treatment causes sun sensitivity reaction, and, if so, the impact of sun sensitivity reaction on daily life	Sun sensitivity reaction, causing a large impact on quality of daily life and discontinuation of medication
	Sun sensitivity reaction, causing a large impact on quality of daily life and patient feels better with reduced dose
	Sun sensitivity reaction, but low impact on daily life and continuation of medication
	No sun sensitivity reaction
Initial prescription and titration period: How simple the initial prescription period is for a treatment, and whether it requires a titration period	Complicated titration period with multiple dosages, and with a risk of not achieving clinical targets
	Straight-forward titration period and only one dosage
	No titration period and only one dosage

Abbreviations: DCE, discrete choice experiment; GI, gastrointestinal; IPF, idiopathic pulmonary fibrosis.

DCE Implementation and Administration

After the DCEs were finalized, they were transferred onto an online survey platform for data collection (Qualtrics LLC). To complete the DCE, the participating pulmonologists, patients and caregivers were required to grade their preferences based on pre-defined attribute levels.

Participants were recruited between November 2021 and January 2022. The method of recruitment varied across participant type and country; however, all methods involved potential participants being presented with a study summary and a link to an online survey. The patient and caregiver surveys were distributed by EU-PFF and local patient groups. In Belgium and the Netherlands, the survey was also distributed by local nurses. There was no patient or caregiver survey for Greece since it was advised that the surveys would have to be paper-based and this was not feasible due to project constraints. There were no exclusion criteria implemented for the patient and caregiver surveys; the only requirements were that the patient currently had IPF, and caregivers were treating, or had been treating, a patient with IPF. No incentives were offered to patients or caregivers. The pulmonologist surveys were distributed by a third-party market research company (IQVIA). In addition, the three expert clinicians who participated in the advisory boards shared the study summary and link with their colleagues. To be eligible to complete the survey, pulmonologists were required to be reviewing at least three IPF patients per year. Pulmonologists were compensated for their time by the study sponsor at a fair market rate to incentivize participation, although the study sponsor was not involved in the recruitment of pulmonologists.

Statistical Analysis

The DCE was designed and analyzed in R Studio (version 4.1.1) statistical software using the following packages: idefix, support.CEs and apollo.[10,15–17] The DCE was designed so that participants were presented with two hypothetical drugs: Drug A and Drug B. For each attribute, the hypothetical drug was assigned one of the attribute levels. The participant was asked to read through each scenario (or "choice set") and choose which drug they would prefer. The combination of attributes and levels meant that a simple orthogonal design (where all participants complete the same choice sets) was not possible as this would result in too many questions and a high burden on the participant. A blocked design was therefore presented with the patients and caregivers divided into 6 blocks of 12 choice sets and the healthcare professionals (HCPs) into 4 blocks (12 choice sets). Each participant was randomly allocated to complete one of the blocks (12 choice sets) using a randomizer that ensured each block was shown an even number of times. The nature of the DCEs meant that only participants who completed the entire DCE were included in the final analyses.

The relative importance of the attribute levels in driving drug choice was estimated through conditional multinomial logit (MNL) regression analysis. This model represents a variation of the logistic regression that can be used for matched, clustered, or longitudinal data. The same MNL regressions were run separately using DCE data from patients, caregivers, and pulmonologists. Dummy coding was applied to the models. The model (shown in Equation 1) only included DCE choice data. The beta coefficients in the equation represent the participants' preference weights for each individual attribute level, relative to a reference level (eg, the beta coefficient for SUN_2 represents the preference for SUN_2 over SUN_1). Once the beta value for each attribute level was determined, it was used to calculate an odds ratio for preference over the baseline level. This odds ratio represented how much more preferred a level was over the baseline level. Statistical significance was defined as $p \leq 0.05$. The aim was to conduct multivariate analyses that included other predictors such as age and sex. Several univariate analyses were also conducted, with the cohorts based on answers from the questionnaire portion of the survey. The following subgroups are age (patients aged ≤70 versus those >70 years), gender (male versus female) and disease severity (self-reported mild or moderate versus self-reported severe) and current treatment (of the cohort who is currently treated, patients who self-reported currently taking nintedanib versus patients who self-reported currently taking pirfenidone).

$$Drug\_Choice_{ij} = \alpha_i + \beta_1 Drug\_Choice\_Level_{ij} \quad (1)$$

i = *individual*

j = *drug choice profile*

Drug_Choice_Level = Level of the attribute

α = *intercept*

β_1 = *coefficient*1

Results

Recruitment and Socio-Demographic Data

A total of 111 patients were recruited into the study; 95 of these completed the DCE in full (85.6%). The majority of patients were men (62%) aged between 61 and 70 years (44%). Ninety-one percent of the patients recruited were white, and 95% had completed secondary or tertiary education. In terms of disease severity, 47% of patients self-reported severe disease, 40% self-reported moderate disease and 13% self-reported mild disease. The breakdown of those currently taking an IPF medicine was 54% taking nintedanib, 42% taking pirfenidone and 4% taking another IPF medicine. Further details of the demographic data for the patients are reported in Hollmen et al.[12]

There were 22 caregivers recruited to the study, of whom most were from Finland, France and the UK. The majority of caregivers were women aged between 51 and 70 years, living with the patient (82%) (their partner/spouse, 91%). Most caregivers provided three or more hours of care every week. Further details of the demographic data for the caregivers are reported in Hollmen et al.[12]

There were 140 pulmonologists recruited into the study, of whom 115 (82%) completed the entire survey. The largest number of HCPs was recruited from the UK (51%). The majority of HCPs were in public practice (80%), and 55% had experience in managing IPF for up to ten years. Further details of the demographic data for the pulmonologists are reported in Hollmen et al.[12]

Table 3 DCE Coefficients – Patients

Choice	Description	B	SE	95% CI	OR	OR CI: 95%	P value
DIS_1	Disease progression unchanged	Reference					
DIS_2	Disease progression slower	0.72	0.159	0.41 to 1.04	2.06	1.51 to 2.82	0.000
DIS_3	Disease progression stopped	1.01	0.145	0.72 to 1.29	2.73	2.06 to 3.63	0.000
DIS_4	Disease progression reversed	0.91	0.153	0.61 to 1.21	2.49	1.85 to 3.37	0.000
SURV_2	No survival benefit	Reference					
SURV_2	Up to one year longer life	0.64	0.141	0.36 to 0.92	1.90	1.44 to 2.51	0.000
SURV_3	More than one year longer life	1.11	0.153	0.81 to 1.41	3.03	2.25 to 4.1	0.000
EXAC_1	No effect on number of exacerbations	Reference					
EXAC_2	Reduction in exacerbations	0.36	0.104	0.16 to 0.56	1.43	1.18 to 1.76	0.001
DI_1	Severe diarrhea, or hard to manage in daily life	Reference					
DI_2	Mild or moderate diarrhea, manageable in daily life	1.25	0.124	1 to 1.49	3.48	2.74 to 4.44	0.000
DI_3	No diarrhea	1.49	0.155	1.19 to 1.79	4.44	3.28 to 6.01	0.000
SUN_1	Sun sensitivity that restricts outside activities by time-of-day despite sun cream and clothing	Reference					
SUN_2	Sun sensitivity manageable with sun cream/clothing	0.27	0.130	0.02 to 0.52	1.31	1.02 to 1.69	0.038
SUN_3	No sun sensitivity	0.77	0.133	0.51 to 1.04	2.17	1.68 to 2.82	0.000
NAU_1	Severe nausea, or hard to manage in daily life	Reference					
NAU_2	Mild or moderate nausea, but manageable in daily life	1.02	0.155	0.72 to 1.32	2.78	2.05 to 3.76	0.000
NAU_3	No nausea	1.35	0.156	1.04 to 1.66	3.85	2.84 to 5.24	0.000
Constant		0.01	0.070	−0.12 to 0.15			0.855

Abbreviations: B, beta; SE, standard error; CI, confidence interval; OR, odds ratio.

Patient and Caregiver Preferences

The results of the patient DCE are shown in Table 3 and Figure 1. There is a consistent, logical pattern with "better" outcomes preferred over less beneficial outcomes for five of the 6 attributes. For example, slower disease progression (DIS_2) is "preferred" more than twice as much as disease progression remaining unchanged (odds ratio [OR]: 2.06). Similarly, patients' preferences for extending life beyond a year are three times greater than no survival benefit (OR: 3.03). Similar preferences are seen for mild or moderate diarrhea relative to severe diarrhea (OR: 3.48) and having no nausea compared with severe nausea (OR: 3.85). The only exception to this pattern is the preference reversal between "disease progression stopped" and "disease progression reversed". Here, patients seem to prefer disease progression being stopped over disease reversal. Overall, patients preferred management of treatment-related adverse events over both survival benefits and disease progression. Reduction in exacerbations was the least important criteria to patients.

Multivariate analysis was not possible due to sample size limitations. Although there were relative differences between the univariate subgroups in terms of the preference weights, most of these were not statistically significant. The results of these univariate analyses are shown in Figures S1–S4. Managing nausea and diarrhea was statistically more important to men than women. There were also statistically significant differences between age groups, with those aged ≤70 years valuing efficacy criteria such as reversal of disease progression or survival more than older patients (aged >70 years). There was a statistically significant higher preference for "disease progression stopped" among the nintedanib cohort compared with the pirfenidone cohort, but no statistically significant difference was observed with regard to adverse event management by treatment group. For

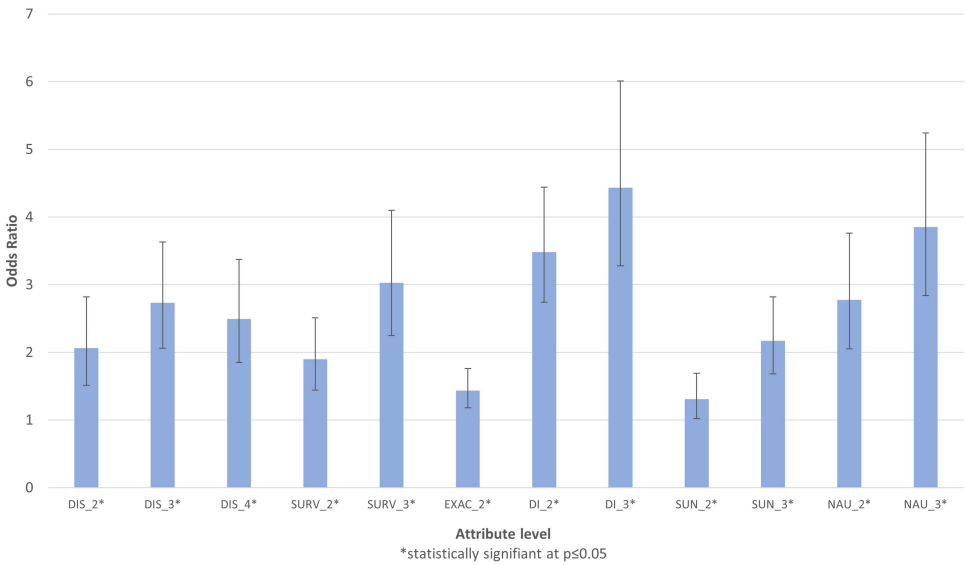

Figure 1 Patient DCE preferences. DI_2 mild or moderate diarrhea, manageable daily life; DI_3 no diarrhea; DIS_2 disease progression slower; DIS_3 disease progression stopped; DIS-4 disease progression reversed; EXAC_2, reduction in exacerbations; NAU_2, mild or moderate nausea but manageable daily life; NAU_3, no nausea; SUN_2, sun sensitivity manageable with sun cream/clothing; SUN_3, no sun sensitivity; SURV_2, Up to one year longer life; SURV_3 more than one year longer life.

those with severe disease, there was a lower preference for "number of exacerbations reduced" compared with those without self-reported severe disease.

The results for the caregiver DCE coefficients are shown in Table 4 and Figure 2. There was a consistent, logical pattern for each attribute, and slightly stronger relative magnitudes of preferences for "better" levels than in the patient DCE.

Table 4 DCE Coefficients – Caregivers

Choice	Description	B	SE	95% CI	OR	OR CI: 95%	P value
DIS_1	Disease progression unchanged	Reference					
DIS_2	Disease progression slower	1.03	0.48	0.10 to 1.97	2.80	1.10 to 7.14	0.031
DIS_3	Disease progression stopped	2.15	0.44	1.28 to 3.01	8.54	3.61 to 20.22	0.000
DIS_4	Disease progression reversed	1.89	0.46	0.98 to 2.79	6.60	2.67 to 16.30	0.000
SURV_2	No survival benefit	Reference					
SURV_2	Up to one year longer life	1.84	0.48	0.91 to 2.77	6.30	2.48 to 16.01	0.000
SURV_3	More than one year longer life	2.41	0.52	1.38 to 3.43	11.09	3.99 to 30.82	0.000
EXAC_1	No effect on number of exacerbations	Reference					
EXAC_2	Reduction in exacerbations	0.67	0.30	0.07 to 1.26	1.95	1.08 to 3.53	0.028
DI_1	Severe diarrhea, or hard to manage in daily life	Reference					
DI_2	Mild or moderate diarrhea, manageable in daily life	2.34	0.41	1.52 to 3.15	10.33	4.59 to 23.26	0.000
DI_3	No diarrhea	2.40	0.46	1.51 to 3.30	11.06	4.53 to 27.00	0.000
SUN_1	Sun sensitivity that restricts outside activities by time-of-day despite sun cream and clothing	Reference					
SUN_2	Sun sensitivity manageable with sun cream/clothing	0.63	0.37	−0.10 to 1.36	1.88	0.91 to 3.88	0.089

(*Continued*)

Table 4 (Continued).

Choice	Description	B	SE	95% CI	OR	OR CI: 95%	P value
SUN_3	No sun sensitivity	0.66	0.38	−0.08 to 1.40	1.93	0.92 to 4.05	0.082
NAU_1	Severe nausea, or hard to manage in daily life	Reference					
NAU_2	Mild or moderate nausea, but manageable in daily life	1.79	0.46	0.89 to 2.69	5.99	2.44 to 14.74	0.000
NAU_3	No nausea	2.20	0.47	1.27 to 3.12	8.98	3.55 to 22.74	0.000
Constant		0.37	0.21	−0.04 to 0.77			0.076

Abbreviations: B, beta; SE, standard error; CI, confidence interval; OR, odds ratio.

Pulmonologist Preferences

The DCE coefficients for the pulmonologists are shown in Table 5, and Figure 3. This shows a linear progression in terms of preferences with the exception of a reversal between the last two sun sensitivity categories (ie, more extreme levels had more extreme preferences). In contrast to the patients, the pulmonologists showed a greater preference for control of lung function and exacerbations over adverse events (ie, GI and photosensitivity). Titration was not deemed relevant by the pulmonologists.

Discussion

The DCE outcomes from the I-PreFer study showed that while patient and caregiver treatment preferences were very similar, pulmonologists did not share those same preferences. Patients and caregivers tended to prefer the control or management of adverse events, whilst pulmonologists tended to prefer improvements in lung function.

Patient and Caregivers

Adverse events, especially GI problems, such as diarrhea and nausea, were important to patients. Having no diarrhea was preferred 2.05 times more than having no sun sensitivity based on the OR results. This result is in line with previous research.[11] This preference might be influenced by the time spent outside by the patient of the current cohort and the

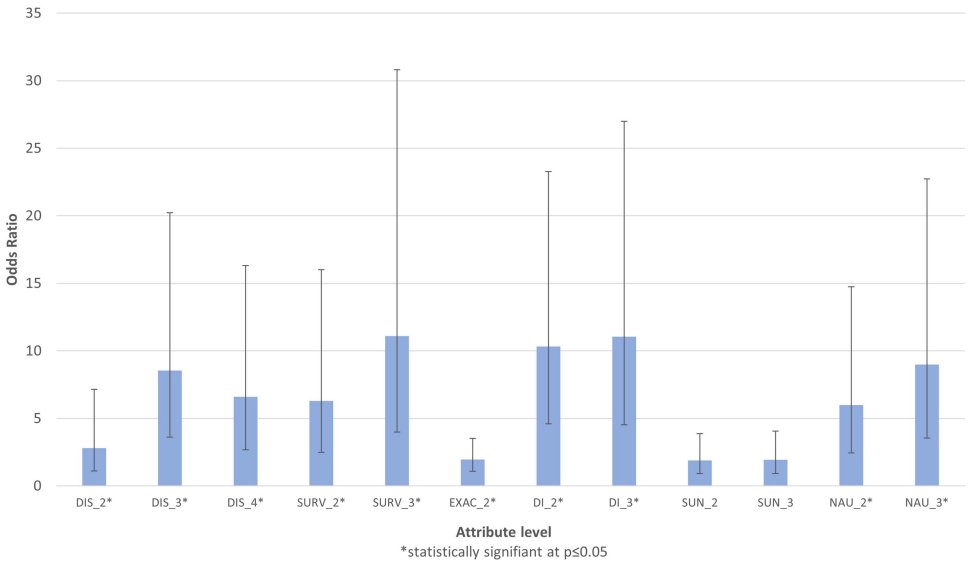

Figure 2 Caregiver DCE Preferences. DI_2 mild or moderate diarrhea, manageable daily life; DI_3 no diarrhea; DIS_2 disease progression slower; DIS_3 disease progression stopped; DIS-4 disease progression reversed; EXAC_2, reduction in exacerbations; NAU_2, mild or moderate nausea but manageable daily life; NAU_3, no nausea; SUN_2, sun sensitivity manageable with sun cream/clothing; SUN_3, no sun sensitivity; SURV_2, Up to one year longer life; SURV_3 more than one year longer life.

Table 5 DCE Coefficients – Pulmonologist

Choice	Description	B	SE	95% CI	OR	OR CI: 95%	P value
DIS_1	Large decline, despite the treatment, in lung function	Reference					
DIS_2	Small decline	1.48	0.16	1.17 to 1.79	4.40	3.21 to 6.01	0.000
DIS_3	Stabilization of lung function	2.04	0.18	1.69 to 2.40	7.70	5.4 to 11.00	0.000
DIS_4	Improvement in lung function	2.52	0.18	2.16 to 2.89	12.49	8.70 to 17.91	0.000
EXAC_1	Exacerbations despite treatment	Reference					
EXAC_2	No exacerbations	1.92	0.10	1.71 to 2.12	6.79	5.54 to 8.34	0.000
GI_1	GI effects causing a large impact on QoL and discontinuation of medication	Reference					
GI_2	GI causing large impact on QoL but patient feels better	0.72	0.15	0.42 to 1.02	2.05	1.52 to 2.77	0.000
GI_3	GI causing low impact on QoL	1.18	0.16	0.87 to 1.48	3.25	2.4 to 4.40	0.000
GI_4	No GI effects	1.34	0.16	1.02 to 1.65	3.80	2.77 to 5.22	0.000
SUN_1	Sun sensitivity reaction, causing a large impact on QoL and discontinuation of medication	Reference					
SUN_2	Sun sensitivity causing large impact on QoL but patient feels better	0.11	0.17	−0.22 to 0.43	1.11	0.80 to 1.54	0.519
SUN_3	Sun sensitivity causing low impact on QoL	0.88	0.15	0.59 to 1.18	2.42	1.80 to 3.26	0.000
SUN_4	No sun sensitivity	0.68	0.17	0.34 to 1.01	1.96	1.40 to 2.75	0.000
PRE_1	Complicated titration period with multiple dosages and with a risk of not achieving clinical targets	Reference					
PRE_2	Straightforward titration	0.40	0.10	0.20 to 0.60	1.49	1.22 to 1.83	0.000
PRE_3	No titration	0.26	0.13	0.01 to 0.51	1.30	1.01 to 1.67	0.041
Constant		−0.10	0.07	−0.24 to 0.03			0.138

Abbreviations: B, beta; SE, standard error; CI, confidence interval; GI, gastrointestinal; OR, odds ratio; QoL, quality of life.

climate and season, and it is also possible that patients were spending less time outside because the DCEs were completed during the Covid-19 pandemic.

It was originally anticipated that patients on pirfenidone would have a higher preference for treatments that minimized photosensitivity, given that the AEs (adverse events) associated with this treatment are skin rash and photosensitivity. However, the results from the univariate analysis showed that current antifibrotic treatment had no significant impact on patient preferences for management of diarrhea or photosensitivity.

In general, the overall preference for reduction in exacerbations (ie, sudden accelerations in disease progression resulting in reduction in lung function) was lower than the preferences for other treatment attributes. This study showed that patients tended to prefer manageable adverse effects more than an impact on mortality or lung function decline. This could be due to the fact that current treatments limit disease progression but do not halt disease nor improve symptoms. The exception to this was that patients who graded their disease as "not severe" had a significantly higher preference for a reduction in exacerbations as shown in Figure S4.

When compared with previous IPF preference studies, it appears that the higher preference for management of diarrhea over improvements in survival in this study, was in contradiction to the findings reported by Hollin et al, where improving lung function was 1.6 times as important as decreasing the risk of GI problems.[11] Similarly, results from

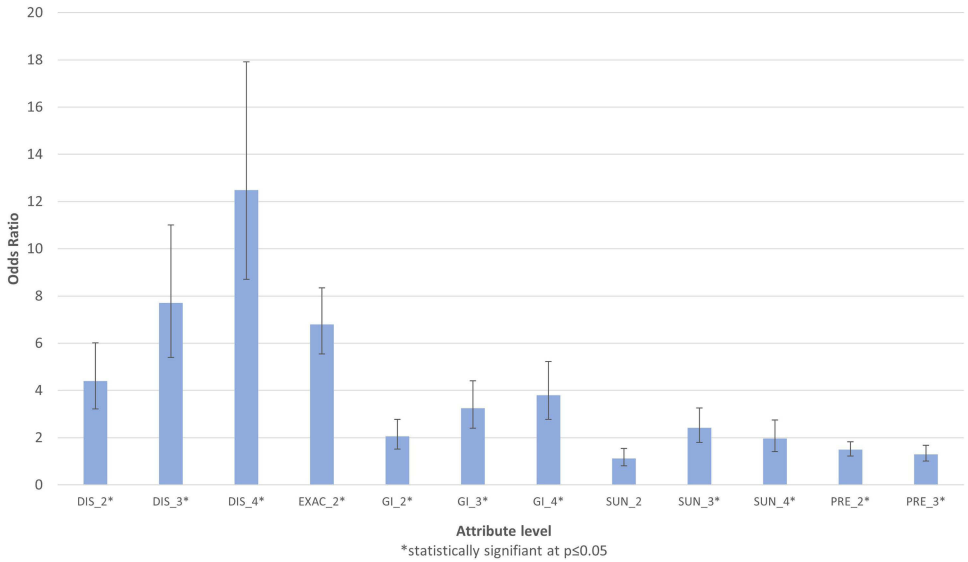

Figure 3 Pulmonologist DCE Preferences. DIS_2 Small decline; DIS_3 Stabilization of lung function; DIS_4 Improvement in lung function; EXAC_2 No exacerbations; GI_2 GI causing large impact on QoL but patient feels better; GI_3 GI causing low impact on QoL; GI_4 No GI effects; SUN_2 Sun sensitivity causing large impact on QoL but patient feels better; SUN_3 Sun sensitivity causing low impact on QoL; SUN_4 No sun sensitivity; PRE_2 Straightforward titration; PRE_3 No titration.

a survey of IPF treatment preferences conducted by Camponeschi et al revealed that the most important treatment attribute was effect on lung function (35%) followed by the risk of GI problems (23%).[18] However, both the Hollin et al and Camponeschi surveys were much smaller than the I-Prefer study (33 and 35 patients respectively) meaning the robustness of the findings from these studies is less certain.[11,18] Furthermore, the wording used in these studies was different to that used in the I-Prefer DCE, so a direct comparison cannot be made.

The small sample size and blocked approach of the DCEs led to large confidence intervals in the caregiver DCE. The main trends of the caregiver DCE matched those of the patient DCE. However, drawing strong conclusions from the caregiver DCE should be cautioned.

Pulmonologists

For the pulmonologists, there was a logical, linear pattern observed, as preferences increased for greater control over lung function and amelioration of adverse events. The exception to this pattern was for sun sensitivity causing low impact on HRQoL (OR: 2.4) compared with "no sun sensitivity" (OR 1.96) although there was no statistically significant difference between the two preferences. In general, stabilization or improvement in lung function, as well as no exacerbations, took precedence over management of GI problems and sun sensitivity. Pulmonologists had the strongest preference for lung improvement. Specifically, pulmonologists preferred improvement in lung 12 times more than a slowdown in disease (or large decline, $p < 0.05$) and almost three times more than preventing a small decline in lung disease. Improvement in lung function was significantly more preferred than management and control of GI symptoms, sun sensitivity and a straightforward medication titration process. Pulmonologists had greater preferences for the management of GI adverse events compared with sun sensitivity adverse events.

Strengths

The I-Prefer study builds on previous results from Hollin et al[11] and Camponeschi et al[18] by providing preference data from a larger cohort of IPF patients and caregivers. In addition, the I-Prefer study is the first study to collect treatment preference data from pulmonologists and investigate the effect of patient characteristics on patient preferences. The DCE design to elicit stakeholder preferences is advantageous in that participants simply choose one option over another, which is less cognitively complex than providing a free-text response to a question.[19] This minimizes the chance of bias.

Limitations

While most results followed a logical preference order, in that "better" outcomes were preferred over "worse" outcomes, there was a reversal of preference order with regard to "disease reversal" and "disease progression stopped" with patients selecting a higher preference for "disease progression stopped" over "disease reversal". This implies that there may be a misunderstanding of the two terms, or it could be reflective of a pragmatic acknowledgement that there is no curative treatment of IPF. Similarly, the lower preference for reduction in exacerbations may indicate a lack of understanding of what an exacerbation is. Future DCEs could be piloted on a small number of patients and caregivers to ensure that all terms are likely to be understood by participants.

Another limitation is that the patient respondents to the DCE were all based in northern Europe. It is possible that including patients from more southern countries (ie, with greater sun exposure or other dietary habits) would have revealed different preferences around adverse event. Future studies are needed to explore this.

A third limitation is the lack of multivariate analyses. The study had originally planned to include socio-demographic covariates in the DCE MNL models. However, the lower-than-expected sample sizes collected meant that this could not occur without reducing the quality of the models.

Conclusion

This DCE has shown that patients and caregivers have different preferences compared to pulmonologists with regard to the benefits they would most like from their treatment. Among patients and caregivers, the strongest preferences were for control of adverse events, especially gastro-intestinal, whereas among pulmonologists, the strongest preferences were for efficacy, with treatments that could improve lung function or prevent exacerbations. This discord in preference demonstrates that more education by the pulmonologist to the patient is required on the benefits of treatments and on the management of adverse events. Finally, the findings also suggest that clinicians should better involve patients in treatment decision-making for IPF.[20]

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