

Original article

Patient preferences for the treatment of systemic sclerosis-associated interstitial lung disease: a discrete choice experiment

Cosimo Bruni ^{1,*}, Sebastian Heidenreich^{2,*}, Ashley Duenas², Anna-Maria Hoffmann-Vold ³, Armando Gabrielli⁴, Yannick Allanore⁵, Emmanuel Chatelus⁶, Jörg H.W. Distler⁷, Eric Hachulla⁸, Vivien M. Hsu⁹, Nicolas Hunzelmann¹⁰, Dinesh Khanna^{11,12}, Marie-Elise Truchetet¹³, Ulrich A. Walker¹⁴, Margarida Alves¹⁵, Nils Schoof¹⁵, Lesley Ann Saketkoo^{16,17,†} and Oliver Distler^{18,†}

Abstract

Objectives. Treatments for SSc-associated interstitial lung disease (SSc-ILD) differ in attributes, i.e. mode of administration, adverse events (AEs) and efficacy. As physicians and patients may perceive treatments differently, shared decision-making can be essential for optimal treatment provision. We therefore aimed to quantify patient preferences for different treatment attributes.

Methods. Seven SSc-ILD attributes were identified from mixed-methods research and clinician input: mode of administration, shortness of breath, skin tightness, cough, tiredness, risk of gastrointestinal AEs (GI-AEs) and risk of serious and non-serious infections. Patients with SSc-ILD completed an online discrete choice experiment (DCE) in which they were asked to repeatedly choose between two alternatives characterized by varying severity levels of the included attributes. The data were analysed using a multinomial logit model; relative attribute importance and maximum acceptable risk measures were calculated.

Results. Overall, 231 patients with SSc-ILD completed the DCE. Patients preferred twice-daily oral treatments and 6–12 monthly infusions. Patients' choices were mostly influenced by the risk of GI-AEs or infections. Improvement was more important in respiratory symptoms than in skin tightness. Concerning trade-offs, patients accepted different levels of increase in GI-AE risk: +21% if it reduced the infusions' frequency; +15% if changing to an oral treatment; up to +37% if it improved breathlessness; and up to +36% if it reduced the risk of infections.

Conclusions. This is the first study to quantitatively elicit patients' preferences for treatment attributes in SSc-ILD. Patients showed willingness to make trade-offs, providing a firm basis for shared decision-making in clinical practice.

Key words: SSc, interstitial lung disease, patient preference, discrete choice experiment

¹Department of Experimental and Clinical Medicine, Division of Rheumatology, University of Florence, Florence, Italy, ²Patient-Centered Research, Evidera, London, UK, ³Department of Rheumatology, Oslo University Hospital, Oslo, Norway, ⁴Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Ancona, Italy, ⁵Department of Rheumatology A, Cochin Hospital, Paris Descartes University, Paris, ⁶Department of Rheumatology, University Hospital of Strasbourg, Hôpital de Hautepierre, Strasbourg, France, ⁷Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, ⁸Department of Internal Medicine and Clinical Immunology, Referral Centre for Centre for rare systemic autoimmune diseases North and North-West of France (CeRAINO), CHU Lille, University of Lille, Inserm, U1286 - INFINITE—Institute for Translational Research in Inflammation, Lille, France, ⁹Department of Medicine, Division of Rheumatology, Rutgers–Robert Wood Johnson Medical School, New Brunswick, NJ, USA, ¹⁰Department of Dermatology, University of Cologne, Cologne, Germany, ¹¹Scleroderma Program, ¹²Division of Rheumatology, Department of Internal Medicine, University of

Michigan, Ann Arbor, MI, USA, ¹³Department of Rheumatology, CHU Bordeaux, Bordeaux, France, ¹⁴Department of Rheumatology, University Hospital Basel, Basel, Switzerland, ¹⁵TA Inflammation, Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany, ¹⁶New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, ¹⁷Departments of Internal Medicine, Louisiana State University, and Tulane University Schools of Medicine, New Orleans, LA, USA and ¹⁸Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

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Correspondence to: Sebastian Heidenreich, Patient-Centered Research, Evidera, The Ark, 201 Talgarth Road, London W6 8BJ, UK. E-mail: Sebastian.Heidenreich@evidera.com

*Cosimo Bruni and Sebastian Heidenreich contributed equally to this study.

†Shared senior authorship.

Rheumatology key messages

- Medication selection for SSc-associated interstitial lung disease is complex, requiring careful weighting of multiple treatment and disease aspects.
- Patients balanced the risk of experiencing adverse events with symptom improvement or administration inconvenience.
- Understanding patient preferences and trade-offs may sensitize clinicians to common patient concerns during shared decision-making.

Introduction

SSc is characterized by a heterogeneous combination of vascular injury, inflammation and fibrosis. Interstitial lung disease (ILD) is one of its major organ manifestations and the most frequent cause of death in SSc [1, 2]. SSc-associated ILD (SSc-ILD) may manifest with various symptoms, including shortness of breath, dry disabling inspiratory cough and decreased exercise tolerance, which can impair daily activities and physical functioning, health-related quality of life and socio-economic status [3–5].

High-resolution CT along with serial pulmonary function testing are essential for the early detection of SSc-ILD [6]. Diverse treatments have demonstrated efficacy in SSc-ILD [7–9]. Haematopoietic stem cell transplantation has been shown to stabilize lung function and improve long-term survival, although the procedure has high treatment-related mortality and the risk of severe cardiopulmonary complications limits its applicability in advanced cases, especially those with severe ILD [9–11]. Among immunosuppressants, CYC and MMF improved forced vital capacity (FVC) and had comparable effects in the Scleroderma Lung Studies [12–14]. Tocilizumab exhibited efficacy in SSc-ILD in two randomized controlled trials in patients with early diffuse inflammatory SSc and has recently been approved by the US Food and Drug Administration for the treatment of SSc-ILD [15, 16]. There is also significant accrual of lower levels of evidence for rituximab as a potential effective treatment [17, 18]. Nintedanib has been shown to slow the decline in FVC compared with placebo in SSc-ILD in the SENSICIS trial [19], leading to its approval for SSc-ILD in various countries [20, 21].

Shared decision-making aims to find mutually acceptable treatment choices given the disease complexity and range of treatment options, especially in the presence of differences between patients' and physicians' perspectives [22]. Although physicians often consider the overall multi-organ biophysical burden of disease in the context of projected survival and prevention of disability, patient preferences tend to be driven by tolerability, administration route, frequency of administration and adverse event (AE) profiles [22–24]. Importantly, the probability that the intervention is perceived by patients to reduce or reverse symptom burden, improve the disease profile or provide a cure, and the degree to which these are relevant, is pivotal in these decisions.

Making trade-offs between anticipated medication benefits and risks drives patients' treatment selection [9, 25]. Although investigated in other rheumatological conditions, patient perspectives in decision-making (including acceptable trade-offs) have not been addressed in SSc-ILD [26, 27]. Discrete choice experiments (DCEs) are widely used to quantify the relative importance that patients place on treatment attributes, and may provide insight into patients' perceptions of treatment decision-making [28–30].

Against this background we set out to: (i) identify treatment attributes that are relevant to patients with SSc-ILD; (ii) elicit the effect of changes in these attributes on patients' treatment preferences using a DCE; and (iii) assess acceptable trade-offs between attributes as relative attribute importance (RAI) and maximum acceptable risk (MAR).

Methods

Development of the DCE

A literature review was performed, and the results were discussed in an advisory board with patients and caregivers (for more details, see [supplementary Data S1](#) and [supplementary Table S1](#), available at *Rheumatology* online). In addition, nine patients with SSc-ILD from New Orleans, Louisiana, underwent qualitative interviews that explored symptoms, impact of symptoms, treatment experience, treatment expectations, treatment risk and candidate attributes (see [supplementary Data S2](#) and [supplementary Table S2](#), available at *Rheumatology* online).

The above-mentioned qualitative data were then reviewed in a workshop involving two clinicians experienced in SSc-ILD treatment (O.D.) or knowledgeable in aspects regarding patients with SSc-ILD and their treatments (M.A.). Following a thematic content analysis of the interview data, seven attributes important to treatment decision-making were chosen during the workshop, and all were included in the DCE: (i) mode of administration; (ii) shortness of breath; (iii) skin tightness; (iv) coughing; (v) tiredness; (vi) risk of gastrointestinal AEs (GI-AEs); and (vii) risk of serious and non-serious infections. Risk levels were selected by reviewing AE frequencies observed for CYC, MMF and nintedanib in clinical trials and by testing whether the selected levels

were patient-relevant in a qualitative pilot study. The levels for mode of administration were chosen based on the available SSc-ILD medications used in clinical practice and in published studies [12–15, 18, 19]. The process of gathering information to create the DCE is summarized in [supplementary Table S3](#), available at *Rheumatology* online. All the attributes and levels were jointly reviewed and approved by the study team, including the involved clinicians.

The attribute levels were systematically paired together to ensure that their effects on preferences can be identified independently. A D-efficient design algorithm that assumed a multinomial logit (MNL) model with directional priors for naturally ordered attributes was generated using Ngene software (see [supplementary materials](#) for details, available at *Rheumatology* online) [31]. The resulting DCE design contained 24 different scenarios between two hypothetical treatment options (i.e. A vs B). The 24 scenarios were divided into two blocks of 12 experimental choice tasks, and each respondent was randomly assigned to complete all choice tasks from the allocated block. Each choice task asked respondents to select one of the two hypothetical SSc-ILD treatment alternatives (see [Fig. 1](#) as an example choice task). The DCE also included four non-experimental scenarios to test the internal validity and intra-responder consistency [32], and a dominance test to test if patients would systematically choose the dominant option. If patients selected the dominant choice, it suggested that they may not have understood the task, were less engaged in the DCE or the difference in attribute levels between the alternatives was not relevant to them.

Questionnaire design and target population

The DCE was integrated into an online survey and was qualitatively pretested in English with three patients. One patient from the US was asked to think aloud when completing the DCE to explore whether all attributes were considered in a compensatory choice process [33]. Two patients in Europe completed the survey and provided feedback in the form of a debriefing questionnaire. Finally, the survey underwent translation–reverse translations into three different languages (French, German and Norwegian); the resulting translations were compared with the English study protocol by native speakers to ensure all participants were asked similar questions.

Patients with high-resolution CT-confirmed SSc-ILD aged ≥ 18 years were recruited by physician referral from France, Germany, Norway, Switzerland and the USA, with approximately half of them being identified through EULAR Scleroderma Trials and Research (EUSTAR) centres. Leaflets, mail and email correspondence directed those interested to a dedicated study website.

After providing online informed consent on the study website (see [supplementary Table S4](#), available at *Rheumatology* online), participants were randomly

assigned to one of the two DCE design blocks. All DCE choice tasks were randomized between participants to mitigate potential ordering effects [34]. In addition, patients answered questions regarding self-reported symptoms and other clinical aspects (Section 1), ranking and rating (Section 2), health literacy, numeracy, perceived difficulty of the DCE choice tasks (Section 3), and sociodemographic information (Section 4). The time to complete the survey was also recorded.

No data were collected on patients' race, ethnicity or gender. The study was approved by local or national institutional review boards in all participant countries (see [supplementary Table S4](#)). All patients provided informed consent via tick box for participation in the study.

Data analysis

Descriptive statistics were obtained for sociodemographic and self-reported clinical characteristics, symptoms, health literacy, numeracy, internal validity tests and response time. The choice data were analysed within the random utility maximization framework by assuming that respondent n chooses alternative j in choice task t only if it resulted in the highest utility of all available alternatives [35, 36].

The utility was an ordinal measure of preference and was defined as:



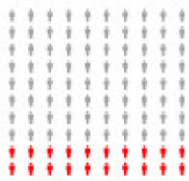
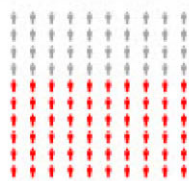
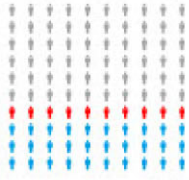
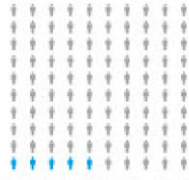
$$\begin{aligned}
 u_{ntj} = & \alpha + \beta_1 \text{admin}_{injection} n_{ntj} + \beta_2 \text{admin}_{oral} l_{ntj} \\
 & + \beta_3 \text{admin}_{infusion} 6\text{to}12\text{month} s_{ntj} + \beta_4 \text{breathless}_{moderate} e_{ntj} \\
 & + \beta_5 \text{breathless}_{mild} d_{ntj} + \beta_6 \text{breathless}_{non} e_{ntj} \\
 & + \beta_7 \text{tired}_{most} \text{some} e_{ntj} + \beta_8 \text{tired}_{some} \text{some} e_{ntj} \\
 & + \beta_9 \text{tired}_{some} \text{most} e_{ntj} + \beta_{10} \text{cough}_{occasional} \text{difficult} e_{ntj} \\
 & + \beta_{11} \text{cough}_{persistent} \text{easy} e_{ntj} + \beta_{12} \text{cough}_{occasional} \text{easy} e_{ntj} \\
 & + \beta_{13} \text{skin}_{limited} \text{activities} e_{ntj} + \beta_{14} \text{skin}_{not\ limited} \text{activities} e_{ntj} \\
 & + \beta_{15} \text{skin}_{not\ tightness} s_{ntj} + \beta_{16} \text{AE}_{GI60\%} e_{ntj} + \beta_{17} \text{AE}_{GI40\%} e_{ntj} \\
 & + \beta_{18} \text{AE}_{GI20\%} e_{ntj} + \beta_{19} \text{AE}_{infection} 15\% e_{ntj} \\
 & + \beta_{20} \text{AE}_{infection} 20\% e_{ntj} + \beta_{21} \text{AE}_{infection} 5\% e_{ntj} + \varepsilon_{ntj}
 \end{aligned} \tag{1}$$

where α controlled for left–right bias, ε_{ntj} captured random unexplained effects on patients' choices, and the estimated parameters β_1 to β_{21} ('marginal utilities') captured the effect of deviations from the reference level on utility. Reference levels and an explanation of what each of the parameters in the equations means can be found in [supplementary Table S5](#), available at *Rheumatology* online.

All parameters were estimated using the R 3.6.1 software based on an MNL model [37]. For all estimated models, t -tests were used to determine whether estimated parameters were significantly different from zero. Model evaluation was assessed using goodness-of-fit statistics, such as the adjusted McFadden Pseudo- R^2 and Bayesian information criterion.

Marginal utilities were estimated and indicated the effect of changes in the attributes on patients' treatment preference. Two behavioural output measures were obtained: (i) RAI (with a higher score suggesting a larger

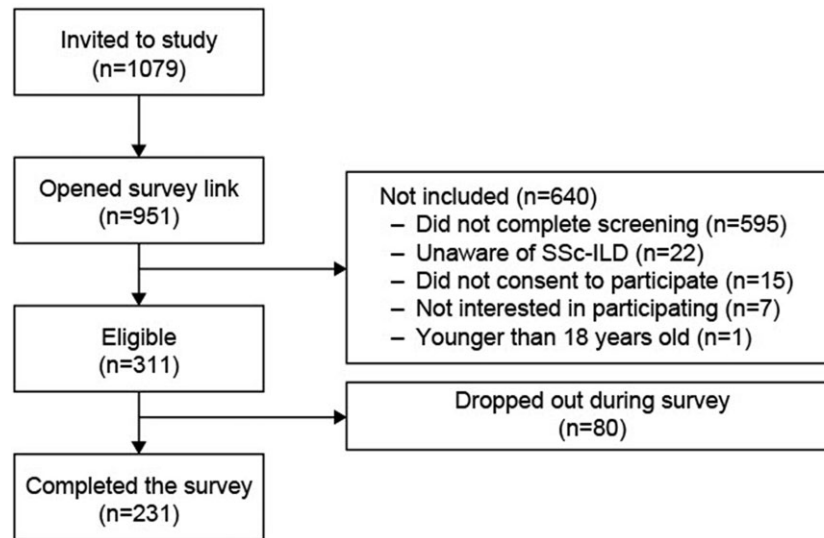
Fig. 1 Example choice task

	Treatment A	Treatment B
Mode of administration	 Oral (twice daily)	 Infusion (every 6–12 months at hospital or local clinic)
Skin tightness	Tightness in your hands or arms is present, but <i>does not limit</i> daily activities	Tightness in your hands or arms is present, but <i>limits</i> daily activities
Shortness of breath	You are short of breath when walking up hills or stairs (<i>no problems with breathlessness</i>)	You are short of breath when sitting or lying still (<i>severe breathlessness</i>)
Tiredness	You feel tired some days a week and complete most usual activities	You feel tired most days a week and complete few usual activities
Coughing	You have a persistent cough that is easy to tolerate	You have an occasional cough that is easy to tolerate
Risk of diarrhoea, nausea and/or vomiting	 <p>↑ 20 have diarrhoea, nausea or vomiting ↑ 80 do not have diarrhoea, nausea or vomiting</p>	 <p>↑ 60 have diarrhoea, nausea or vomiting ↑ 40 do not have diarrhoea, nausea or vomiting</p>
Infections	 <p>↑ 30 have non-serious infections ↑ 10 have serious infections ↑ 60 have no infections</p>	 <p>↑ 5 have non-serious infections ↑ 0 have serious infections ↑ 95 have no infections</p>

impact on preferences); and (ii) MAR of obtained AEs for changes in each attribute. MAR was used to evaluate the trade-offs that patients with SSc-ILD were willing to make and measured respondents' valuation of each treatment attribute using a common unit of measurement. To do this, the MAR needed to be modelled based on a continuous attribute. This was done by estimating Eq. (1) using a linear-coded parameter for risk of GI-AEs (one parameter instead of

β_{16} to β_{18}) as the denominator, allowing it to be expressed in terms of risk (%). The remaining marginal utilities were then divided by the negative of this parameter. Computation of the MAR measures was based on estimated preferences from a linear-coded MNL model. Heterogeneity in the preference data was explored (e.g. mixed MNL) in several sensitivity analyses (see [supplementary Data S3](#), available at *Rheumatology* online).

Fig. 2 Patient flow diagram



SSc-ILD, SSc-associated interstitial lung disease.

Results

Patient characteristics

Among 1079 patients with SSc-ILD invited to participate in this study, 231 [mean (s.d.) age 52.6 (\pm 13.2) years, 54% diagnosed for >5 years] completed the entire survey (Fig. 2). The sociodemographic and clinical characteristics are summarized in Table 1. Participants also demonstrated a high level of health literacy ($n=228$; 99%) and numeracy ($n=210$; 91%) (supplementary Table S6, available at *Rheumatology* online).

Patients' preferences

For the mode of administration, patients with SSc-ILD significantly preferred twice-daily oral treatments ($\beta_2=0.30$; $P<0.001$) and infusion every 6–12 months ($\beta_3=0.42$; $P<0.001$) over monthly infusions (reference level). However, self-administered s.c. injections (once a week at home) were not significantly preferred over monthly infusions ($\beta_1=0.15$; $P=0.074$) (Fig. 3).

Similarly, patients significantly preferred lower levels of severity and minor impact of disease-related symptoms compared with more severe counterparts; for example, cough (i.e. occasional coughing over persistent coughing; $P<0.001$), shortness of breath ($P<0.01$) and skin tightness ($P<0.001$). Compared with tiredness most days a week and completing few activities (reference), patients significantly preferred tiredness some days a week and completing most activities ($P<0.01$). In addition, patients significantly valued a lower risk vs a higher risk of GI-AEs (20% over the 80% risk reference level, $\beta_{18}=1.22$; $P<0.001$) and infections (5% non-serious and 0% for serious infection vs 30% non-serious and 10% serious infections; $\beta_{21}=0.98$;

$P<0.001$) (Fig. 3 and supplementary Table S7, available at *Rheumatology* online).

Patients' choices of treatment preferences were mostly affected by the risk of GI-AEs (RAI=25%; 95% CI 22, 28%), followed by risk of infection (RAI=20%; 95% CI 16, 24%), and improvement in the presence/severity of shortness of breath (RAI=18%; 95% CI 15, 22%) and coughing (RAI=14%; 95% CI 11, 17%) (Fig. 4).

When considering symptoms, an improvement in the type and severity of coughing and an improvement in shortness of breath were each more important to patients with SSc-ILD than improvement in skin tightness (RAI=8%; 95% CI 6, 12%).

Patients' willingness to make trade-offs

Fig. 5 reports the MAR of increase in risk of GI-AEs that patients were willing to accept for an improvement in the type or severity of disease-related symptoms and AE attribute levels. In these scenarios, GI-AEs were considered as mild to moderate. Patients were willing to accept a 21% (95% CI 13, 29%) increase in GI-AEs if they could reduce the frequency of an infusion from monthly to every 6 or 12 months, or a 15% (95% CI 7, 23%) increase in GI-AEs if the treatment was changed to an oral treatment twice daily. In addition, patients were willing to accept a 37% (95% CI 28, 46%) increase in GI-AEs if it resulted in breathlessness occurring during routine activities such as walking on level ground rather than at rest. For AE trade-offs, patients were willing to accept a 36% risk (95% CI 27, 45%) of GI-AEs if it reduced the risk of non-serious infections from 30% to 15% and of serious infections from 10% to 5%. Regardless of the change in activity levels, patients were willing to accept an 11% risk increase in GI-AEs for a change from most days a week to tiredness some days a week.

TABLE 1 Summary of sociodemographic and self-reported clinical characteristics

	Total (N = 231)
Sociodemographic characteristics	
Country, <i>n</i> (%)	
France	33 (14)
Germany	42 (18)
Norway	19 (8)
Switzerland	29 (13)
USA	108 (47)
Age	
Mean (years) (s.d.)	52.6 (13.2)
18–34 years, <i>n</i> (%)	22 (10)
35–64 years, <i>n</i> (%)	163 (71)
≥65 years, <i>n</i> (%)	46 (20)
Employment status, <i>n</i> (%)	
Full-time work	57 (25)
Part-time work	28 (12)
Homemaker/housewife	17 (7)
Student	2 (1)
Unemployed	11 (5)
Retired	60 (26)
Unable to work due to disability	78 (34)
Other ^a	2 (1)
Prefer not to say	2 (1)
Education, <i>n</i> (%)	
Elementary school/no formal qualification	4 (2)
High school	78 (34)
College/university	83 (36)
Postgraduate degree (Master's, MD, PhD)	49 (21)
Other ^b	17 (7)
Prefer not to say	2 (1)
Marital status, <i>n</i> (%)	
Single, never married	27 (12)
Living with partner	23 (10)
Married	151 (65)
Separated	5 (2)
Divorced	22 (10)
Widowed	3 (1)
Prefer not to say	0 (0)
Medical insurance, <i>n</i> (%)	
Private	74 (41)
Public (Medicare, Medicaid)	103 (58)
Veterans Affairs	1 (<1)
None	1 (<1)
Clinical characteristics	
Time since SSc diagnosis	
Mean (years) (s.d.)	8.9 (6.9)
Median (years) (Q1–Q3)	7.5 (3.7–12.2)
Time since ILD diagnosis	
Mean (years) (s.d.)	7.1 (5.8)
Median (years) (Q1–Q3)	5.6 (2.6–10.4)
Symptoms experienced, <i>n</i> (%)	
Coughing	135 (58)
Shortness of breath	179 (77)
Tiredness	190 (82)
Dizziness	69 (30)
Pain in your hands	161 (70)
Pain in your chest	70 (30)

(continued)

TABLE 1 Continued

	Total (N = 231)
RP	212 (92)
Swelling/oedema in hands	116 (50)
Itching	89 (39)
Bloating	98 (42)
Other ^c	63 (27)
Severity of symptoms today, <i>n</i> (%)	
Very mild	11 (5)
Mild	38 (16)
Moderate	123 (53)
Severe	51 (22)
Very severe	8 (3)

^aSelf-employed. ^bResponse option did not have open text or follow-up response. ^cOther symptoms include: general; GI issues; skin symptoms; body, joint, or muscle pain; and other impacts. GI: gastrointestinal; ILD: interstitial lung disease; Q1: first quartile; Q3: third quartile.

MAR estimates can be used to understand trade-offs that patients would be willing to accept by comparing the relative magnitudes of the MAR values. For example, a twice-daily oral treatment was considered at least as good as a monthly infusion (MAR = 15%) even if tiredness increased from some days to most days (MAR = 11%) (Fig. 5).

DCE performance qualities

Internal validity

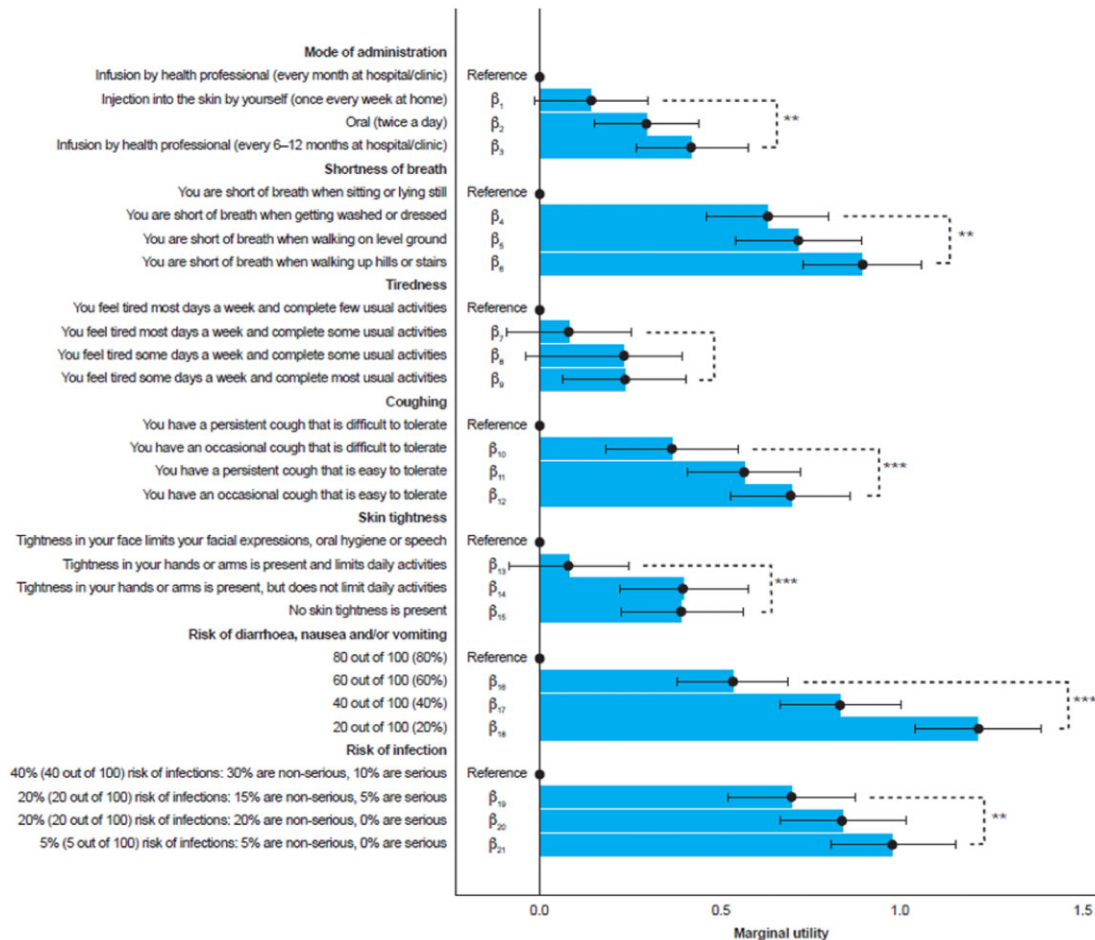
In total, 33% (*n* = 77) of patients failed one repeated choice task test and 8% (*n* = 18) failed both tests. Almost all patients (*n* = 228; 99%) varied their choices and did not always select the same treatment. Overall, 12% (*n* = 27) of patients failed the dominated choice test by selecting the answer with a higher symptom severity and risk. These internal validity measures are in line with other health DCEs in the literature [32].

Sensitivity analysis

Based on a Lagrange multiplier test (for a mixed logit) the effect of two attribute levels on preferences were found to vary in the patient population. Heterogeneity was observed for: (i) shortness of breath when walking up hills compared with shortness of breath when lying or sitting still ($P < 0.001$); and (ii) 5% risk of infection compared with 40% risk of infection ($P < 0.001$). A latent class model that aimed to find groups of preferences was unable to segment the patient into preference groups based on the Bayesian Information Criterion (see [supplementary Tables S8–S12](#), available at *Rheumatology* online).

Accounting for preference heterogeneity based on patients' characteristics did not improve the models' ability to explain patients' choices in the DCE observed (see [supplementary Data S3](#); [supplementary Tables S13–S24](#), available at *Rheumatology* online).

Fig. 3 Main model estimates



Whiskers denote 95% CI. Constant of left alternative was 0.06 (SE 0.05). Final log-likelihood at convergences: -1563. Number of respondents: 231. Adjusted McFadden R^2 : 0.176. Bayesian information criterion: 3300. Estimation via maximum likelihood method: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. This figure presents the main model estimates. Estimates denote how preferences are affected by deviating from the reference level (first level) in each attribute. Bars with a CI that does not cross zero capture a positive effect on preferences. The longer the bar, the impact on preferences. However, the relative magnitude of the difference between bars should not be interpreted due to the ordinal nature of underlying preferences and an arbitrary scale. Please see [supplementary Table S7](#), available at *Rheumatology* online for more detail.

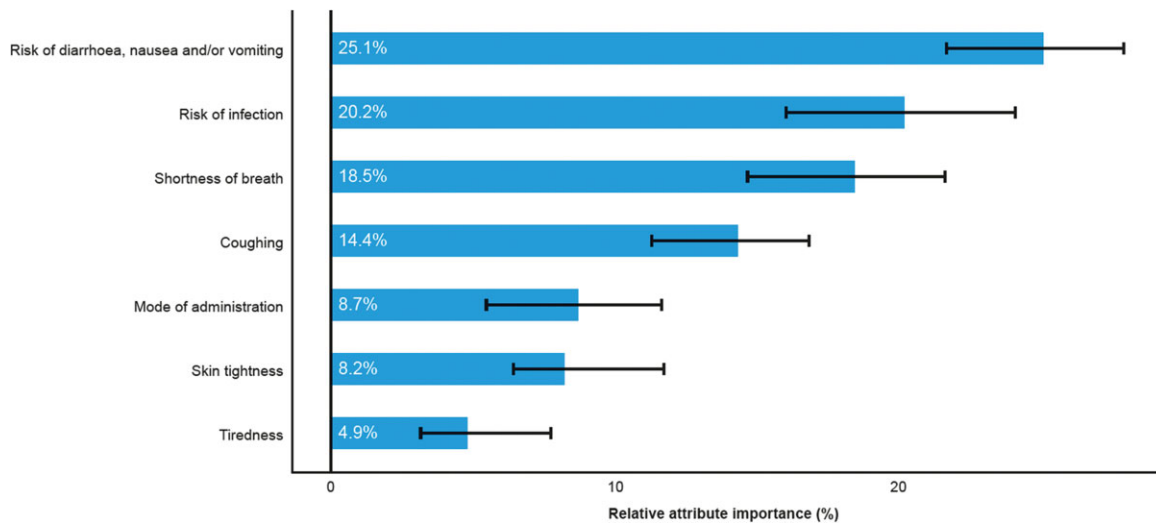
Subgroup analysis was conducted based on age, self-reported changes in overall symptoms, time since SSc-ILD diagnosis, time since SSc diagnosis, self-reported severity of SSc symptoms, self-reported change in lung symptoms, self-reported change in skin symptoms, number of reported symptoms, employment status and experience with oral treatments only. None of the subgroup analyses significantly improved the model estimates and they are subject to small sample bias.

Discussion

Patients in our study had established preferences, placed high importance on avoiding AEs and were

willing and able to make trade-offs between attributes when considering treatment options. This suggests that risks of experiencing AEs can be balanced with symptom improvement or administration convenience. Specifically, we found that patients with SSc-ILD were concerned with mode of administration, shortness of breath, skin tightness, coughing, tiredness, risk of GI-AEs, and risk of serious and non-serious infections.

The complexity of disease management in SSc-ILD and the lack of curative therapies are highlighted as an unmet need by patients with SSc-ILD [38]. In addition, treatment decisions require an informed consideration of multiple treatment attributes. The patient's perspective can therefore be a relevant factor to consider in clinical decision-making, especially if the decline in lung function

Fig. 4 RAI for patients to choose a treatment preference

The relative importance that patients place on each attribute—calculated as the normalized utility impact of the most preferred level of each attribute—is presented. Relative attribute importance scores sum to 100% and measure how much variation in utility (a measure of preference) is due to changes in each attribute. RAI: relative attribute importance.

is progressive and difficult to manage [39]. However, limited data is available on how patients with SSc-ILD are willing to trade off between different treatment aspects. This is the first study that set out to quantitatively elicit patients' preferences for SSc-ILD treatments as well as the benefit-risk trade-offs they are willing to make.

Overall, patients placed as much importance on treatment-related AEs as they placed on beneficial effects, which implies that treatment decisions can be complex and involve multidimensional trade-offs. However, not all considered treatment attributes had the same relative importance to patients. Notably, respiratory symptoms, such as shortness of breath or coughing, were more important to patients than skin tightness. This may be driven by the fact that the presence of ILD is prevalent in all subtypes of SSc [40]. Our data did not account for lcSSc vs dcSSc subtype, nor for disease duration; therefore, these results may not be applicable to all SSc patients, particularly to those with more severe skin fibrosis and minor respiratory symptoms. Cough has previously been highlighted as an important symptom in CTD-related ILDs [26, 41]. Our findings also align with studies that have demonstrated that the health-related quality of life of patients with SSc-ILD is driven by lung function [42].

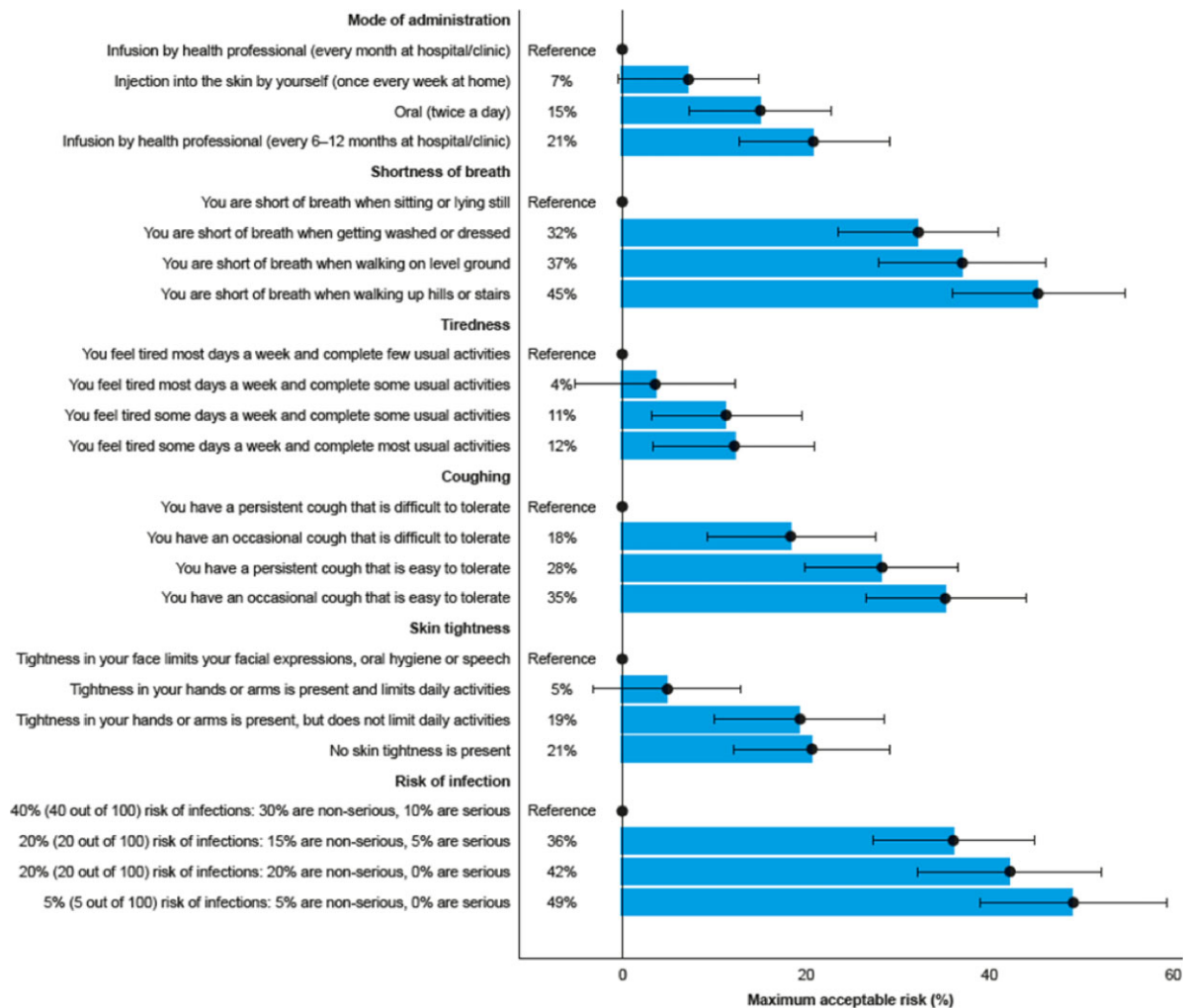
Regarding AEs, safety data from clinical trials have shown that diarrhoea is common with both immunosuppressant and antifibrotic treatments [19, 43], suggesting that GI tract events will likely impact how patients value treatments. In line with this expectation, patients' choices in our DCE were slightly more affected by GI-AEs than by the risk of infections, despite patients being especially averse to serious infections that required hospitalization.

Patients were also found to prefer twice-daily oral treatments and infusion every 6–12 months compared with monthly infusions. Similarly, in a single-centre study in Italy, El Aoufy *et al.* identified a preference for oral administration among patients with SSc, given its feasibility [23].

Our study has certain strengths. The study considered patient and physician input over multiple phases to ensure that the final design of the DCE was relevant to both patients and clinicians. All study protocols were reviewed by at least two physicians with significant experience in treating SSc-ILD or who were knowledgeable in aspects regarding patients with SSc-ILD. Moreover, the study followed best practice guidelines to ensure that a valid instrument was developed and to minimize the risk of bias [44]. Our site-based recruitment was based on physician-confirmed SSc-ILD, whereas most preference studies rely on self-reported diagnosis and panel recruitment. To understand the data quality of the study, several established internal validity measures were compared, and all data-quality measures were both in the expected ranges and in line with other DCE studies in the literature [32], suggesting that patients were engaged with the survey and capable of understanding and completing the choice tasks.

Our study also had limitations. While comparable to other survey studies in the literature, the response rate was relatively low (21.4%) and no data were collected on the characteristics of non-respondents. Thus, results should be interpreted within the context of the sampled population. In addition, this study focused on northern European and US patients, with a high health literacy rate along with high national levels of education (57% of patients reporting a university or postgraduate degree).

Fig. 5 MAR of GI-AEs



Whiskers denote 95% CI. MAR estimates are used to make the length of the bars comparable by measuring the value that patients placed on each attribute using a common unit of measurement (i.e. risk of GI events equivalences). The values provide insights into the trade-off with GI-AE risks, but estimates can also be compared across attributes for the purpose of value comparisons. GI-AEs: gastrointestinal adverse events; MAR: maximum acceptable risk.

The qualitative research study only recruited patients from New Orleans, Louisiana, with a specific cultural background and demographic distribution. However, despite single-centre recruitment during the instrument development phase, the surveys and the instrument performed well across different cities and languages. Patient input was also collected from a diverse group across 12 countries at an advisory board meeting, with representation from 15 patients and 2 caregivers. Another potential limitation was the small number of patients who provided feedback on the programmed survey during the qualitative pilot study, which was due to unforeseen circumstances (i.e. a severe hurricane in Louisiana). Nevertheless, the feedback obtained was supportive of the DCE and survey approach. Our study did not analyse mortality, so patients were not asked

which AEs or risks they would trade for avoiding death as an outcome of lung fibrosis. This study also does not explore trade-offs between AEs and a reduction in the worsening of respiratory symptoms. Realistically, patients may have suffered irreversible loss of respiratory function and may not improve. The majority of patients had a disease duration longer than 5 years, and may have included a substantial number of patients with lcSSc, with milder skin involvement [45]. Detailed clinical characteristics (e.g. Rodnan skin score, FVC) were not available in this study due to data protection requirements, which may limit the generalizability of the data. Furthermore, our study considered a subset of patients with specific needs and concerns. Additional factors not considered in this research, such as health values and patients' perceived prognosis, may be important drivers

of preferences for a wider and more diverse population of patients with SSc [46, 47]. For example, patients with a lower health status or fewer treatment options may be more willing to accept benefit–risk trade-offs. However, further research is needed to understand preference heterogeneity. In addition, all DCEs have a risk of hypothetical bias (i.e. responses made in hypothetical situations may differ in real life) [48, 49]. The proportion of respondents with self-reported shortness of breath or coughing, as well as the average time since ILD diagnosis, suggested that most patients might have already presented with an advanced form of the disease [19, 39]. Therefore, the recruited cases may not have sufficiently captured preferences of untreated patients with SSc-ILD or those with mild symptoms. Several patients who were unaware of their ILD were excluded during the screening process, as a lack of disease awareness may have induced hypothetical bias due to patients being unfamiliar with the concepts under discussion.

Conclusion

Patients' willingness and ability to consider and trade off multiple treatment attributes provide a solid foundation for shared decision-making in routine clinical practice. The treatment valuations of patients with SSc-ILD were driven by multiple treatment attributes, with a focus on avoiding the risk of GI-AEs and infections, as well as benefits to breathlessness and reduction in coughing. The results of this study can help inform discussions between patients and physicians regarding risks and benefits. Knowledge about preferences can also help tailor information materials to support informed decision-making [50]. In addition to lung function, future studies should explore treatment effects on coughing as well as the development and validation of outcome measures that are relevant to patients' experiences of SSc-ILD and reflect each patient's individual treatment priorities.

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Ethics: This study complies with the Declaration of Helsinki. The study protocol and informed consent forms were approved by the local ethics committee in each country. All patients provided online informed consent via tick box for participation in the study. Written informed consent was waived by the Institutional Review Board since data collection was anonymous.

Data availability statement

The data underlying this article may be shared on reasonable request to the corresponding author and agreement by the sponsor for applied research that aligns with study participants' consent.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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