Clinical Outcomes in Interstitial Lung Diseases

Measuring and improving quality of life

Mirjam van Manen

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Mirjam Johanna Gerdina van Manen

The work described in this thesis was conducted at the Department of Respiratory Medicine, Erasmus MC, Rotterdam, the Netherlands

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Clinical Outcomes in Interstitial Lung Diseases

Measuring and improving quality of life

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Meten en verbeteren van kwaliteit van leven

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Chapter 1

General introduction

"The real purpose of the scientific method is to make sure nature hasn't misled you into thinking you know something you actually don't know"
Robbert M. Pirsig

GENERAL INTRODUCTION

Interstitial lung diseases

Interstitial lung diseases (ILDs) are also known as diffuse parenchymal lung diseases (DLPDs), and affect around 50 million people worldwide.[1,2] DLPDs are characterized by alterations of the interstitium, but can also effect the alveoli, respiratory tract, pleura and blood vessels, and contain more than 200 diverse disorders.[2] During the past decades the classification of DLPDs has been a dynamic process with new insights driving adaptations.[1,3-8] In this thesis, the most recent classification of 2013 is used.[6] The DLPDs can roughly be divided in four groups (figure 1).[1] The *first group* consists of DLPDs with a known cause, such as an underlying collagen vascular disease or environmental or drug related DLPD. The *second group* contains disorders of unknown cause, called the idiopathic interstitial pneumonia's (IIPs). IIPs are a group of non-neoplastic disorders were the pulmonary parenchyma is affected by inflammation and/or fibrosis.[1] The presence of crackles and/or finger clubbing is suggestive for fibrosis.[1] IIPs are diagnosed based on clinical, radiological and pathological features, and can be subdivided in unclassifiable IIP's, rare IIP's and major IIP's.[6] The latter being the largest group, containing several heterogeneous disorders with the most common one idiopathic pulmonary fibrosis (IPF). The *third group* consist of other forms of DLPD such as lymphangioleiomyomatosis, pulmonary Langerhans' cell histiocytosis and eosinophilic pneumonia.[1,2] The *fourth group* of DPLD consists of granulomatous diseases, which are characterized by an accumulation of epithelioid macrophages, called granulomas. The most common granulomatous disease is sarcoidosis. This thesis will mainly focus on the most common ILDs: IPF and sarcoidosis.

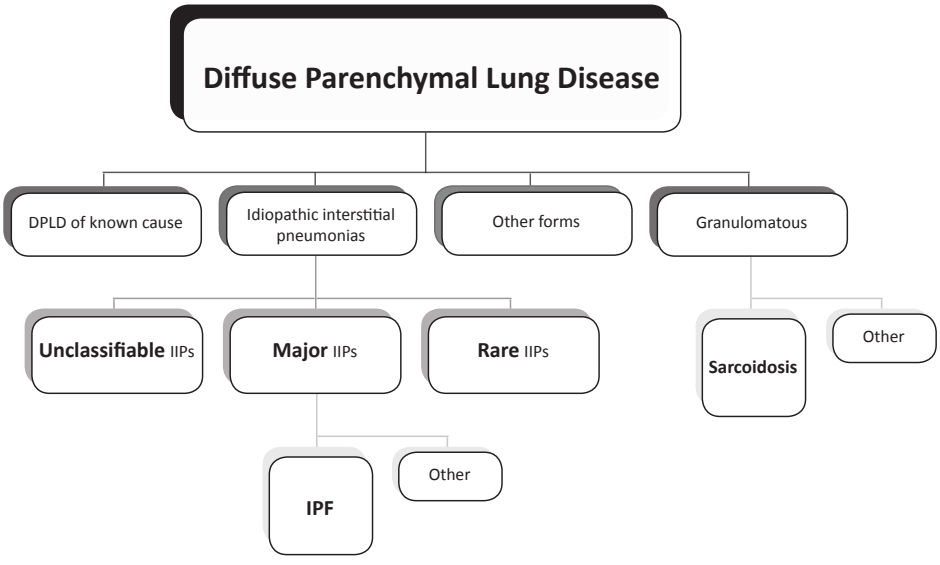

Figure 1. Classification of interstitial lung diseases
DLPD, Diffuse parenchymal lung disease; IIPs, idiopathic interstitial pneumonias; IPF, idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis

Epidemiology

IPF is a progressive fibrotic lung disease of unknown cause. Estimated incidence of IPF in Europe and North America is about 3-9 cases per 100.000 per year.[9] For the Netherlands this would mean between 500 and 1500 new cases yearly diagnosed. Patients are typically aged 60 years or older at diagnosis, and the disease is more common in men and in former smokers.[5,10]

Pathogenesis

The exact pathogenesis of IPF is unknown. It is hypothesized that various exposures can cause repeated epithelial injury, which may lead to the activation of fibrotic cascades and abnormal wound healing, resulting in excessive collagen production that leads to scarring of the lung.[11] Risk factors associated with the development of the disease include smoking, occupational exposure, chronic microaspiration, microbiome and genetic predisposition.[12-14]

Diagnosis

In IPF, chest auscultation can reveal fine basal end-inspiratory crackles, and around 25-50% of patients develop digital clubbing.[1,10,12] A restrictive pattern is generally found on pulmonary function tests and reduced oxygen transport measured by the transfer factor for carbon monoxide (TLCO).[10] Though, normal pulmonary function does not exclude IPF.

In the Netherlands, it is agreed that a diagnosis of IPF should be made in an experienced multidisciplinary team, with at least a pulmonologist, pathologist and radiologist. IPF is characterized by a histological and radiological pattern of usual interstitial pneumonia (UIP). A chest X-ray can reveal diffuse bilateral and reticular abnormalities, mainly at the periphery and lung bases.[5] To diagnose IPF, a high-resolution computed tomography (HRCT) is needed. The HRCT scan is consistent with an UIP pattern when there is predominantly basal and subpleural reticulation, honeycombing with absence or presence of traction bronchiectasis, and absence of radiologic clues for other ILDs.[5] Other causes of the UIP pattern, such as treatment-related lung damage and auto-immune disease, should be excluded.[5] If the combination of the clinical picture and HRCT is inconclusive, a diagnostic biopsy of the lung tissue should be considered. In clinical practise, a biopsy is not always possible or desired by patients, and an experienced multidisciplinary team may decide on a “working diagnosis” of IPF, based on imaging, clinical characteristics and likelihood.

Clinical course and symptoms

The main symptoms patients experience are progressive breathlessness, cough and fatigue.[15] Especially cough and fatigue are often difficult to treat. Eventually, the progressive fibrosis results in hypoxemia and the use of supplemental oxygen in the majority of

patients. Though the disease course varies between patients, life expectancy is around 3-5 years without treatment, which is worse than many forms of cancer.[16-18]

Treatment

Currently, the only cure for IPF patients is lung transplantation. Unfortunately, only few patients are eligible due to generally older age of IPF patients and associated comorbidities. Nowadays, there are two drugs approved for treatment of IPF: pirfenidone and nintedanib. They slow down disease progression and prolong survival, but cannot cure the disease.[19,20] Both drugs show a similar effect on slowing down lung function decline, but differ in their side-effect profile.[19,20]

Quality of life

The progressive nature of the disease, reduced life expectancy, often high symptom burden, and limited treatment options have a major impact on patients with IPF. Several studies show that quality of life (QoL) in patients with IPF and their caregivers is substantially decreased, and that there is a great need for adequate information, ILD specialist nurses, psychological support, access to treatment, and interventions aiming at improving QoL.[21-26] In the trials with the two anti-fibrotic drugs that significantly slowed down disease decline, no convincing effect on QoL was shown.[19,20] This lack of effect of treatment may be because we are not able to measure the effect, as there is a paucity of well-developed and validated IPF-specific measures to capture symptoms and health-related QoL (HRQoL). Another reason might be that disease-specific therapies may address the underlying pathophysiology, but they do not necessarily improve patient's symptoms. Therefore, in addition to the disease-centered care, there is a need for a different and complementary approach to manage and measure symptoms.

Sarcoidosis

Epidemiology

Sarcoidosis is a multisystem granulomatous disease with unknown etiology. The disease can affect various organs, but is most commonly seen in the lung (90%), skin, eyes, liver and peripheral lymph nodes.[27] Sarcoidosis is usually diagnosed in patients aged 25-50 years, but can also occur at older age, and is more frequent in women and in Afro-Caribbeans and African-Americans than in Caucasians or Asians.[4,28-30] Incidence and prevalence rates differ between countries and ethnic groups, with worldwide annual incidences ranging from 5-40 per 100.000, and an estimated prevalence in the Netherlands of 50 per 100.000.[28,31,32]

Pathogenesis

The etiology of sarcoidosis still needs to be unraveled, but it seems that both genetic susceptibility and environmental factors play a part.[33,34] An immunological response to infectious agents, such as mycobacteria and Propionibacterium might play a role, which results in an excessive T-cell response, characterized by enhanced Th1/Th17 cells,

and impaired functioning of immunosuppressive regulatory T-cells and possibly also of checkpoint inhibitors such as CTLA-4.[35,36]

Diagnosis

A diagnosis of sarcoidosis is established when histological (mostly non-caseating epithelioid cell) granulomas are present, clinico-radiological findings are consistent with sarcoidosis, and other causes of granulomatous inflammation and local sarcoid reaction are excluded.[4,27] Physical examination can show skin lesions, ocular abnormalities and in some cases abnormalities on chest auscultation. Pulmonary function tests may reveal an obstructive or restrictive pattern, with or without a reduced diffusion capacity.[4,27] Hypercalcemia and hypercalciuria are present in 10-40% of sarcoidosis patients.[31]

Clinical course and symptoms

Sarcoidosis has multiple manifestations, ranging from asymptomatic to life-threatening pulmonary fibrosis or cardiac disease.[4,37] The disease can have an acute onset and resolve spontaneously or after treatment; or an insidious one with a chronic progressive course, and in a minority of patients permanent clinical symptoms.[4,37,38] The majority of patients with sarcoidosis have a normal life expectancy, it is estimated that around 5% of patients will die of sarcoidosis.[39-41] Symptoms in sarcoidosis are often non-specific and dependent on organ involvement and disease course.[4,42] Most common symptoms are cough, dyspnoea, pain and fatigue.[42-44]

Treatment

A large group of sarcoidosis patients will never require treatment.[45,46] Treatment options for the others differ due to heterogeneity of disease, and are based on expected prognosis, organ involvement, impact, activity and severity of disease, and possible side-effects of treatments.[47,48] No curative treatment is currently available for sarcoidosis. Corticosteroids are the mainstay of treatment, but also cytotoxic agents, such as methotrexate, and biologicals as infliximab and adalimumab are prescribed as second or third line therapy.[48-52]

Quality of life

QoL is reduced in many patients with sarcoidosis.[53,54] Disease-related symptoms are one of the factors contributing to the impaired QoL found in these patients. Depending on location and severity of disease, patients can experience a vast range of bothersome symptoms including cough, dyspnea, arthralgia, muscle pain, fever, eye problems, skin injury, sleep disturbances, headache, anorexia, dizziness, neurological pain, general weakness, cognitive failure, small-fiber neurological impairment and fatigue.[29,32,53] Of these, chronic fatigue seems to have the greatest impact on QoL.[55,56] Comorbidities and side-effects of treatment might also influence QoL in sarcoidosis patients.[53,57,58] All the factors may influence mobility, social interaction, working capacity and activities of everyday life, which may induce psychological distress, and might be another factor contributing to the impaired QoL found in sarcoidosis patients.[53] QoL in sarcoidosis is

difficult to measure, due to the multisystem and heterogeneous nature of the disease. Current sarcoidosis-specific measures for QoL do often not take into account the multiple-organ involvement. QoL interventions in sarcoidosis are scarce and mostly focused on pulmonary rehabilitation.[59,60] Comprehensive measures of sarcoidosis-specific QoL and interventions on improving QoL of patients with sarcoidosis are needed.

The past years, more attention has been paid in ILDs to the needs of patients, patient-centered care and participation of patients in care. Also, studies have started to engage patients in the set-up and design of clinical trials, and patient-reported outcome measures (PROMs) are increasingly used as outcome measure.[19,20,61,62] It is expected that in the coming years more emphasis will be placed on PROMs, not only in interventions aiming at improving QoL, but also in trials aiming at disease modification.

Outcome measures in interstitial lung diseases

Outcomes can be divided in four groups: 1. physiological outcomes, 2. physiological outcomes reported by patients, 3. patient-relevant outcomes, and 4. patient-driven outcomes (figure 2). These outcomes are all considered *patients-centered outcomes* (PCOs), as they present medical outcomes that are important and specific to patients. The last three outcomes are also *patient-reported outcomes* (PROs), which are described as "Any report coming directly from the patient without interpretation by a third party about how they feel or function in relation to a health condition and given intervention."[63] PROs can be measured with PROMs, which are usually questionnaires, mostly focussing on QoL. The use of PROMs both in clinical trials and clinical practice has increased over the last years, and several ILD-specific PROMs have been developed. However, these PROMs have some limitations. Most ILD PROMs were original developed for other lung diseases, such as the St George's Respiratory Questionnaire (SGRQ), which was originally developed for asthma and COPD.[64] This can lead to irrelevant questions, and relevant topics might be lacking. Additionally, most PROMs are developed in English-speaking countries, and are sometimes less appropriate for use by patients from other backgrounds. For example, an US developed questionnaire asks about dyspnea when mowing your lawn or washing your car, which is for a lot of patients around the world not a feasible scenario.[65]

Physiological outcomes

In ILDs, most used physiological outcomes are pulmonary function parameters as FVC, TLCO and the 6-minute walk test. In the two landmark trials with pirfenidone and nintedanib for IPF, FVC has been used as primary endpoint, so FVC will likely be used in new drug trials.[19,20] In sarcoidosis, physiological outcomes are dependent on organs affected. For example, distribution of lesions, lesions' target area and volume are used in cutaneous sarcoidosis, while for pulmonary sarcoidosis lung function tests will be used.[66-68] Symptoms, such as fatigue, have shown to decrease QoL in patients with sarcoidosis and increase psychological distress.[53,57,69] No objective physiological outcome currently

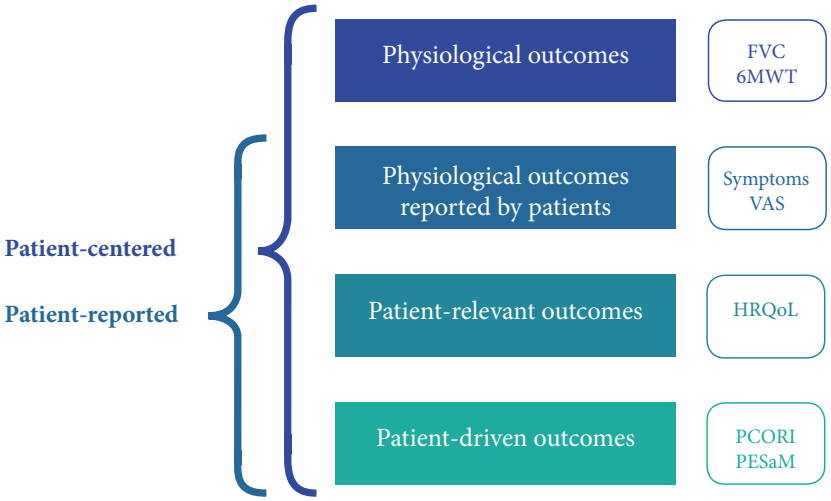

Figure 2. Study outcomes
FVC, forced vital capacity; 6MWT, 6-minute walk test; VAS, visual analogue scale; HRQoL, health-related quality of life; PCORI, patient-centered outcome research institute, PESaM, patient experiences and satisfaction with medication questionnaire.

exists that can capture subjective outcomes of QoL, such as anxiety, depression and psychological distress.

Physiological outcomes reported by patients

Symptoms are physiological outcomes reported by patients, and are often scored with a 100-mm visual analogue scale (VAS). Although it is regularly known which symptoms are the most troublesome to patients, nowadays, many drug development programs do not evaluate these symptoms. Cough, breathlessness and fatigue are the three most bothersome symptoms in IPF according to a study by the Food and Drug Administration on the perspectives of patients with IPF regarding their disease and its impact.[70] Our studies focus on cough as there is currently, little knowledge about mechanisms, pathology and assessment of cough in IPF, and studies on effective treatments for cough in patients with IPF are scarce.

Patient-relevant outcomes

Patient-relevant outcomes are measures of QoL, which may be referred to using terms as QoL, HRQoL and health status.[71] QoL is defined by the World Health Organization as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment."[72] HRQoL is the subset of QoL that is affected by health[71,73], while health status is defined as: "the impact of disease on

patients' physical, psychological and social functioning."[74] Although these terms represent different concepts, in daily care and research, they are often used synonymously.[73] QoL can be measured with questionnaires. There are different types of questionnaires; generic, disease-specific and symptom-specific questionnaires.[75] Generic questionnaires are used to measure QoL independent of disease status and can be used in the general population, while disease-specific questionnaires are developed explicit for a certain disease or patient group.[75] Symptom-specific questionnaires assess how a specific complaint, such as cough or dyspnoea, affects a patient's wellbeing.[65,76] (HR) QoL measures often show poor correlation with physiological outcomes as pulmonary function testing.[77,78] As previously described, QoL is impaired in both patients with IPF and sarcoidosis. In sarcoidosis, QoL has been a focus of research and an outcome of clinical trials for a long time.[60,67,79,80] In IPF, research into QoL has gained more attention the past years.

Patient-driven outcomes

Patient-driven outcomes are outcomes that were developed and chosen together with patients. New initiatives also strive to engage patients not only in outcome development, but also as a meaningful contribution throughout the whole research process. Patients are involved in topic selection for design and conduct of research, and engaged in dissemination of results. An example of such an initiative is the patient-centered outcomes research institute (PCORI), an American independent non-profit organization which focusses on improving clarity of data to enhance health decision making.[81] By supporting studies on PCOs and involving patients, caregivers, clinicians, healthcare stakeholders and researchers in the process, they try to define what the best healthcare options are for individual patients.[81] In the Netherlands, the patient experiences and satisfaction with medication (PESaM) questionnaire for patients with IPF is being developed together with patients, physicians, patient associations, and researchers.[82]

Improving quality of life in interstitial lung diseases

QoL has shown to be decreased in patients with ILDs, due to burdensome symptoms, the chronic and/or progressive nature of disease, and, for some ILDs, the poor life-expectancy. However, little research has been done on how to optimize QoL of these patients.

One of the symptoms with the most impact on QoL in patients with IPF is cough.[15] Patients often have a persistent and refractory chronic cough (≥8 weeks), which has major physical and psychological impact (figure 3). The cough is generally difficult to treat, and often not responsive to conventional anti-tussive therapies. Until now, there is no drug with a convincing effect on chronic cough in IPF. Since recent years, cough is increasingly used as endpoint in clinical pulmonary fibrosis trials, and IPF-related cough is regularly included as subgroup in chronic cough trials. In sarcoidosis, fatigue is one of the symptoms with the most impact on QoL and reported by 50-70% of patients.[55,56] The exact cause of fatigue is unknown, but different factors might play a role, such

as the underlying inflammatory disease process, comorbidities, sleeping problems, psychological distress and side-effects of treatments.[57]

Optimizing QoL requires information on patients' needs and preferences in care. The past years, many initiatives have gained information on the needs of IPF patients. In a recent study of Bonella et al., 12 patient advocacy group representatives from nine European countries developed a European IPF patient charter on the care needs of IPF patients.[25] Besides early and accurate diagnosis, equal access to care, a holistic approach to standardise IPF management, better access to palliative care and end-of-life care, this charter revealed a need for "comprehensive and high-quality information about IPF".[25] Though other studies confirmed this information need, little is known about the best way to educate IPF patients on their disease. In sarcoidosis, well-established studies on needs and preferences in care are currently lacking.

QoL interventions in ILDs are still scarce and mainly focused on pulmonary rehabilitation.[59,83-86] Recently, a study in 142 ILD patients (61 IPF, 22 asbestosis, 8 sarcoidosis, and 51 other ILDs) showed that an 8-week exercise training clinically improved 6MWT,

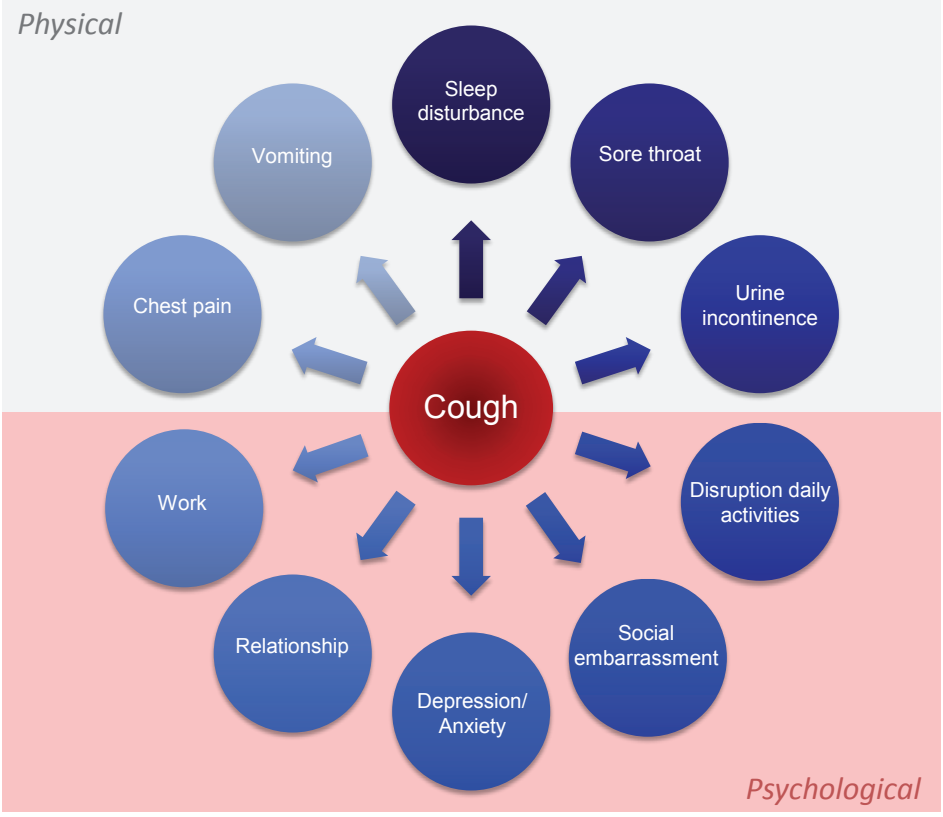

Figure 3. Impact of chronic cough

symptoms and HRQoL scores.[87] Although patients with asbestosis and IPF benefited most of the training, short-term improvements were seen in all types of ILDs. Pulmonary rehabilitation improves muscle strength, exercise endurance and symptoms, and often contains additional disease education and support that can improve QoL.[84,88] The effect of education and psychological support alone on patients' QoL has rarely been studied in ILDs. Two initiatives in IPF were started directly aiming at patient education and support.[86,89] A 6-weeks management-program for IPF patients and their partners resulted in significant deterioration of anxiety and HRQoL scores, even though all participants were positive about the program.[86] The other program focussed on disease education, management of treatment and possible side-effects, and providing psychological support on how to cope with the disease, for patient starting on pirfenidone.[89] Patients were really satisfied with the program, however, no control group was present and data on the effect of the program measured with QoL PROMs are not present.[89] More research on interventions that improve QoL for patients with different ILDs is desperately needed.

Aims and outline of the thesis

Interstitial lung diseases have a major impact on QoL. Though awareness is rising on the importance of improving QoL in these patients, few trials incorporate QoL and good measures for QoL are scarce. The aim of this thesis was to measure and improve QoL in ILDs by generating better clinical outcome measures for QoL (part 1) and developing interventions focussed on improving QoL (part 2).

Part 1: Outcome measures in interstitial lung diseases

Chapter 2 outlines the current knowledge and future prospects on PROMs in IPF.

Chapter 3 describes the translation and validation of the Dutch King's Sarcoidosis Questionnaire, a sarcoidosis-specific PROM.

Chapter 4 reports on a study analyzing the feasibility of scalp hair cortisol and testosterone as biomarker for psychological distress and fatigue in patients with sarcoidosis.

Chapter 5 describes a study in patients with fibrotic ILDs, evaluating the agreement between different clubbing measuring methods, the prevalence of clubbing, and the relationship between clubbing, disease severity and QoL.

Part 2: Improving quality of life in interstitial lung diseases

Chapter 6 reviews the recent insights on improving QoL for patients with IPF, and discusses challenges in the management of this devastating disease. Moreover, it proposes a new model for holistic care in IPF: the ABCDE of IPF care.

Chapter 7 provides an overview of the latest insights into the pathophysiology of cough, methods to assess cough and developments in treatment of cough in IPF.

Chapter 8 describes the results of an international multicenter study on the effect of pirfenidone on cough in patients with IPF.

Chapter 9 reports on the needs of patients with pulmonary fibrosis and their partners, and the value of interactive interviewing as educational method.

Chapter 10 describes the effect of a newly developed multidisciplinary empowerment program on QoL in patients with IPF and their partners.

Chapter 11 discusses the findings presented in this thesis.

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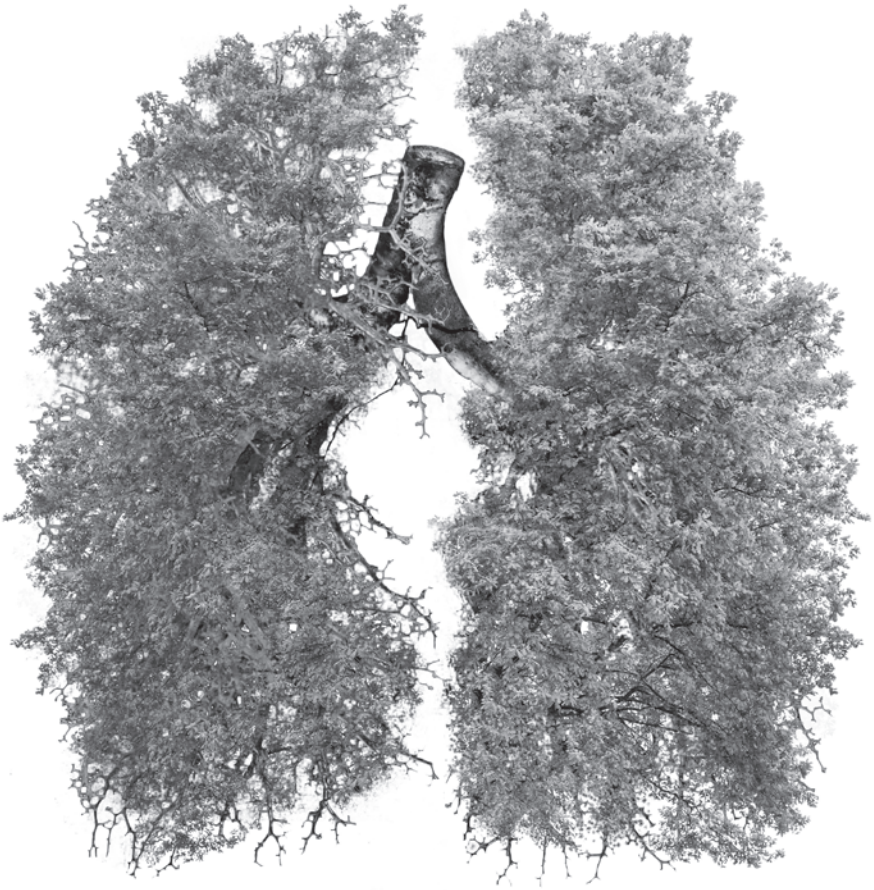

Part 1

Outcome measures in
interstitial lung diseases

Chapter 2

New insights on patient-reported outcome measures in idiopathic pulmonary fibrosis: only PROMises?

"Quality of life depends on quality and quantity of happiness"
Debasish Mridha

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Marlies Wijsenbeek[1], Mirjam van Manen[1], Francesco Bonella[2]

[1]Department of Respiratory Medicine, Erasmus Medical Center, University Hospital Rotterdam, Rotterdam, the Netherlands

[2]Interstitial and Rare Lung Diseases, Ruhrlandklinik University Hospital, University of Duisburg-Essen, Essen, Germany

ABSTRACT

Purpose of review

In a chronic, progressive and ultimately fatal disease like idiopathic pulmonary fibrosis (IPF), the maintenance of patients´ quality of life should be regarded as a major aim of treatment. Although better knowledge and two antifibrotic drugs are now available in IPF, the individual response to treatment and its acceptance remain poorly explored. This review summarizes recent advances in research on patient-reported outcomes and their measures, indispensable instruments to investigate how patients feel and function, and how the disease impacts their lives.

Recent findings

In IPF, there is a paucity of specific well-validated patient-reported outcome measures (PROMs). The use of generic PROMs in past IPF trials revealed a poor correlation of such questionnaires with established endpoints of treatment response. Several attempts are currently ongoing to develop specific IPF PROMs. The King's Brief Interstitial Lung Disease health status questionnaire and the Tool to Assess Quality of Life in IPF are promising questionnaires developed by using institutional recommendations and are currently being validated in large cohorts.

Summary

Well-validated relevant PROMs can be employed for multiple purposes: as outcome measures for daily care or for driving therapeutic decisions, as efficacy endpoints in clinical trials, or as tools to collect useful data for healthcare policy makers in order to improve access and quality of care.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disease with a poor prognosis and a devastating impact on the lives of patients and their families.[1] Although major progress has been made in gaining insights in the mechanism of disease and in the development of two drugs that slow down disease progression,[2,3] IPF still remains a deadly disease with a progressively impaired health-related quality of life (HRQOL).[4-6] Shortness of breath, cough and fatigue are major factors influencing HRQOL in IPF patients.[7-9] In a fatal progressive disease, prolonging life at an acceptable quality is what most people strive for. Although research can provide numbers on safety and efficacy of a drug, it remains challenging to quantify how a patient with IPF subjectively experiences a new treatment and benefits from the drugs. In fact, treatment success is also determined by patient factors such as expectations, experiences and motivations. Patient-reported outcomes (PROs) are therefore important as they attempt to reflect how patients feel and function, and how that impacts their lives.

In IPF, there is a paucity of specific well-validated patient-reported outcome measures (PROMs). Recently the first steps in collaboration between patients and caregivers have resulted in better insights into the burden of disease, symptoms and unmet needs in care for IPF.[4-6,10,11] However, good PROMs are needed, not only as outcome measures or even efficacy endpoints in clinical trials, but also for daily care, enabling patient and doctors to follow up the impact of treatment on patients' lives and guide treatment choices. Furthermore, there is an increasing demand from the healthcare providers and policy makers to obtain insight in the patients' perspectives and experiences during disease course and treatment, to monitor and improve care delivery. In this article, we look at recent insights in the use and development of PROMs and what promises these hold for care and research in IPF.

PATIENT-REPORTED OUTCOMES AND MEASURES

PROs are defined as 'Any report coming directly from the patient without interpretation by a third party about how they feel or function in relation to a health condition and given intervention'.[12] PROs can be physiological outcomes reported by patients, for instance cough severity measured by a visual analogue scale or a Medical Research Council (MRC) dyspnea scale. PROMs can also be questionnaires reflecting what is relevant to patients. HRQOL questionnaires are mostly used as PROMs. They assess a person's satisfaction with aspects of living that are affected by health and can be roughly divided in domain-specific, disease-specific and generic PROMs. Domain-specific PROMs are focused on a particular organ or symptom. Disease-specific PROMs are tailored to the impact and symptoms of a specific disease. Generic PROMs are developed for a total population, irrespective of the presence of disease, and reflect general aspects such as dependency, mobility and mood. Often different types of PROMs are used in

combination. The advantage of disease-specific PROMs is that they are more relevant to the patient and have a better face validity and credibility.[13] Generic PROMs allow comparing between different conditions and with a general population. PROMs should be distinguished from patient-reported experience measures (PREMs) that capture patients' experiences with healthcare or services.[13]

USE OF PATIENT-REPORTED OUTCOME MEASURES

Initially PROMs were developed for use in clinical trials. The use of PROMs is, however, much broader, which is increasingly acknowledged the past years (Fig. 1). Using PROMs in routine practice has shown to improve communication and shared decision-making between patients and care-providers, and improves patients' satisfaction with care and potentially also outcome of care.[14-16] Also, completing questionnaires will increase a feeling of being involved, which might be beneficial itself for health.[17] In a research setting, PROs could not only function as outcome measure, but may also be used to support predictive modelling for researchers, enabling identification of subgroups of patients based on PRO scores that might benefit from a certain treatment.[18,19] Possible practical advantages may be avoidance of observer bias and probably high completion rates. Clinicians are often hesitant to use PROMs in daily care because they consider

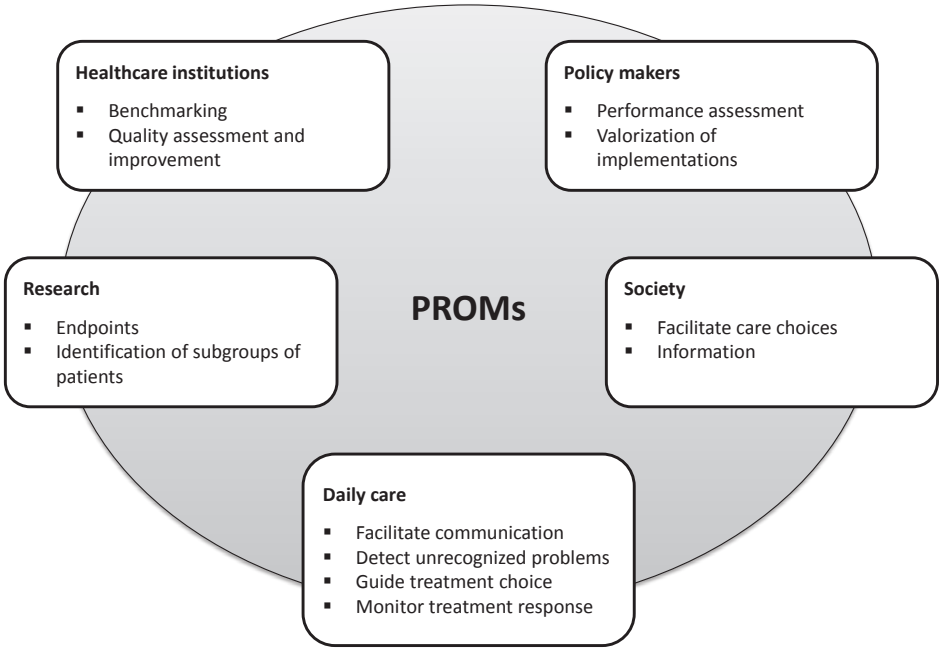

Figure 1. Possibilities of PROM use by different stakeholders.
PROM, patient-reported outcome measurement.

it time-consuming and doubt the additive value to the consultation. Patients are in general more positive to using PROMs on regular basis.[15,20]

DEVELOPMENT OF PATIENT-REPORTED OUTCOME MEASURES

As described above, well-developed PROMs can be used for a lot of purposes. However, clinicians and patients often lack the expertise, time and funding to develop good and broad PROMs. Many PROMs in the past have been developed in trial settings in sub-groups of patients sponsored by industry.[18,21] The Food and Drug administration (FDA) has made criteria about Guidance for Industry on qualification process for PROMs for drug development (Fig. 2).[12] However, as the FDA states 'This guidance does not address the use of PRO instruments for purposes beyond evaluation of claims made about a medical product in labeling'. The Patient-Centered Outcomes Research Institute (PCORI) developed a set of draft minimum standards for the development, selection and use of PROs data, incorporating existing guidance documents including the FDA guidance.[12,22]

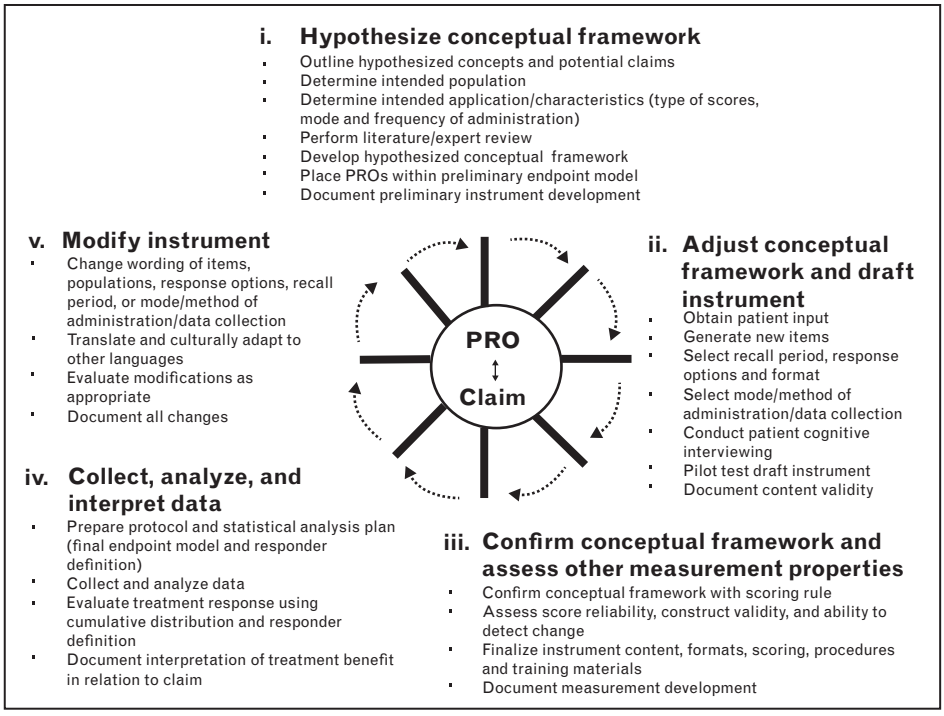

Figure 2. FDA guidance on the development of a PRO instrument for drug development.
By permission of Oxford University Press, USA. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf. FDA, Food and Drug administration; PRO, patient-reported outcome.

PATIENT AS PARTNER IN CARE AND RESEARCH

Collaboration between patients, patient advocacy groups and healthcare providers has greatly improved our knowledge on the impact of IPF on patients and partners, and the need for improvements.[4-6,23] A recent initiative of 11 European IPF patient advocacy and interstitial lung disease (ILD)-physicians identified five key themes of unmet needs for IPF (Fig. 3). This patient-physician initiative underlines the inequalities in IPF care across Europe and was presented at the European parliament to call to action for healthcare policy makers.

In the United States, the FDA conducted a meeting with patients with IPF as part of the agency's Patient-Focused Drug Development initiative, to look at the patients' perspectives on symptoms and treatment approaches, important for the drug development process. This meeting underscored that there is a great need for better medication and symptom relief, in particular shortness of breath, severe cough and fatigue.[7] Understanding what matters to patients is essential for patient-centered care and research, but the next important step is active patient involvement. For the 2015 IPF clinical practice guideline, a patient representative participated for the first time in the development group and his contribution was greatly acknowledged.[1] The PCORI aims to

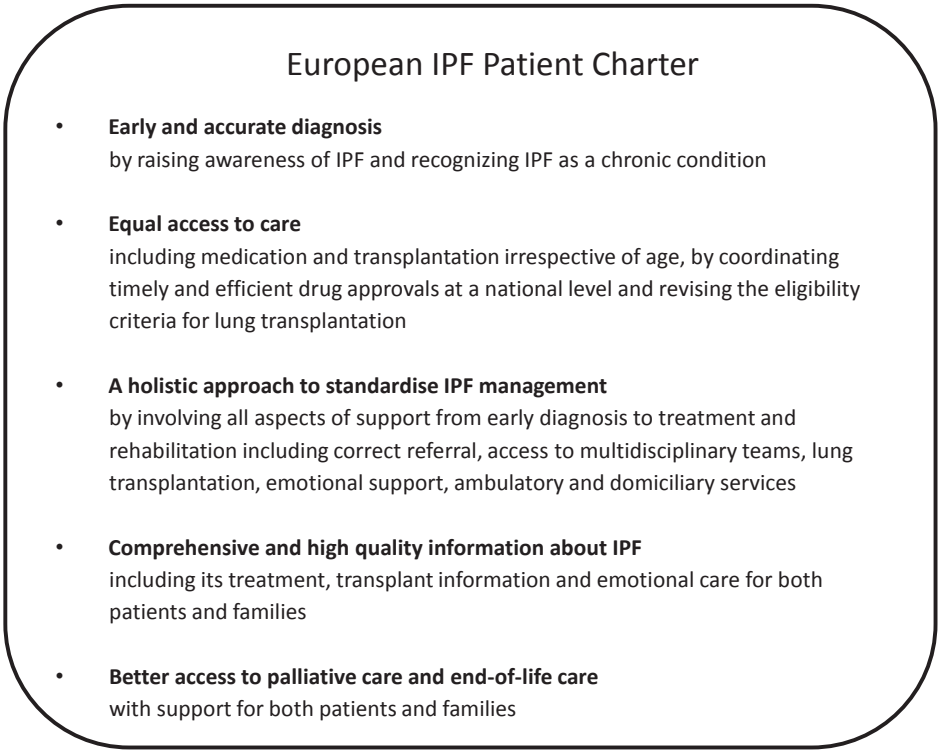

Figure 3. European Idiopathic Pulmonary Fibrosis Patient Charter: five key points.

meaningfully involve patients, caregivers, clinicians and other healthcare stakeholders throughout the research process[24] and provides guidance documents. A unique project in determining domains and outcomes parameters in connective tissue disease-ILD and IPF demonstrated the impact of patients' involvement on the development of the core set of outcome parameters.[25] To patients, cough was an essential parameter that should be included, whilst it did not come out of the Delphi survey of 254 medical experts. The same applied for the patient perspectives on dyspnea and HRQOL, which showed important discordances between healthcare providers and patients. In the Netherlands, the National Pulmonary Foundation (Longfonds) together with patients, health economic experts, government representatives and physicians launched a project to develop a new PREM to better assess patients experience and satisfaction with expensive medication in rare diseases (PESaM-project). These examples of fruitful collaboration between patients and healthcare providers underline the necessity to proceed on this road.[26]

WHAT IS USED IN IDIOPATHIC PULMONARY FIBROSIS?

We can learn from shared experiences of diseases such as chronic obstructive pulmonary disease (COPD) and lung cancer that already have incorporated patient-centered care and have used PROMs much longer.[14,27] IPF has inherent challenges such as the unpredictable disease course and a mostly elderly population, often with co-morbidities, which may also influence HRQOL. In IPF, there has long been an absence of an IPF-specific measure. Mostly used were existing questionnaires that have been adapted from other populations and have subsequently been validated in IPF. For example, the St. George's Respiratory Questionnaire (SGRQ) that was originally developed for COPD has been extensively used in IPF trials and its psychometric properties are well assessed.[28] Only in the trials STEP-IPF (sildenafil) and INPULSIS 2 (nintedanib), some significant favorable changes in SGRQ were seen.[2,29] Its activity domain appears the most sensitive to change in IPF.[2] Although there is also a modified IPF version (SGRQ-I), the experience with this questionnaire is limited.[30] The past years, PROMs also been developed and validated specifically in IPF. The King's Brief Interstitial Lung Disease questionnaire (K-BILD) has been developed in a mixed ILD population including patients with IPF.[31,32] It is short with 15 questions and holds good psychometric properties, and is currently further validated in larger multicultural longitudinal cohorts. The other PROM is A Tool to Assess Quality of Life in IPF (ATAQ-IPF).[33] The original version posed a burden on patients with 89 questions, but the version was reduced to 43 items and validated in the United Kingdom and the United States.[34] However, longitudinal studies on the performance of the K-BILD and ATAQ-IPF over time are still lacking. A recent initiative studied the use of the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) in IPF. PROMIS includes measures of self-reported health and HRQOL for a range of conditions.[6] They found that almost all PROMIS domain scores significantly differed between groups of patients divided according to MRC score and that test-retest reliability was acceptable. Further psychometric validation of the PROMIS-29 is planned.

In IPF, several symptom-specific questionnaires have been used aiming at assessing dyspnea. Patient-reported dyspnea, measured by the MRC dyspnea scale, has been shown to be a predictor of disease progression and survival.[35-37] For dyspnea, the University of California San Diego Shortness of Breath Questionnaire (UCSD)[38] was used as secondary outcome in several clinical trials in IPF. Although in the ASCEND (pirfenidone) trial rate of forced vital capacity (FVC) decline was significantly reduced in the pirfenidone-treated group, no significant effect was found on the UCSD score.[3]

Although cough is one of the symptoms that matter most to patients, experience with cough PROMs in IPF is limited. The Leicester Cough Questionnaire was found to have a high correlation with objective cough frequency measurements and cough visual analogue scales in IPF.[39,40] The cough quality-of-life questionnaire has also been validated in IPF.[41] Both questionnaires need further validation in IPF and are currently included in several trials in IPF (NCT02009293, NCT02502097, NCT01874223). It is intriguing that while fatigue is often a great concern in patients, to our knowledge no validated fatigue PROMs have been used or developed in IPF.

In IPF, PROM-use has mainly been focused on use in clinical trials and registries, though initiatives are taking place to use PROs in a broader sense. For example, in the United Kingdom, the National Institute for Health and Care Excellence developed quality standards incorporating PROMs as performance indicators for ILD specialist centers.[42] In the Netherlands a conditional approval for reimbursement of antifibrotic drugs was granted by the government, requiring a national registry for IPF with physiological outcomes and PROs for all patients treated with antifibrotic medication.[43]

PATIENT-REPORTED OUTCOMES IN IDIOPATHIC PULMONARY FIBROSIS TRIALS

With FVC used as a primary endpoint in the trials of the two drugs that were approved for IPF, there is a strong precedent that new drug trials will also use change in FVC as endpoint.[2,3,44] Even though a physiological endpoint as FVC reflects decline, it does not correlate well with HRQOL in IPF. For instance, K-BILD total and subdomains correlate only moderate with FVC (r=0.47) and transfer factor of the lung for carbon monoxide (TLCO) (r=0.50). For the SGRQ, this is even worse, FVC (r=-0.34), TLCO (r=-0.38).[30,31] Also recently, Ley et al.[45] showed that prediction models that work well for mortality in IPF correlate poorly with functional disease progression, measured with UCSD-SOBQ and 6-minute walk tests. PROMs clearly capture another dimension of disease. All major trials in IPF have used PROMs as secondary outcome measures, but have failed to show a convincing signal (Table 1).[2,3,29,46-54]

We believe there are several potential reasons for this. The most obvious one being the paucity of well-developed and validated IPF-specific PROMs to capture symptoms and

Table 1. Patient-reported outcome measurements used in trials over the past decade

Trial	Treatment	PROM	Outcome
Shionogi[46]	Pirfenidone	Hugh-Jones	ns
		CRQ	ns
IFIGENIA[47]	N-acetylcysteine	SGRQ	ns
Etanercept[48]	Etanercept	SGRQ	ns
		MDI	ns
INSPIRE[49]	IFN-γ	SGRQ	ns
		UCSD	ns
STEP-IPF[29]	Sildenafil	SGRQ	p=0.005
		USCD	p=0.006
		Borg	ns
		SF-36	ns
		EQ-5D	ns
BUILD-3[50]	Bosentan	SF-36	ns
		EQ-5D	ns
CAPACITY 1&2[51]	Pirfenidone	UCSD	ns
BIBF-1120[52]	Nintedanib	SGRQ	150 mg bid, p=0.03
Ambrisentan[53]	Ambrisentan	SGRQ	ns
		TDI	ns
		SF-36	ns
ASCEND[3]	Pirfenidone	UCSD	ns
PANTHER[54]	N-acetylcysteine	SF-36	p=0.03*
		EQ-5D	ns
		SGRQ	ns
		UCSD	ns
		ICE-CAP	p=0.01**
INPULSIS[2]	Nintedanib	SGRQ	ns, INPULSIS2, p=0.02

* mental domain ** summary score

Hugh-Jones, Hugh-Jones Classification Score; CRQ, Chronic Respiratory Questionnaire; EQ-5D, EuroQol-5D; ICE-CAP, ICEpop CAPability measure; MDI, Mahler Dyspnea Index; ns, not significant; SF-36, Short-Form 36; SGRQ, St. George's Respiratory Questionnaire; UCSD, the University of California San Diego shortness of breath questionnaire; Borg, Borg Dyspnea Index; TDI, Transient Dyspnea Index.

burden of disease. Maybe we should also strive for easier straightforward questionnaires that remain close to the day-to-day consultations. Another explanation might be that while we all believe slowing down lung function decline is meaningful, it is the question if this also applies to HRQOL. What is the value of a non-significant improvement or stabilization in HRQOL in a disease with a progressive decline? Minimal important difference (MID) is defined as 'the smallest difference in score in the domain of interest which patients perceive as beneficial which would mandate, in the absence of troublesome side effects and excessive costs a change in patient's (healthcare) management'.[55] Often the MID is not known or only determined in a small subgroup of patients. Also, it might be that disease-modifying treatments do not necessarily improve patients' symptoms and different trial strategies are needed to improve symptoms and HRQOL.

Collaboration between patients, healthcare providers and researcher will be required to fuel advances in this field.

WHICH PATIENT-REPORTED OUTCOME MEASURE SHOULD I CHOOSE FOR MY STUDY?

We believe that PROMs used to date in IPF have not been demonstrated to have the performance characteristics necessary to function as primary endpoints in IPF trials aimed at disease modification. However, in trials aimed at symptom relieve, palliation and improvement of HRQOL, PROMs could hold more prominent endpoint positions, depending on the hypothesis studied. Also, PROMs should be included as secondary or exploratory endpoints in other trials, not only to strive to capture what matters to patients, but also to further develop and validate the instruments in bigger and international cohorts. The choice of PROM will depend on many factors.[8] A PROM must meet certain basic psychometric criteria, especially if it serves as primary endpoint.[12] The FDA has made guidance documents for the use of PROMs.[12] But it is good to realize that validation is an ongoing process and if the choice of PROMs is only based on familiarity and convincing psychometric criteria, PROMs development in IPF will halt, so newer PROMs could well serve as exploratory or secondary endpoints. The intervention being studied should guide the decision on what domains and symptoms are outcomes of interest, for instance, does the investigator wish to assess the severity of cough or the impact on patient's emotional wellbeing. Ideally, this choice should be dominated by the patients' preferences. Also the design of the study, the comparator group and time span are of relevance. In general, the combination of a generic PROM and a disease or even symptom-specific measure is recommended.[8]

CHALLENGES IN PATIENT-REPORTED OUTCOMES

The approval of two drugs for IPF and the fast expansion of studies with promising new compounds, have had a positive effect on interest in PROM development.[2,3] However, there is still a paucity of well-developed and validated IPF PROMs.[4] One of the caveats is the lack of longitudinal data to support validity and assess minimal clinically important differences. Also, currently used scales are often very detailed with the belief that more is better. However, for an individual patient, it will be hard to remember what was scored the previous time, leading likely to changes in scores in every patient, complicating assessment of a meaningful change. Simple, easy to remember scales, like MRC, should be investigated more. Another limitation is that cultural differences are not taking into account; most PROMs are developed in United Kingdom or United States, while international collaboration is needed in IPF trials.[30,31,33,38] PROMs should be linguistically validated for use in other countries, and it is essential to engage patient representatives from different countries and continents throughout the development and validations

process.[12] One of the other challenges in a patient involvement is the burden this may pose on patients especially when disease advances and there is variation in fitness of the patient from day to day. This will require a flexibility of the team in planning and use of technologies to involve patients for whom travelling is too much. Also, partners and caregivers can not only help overcome practical difficulties, but are also an under recognized source of information.[5]

FUTURE PERSPECTIVES

Findings from international registries will provide longitudinal PROM data from different parts of the world in a real life non-selected IPF population.[56-61] The collection of these data will allow for analysis of changes throughout disease course and hopefully guide determination of meaningful and feasible PRO parameters. New structures in organization of care, like the initiative of the European Committee to organize care for rare diseases in European Networks in close collaboration with patient advocacy groups, could facilitate the development and validation of multicultural and multilingual PROMs.[62] New information and communication technologies can facilitate worldwide collaboration. Innovative systems that capture and use PROs are tested. Computerized adaptive testing is a system in which the number and choice of questions are adjusted according to the patient's answers, in this way avoiding non-relevant questions and improving relevance for the patient. The system is used by the NIH PROMIS initiative,[63] but to our knowledge has not been used in IPF yet; it could be of value taking into account the heterogeneity of disease course and burden for patients. With increasing costs and hopefully new drugs, regulatory bodies will ask for proof of value for money. PROMs will play an important role in this, not only reflecting the patients' experiences with new drugs, but also allowing for performance assessment, benchmarking and quality improvement.

CONCLUSION

The use of PROMs holds promises to support changes in how research is done and healthcare is delivered. Although the available tools to explore needs of IPF patients in terms of quality of life are poor, we are undoubtedly at the beginning of a new era. Patients-centered outcome measures focusing on symptoms, psychological and social wellbeing of our patients have the great potential to reveal new aspects to better understand the variable response to treatment and reduce interpretation biases in clinical trials. The next years are likely to bring new well-validated instruments, which will provide useful data to researchers, healthcare providers and policy makers to ameliorate quality and access to IPF care. Patients as partners in care and research are the promise for the future.

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Chapter 3

Validation of the King's Sarcoidosis Questionnaire (KSQ) in a Dutch sarcoidosis population

"The important thing is not to stop questioning"
Albert Einstein

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Mirjam J.G. van Manen[1], Monique Wapenaar[1], Bert Strookappe[2,3], Marjolein Drent[2,4,5], Marjon Elfferich[2,3], Jolanda de Vries[2,6], Harry R. Gosker[7], Surinder S. Birring[8], Amit S. Patel[8], Leon van den Toorn[1], Bernt van den Blink[1], Karin Boomars[1], Elske Hoitsma[3,9], Marlies S. Wijsenbeek[1]

[1]Department of Pulmonary Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands.
[2]Ild care foundation research team, the Netherlands.
[3]Department of Physical Therapy, Hospital Gelderse Vallei Ede, the Netherlands.
[4]Department of Pharmacology and Toxicology, Faculty of Health, Medicine and Life Science, Maastricht University, the Netherlands.
[5]ILD Center of Excellence, St. Antonius Hospital, Nieuwegein, the Netherlands.
[6]Department of Medical Psychology, St. Elisabeth Hospital Tilburg and Department of Medical and Clinical Psychology, Tilburg University, the Netherlands.
[7]NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, Department of Respiratory Medicine, Maastricht, the Netherlands.
[8]Division of Asthma, Allergy and Lung Biology, King's College Hospital, London, UK. [9]Department of Neurology, Alrijne Hospital, Leiden, the Netherlands.

ABSTRACT

Background

The King's Sarcoidosis Questionnaire (KSQ) is a brief questionnaire assessing health status using five modules (General Health Status, Lung, Medication, Skin, Eyes) in patients with sarcoidosis. The KSQ was only validated in one English sarcoidosis cohort.

Objective

The aim of this study was to validate the KSQ in a Dutch sarcoidosis population.

Methods

The KSQ was translated according to international guidelines and tested in interviews with patients. Consecutive outpatients completed multiple questionnaires twice, two weeks apart. Construct validity, internal consistency and repeatability were determined.

Results

Of the 98 patients included 85 had lung, 22 skin and 24 eye disease. There was good construct validity of the KSQ General Health Status module against the World Health Organization Quality of Life-BREF questionnaire. The Medication module correlated weak to moderate with most questionnaires. The correlations with organ-specific questionnaires varied from strong for Eyes (r=0.75), Skin (r=-0.62) to moderate for Lung (r=-0.45 with MRC breathlessness scale). Internal consistency was good for all KSQ modules (Cronbach's α 0.72-0.93). Intraclass correlation coefficients (0.70-0.90) and Bland-Altman plots showed good repeatability of the KSQ.

Conclusion

The Dutch KSQ is the first translation of the English KSQ, validated in a Dutch sarcoidosis population.

INTRODUCTION

Sarcoidosis is a heterogeneous multisystem disease with different clinical phenotypes. Sarcoidosis manifests most commonly in the lungs, but can affect skin, eyes, lymphatic nodes and other organs as well.[1] Health status is impaired in the majority of patients with sarcoidosis due to symptoms such as dyspnea, persistent cough, peripheral pain, fatigue and cognitive dysfunction, leading to limitations in activities, social isolation and depression.[1-3] Therapy for sarcoidosis often leads to side effects impacting health status.[4,5] In recent years patient related outcome measures (PROMs) have gained increasing importance in clinical trials and health status is now a standard outcome measure.[6] Most studies evaluating health status used generic questionnaires such as the World Health Organization Quality of Life-BREF (WHOQOL-BREF) or the MOS 36-item Short Form Health Survey (SF-36), both non-disease specific questionnaires.[7-12] Currently, no sarcoidosis specific instruments measuring health status in patients with sarcoidosis are available in Dutch. In 2012 the King's Sarcoidosis Questionnaire (KSQ) was developed.[13] This self-administered measure for sarcoidosis covers different domains of health status; General Health Status (GHS), Lung (L), Medication (M), Skin (S) and Eyes (E). The aim of this study was to validate the KSQ in a Dutch sarcoidosis population.

METHODS

Translation validation

The KSQ was translated from English to Dutch according to a multi-step forward-backward procedure, following international guidelines[14-16] and was reviewed by sarcoidosis experts and the developers (online supplement 1). The relevance and applicability of the translated KSQ was tested using ten structured patient interviews.

Psychometric validation

Subjects

In July 2014 consecutive sarcoidosis outpatients of the pulmonary department of the Erasmus Medical Center were asked to participate. During the same period sarcoidosis outpatients of the ild care team, Hospital Gelderse Vallei were approached by email. Patients were excluded from the study if they were unable to understand questionnaires due to intellectual impairment or language barrier, when comorbidities that severely impact health status existed (such as malignancies, collagen vascular diseases and cardiac failure other than due to sarcoidosis) or when they had unstable disease as considered by the treating physician. If patients completed less than 85% of a questionnaire they were withdrawn from the study. Formal consultation with the Medical Ethical Committee of the Erasmus Medical Center learnt that, under the Dutch act for medical research involving human subjects (Wet Medisch Onderzoek), approval of this study by the Medical Ethical Committee is not required.

Study procedure

All patients were asked to complete up to seven questionnaires (depending on organ involvement) in addition to the KSQ: WHOQOL-BREF,[7] Fatigue Assessment Scale (FAS),[17] Small Fiber Neuropathy Screening List (SFNSL),[18] Medical Research Council dyspnea scale (MRC dyspnea scale),[19] Dermatology Life Quality Index (DLQI),[20] National Eye Institute Visual Function Questionnaire (NEI-VFQ25)[21] and Euroqol-5D-5 level (EQ-5D-5L).[22] Online supplement 2 shows the organ specific questionnaires and corresponding KSQ modules. Patients also completed two general health status measurements: Punum Ladders[23] and Global Rating of Change-Quality of Life (GRC-QoL).[24] Patients were asked to self-complete the questionnaires at home, two weeks apart.

Results of routinely measured pulmonary function outcomes were gathered from the medical records. The diagnosis of sarcoidosis was established when there was compatible clinical behaviour and pathological or BAL confirmation, according to international guidelines.[25] Patients were asked about their organ involvement during a short face to face interview or interview by telephone.

Statistical analysis

Data are presented as mean values (± standard deviation). KSQ scores were calculated on a logit scale as this scale is more linear and has the potential to perform better at the extreme ends of health related QoL.[26] The validity of the KSQ remains unchanged from the original format.[27] Construct validity between the general and organ specific domains of KSQ and the corresponding questionnaires were determined using Pearson's correlation coefficients. A correlation coefficient of < 0.30 is considered weak, 0.30 – 0.50 moderate and > 0.50 strong.[16] Cronbach's α coefficient was used to determine the internal consistency of the reliability of the KSQ. A minimum of 0.70 is considered a good internal consistency. Bland-Altman plots and intraclass correlation coefficients were used to evaluate the repeatability at baseline and at two weeks, in patients with stable disease. To assess stable disease we used Punum ladders.[23] Patients with ≥ 4 differences in Punum score were excluded in the repeatability analyses. The limits of agreement were calculated as mean ± 1.96 X SD of within-subject differences. Values of $p < 0.05$ were considered statistically significant. All data were analyzed with SPSS version 21.

RESULTS

Translation validation

A Dutch version of the KSQ, achieved after forward and backward translation, was approved by the KSQ developers. Following this approval, ten patient interviews with the Dutch version of the KSQ took place (step T3 online supplement 1). Discussion of these interview results with the KSQ developers did not necessitate any further adaptations of the translation and resulted in the final Dutch KSQ-version (online supplement 3).

Psychometric validation

One hundred and four consecutive outpatients in the Erasmus Medical Center were evaluated for participation, 89 were interested and 54 participated in this study. At the same time 117 patients of the ild care team, Hospital Gelderse Vallei were approached by email, 60 patients responded and 44 were recruited. Reasons for exclusion were: clinical instability (15), comorbidity that severely impacted quality of life (14), no PA/BAL confirmation (9), not able to read or write Dutch (5) or other reasons (8) (not willing to participate, not reachable by telephone or by email, participating in another study). Thus in total 98 patients were included. Eighty-eight (90%) of them completed week zero and 83 (85%) week two (figure 1).

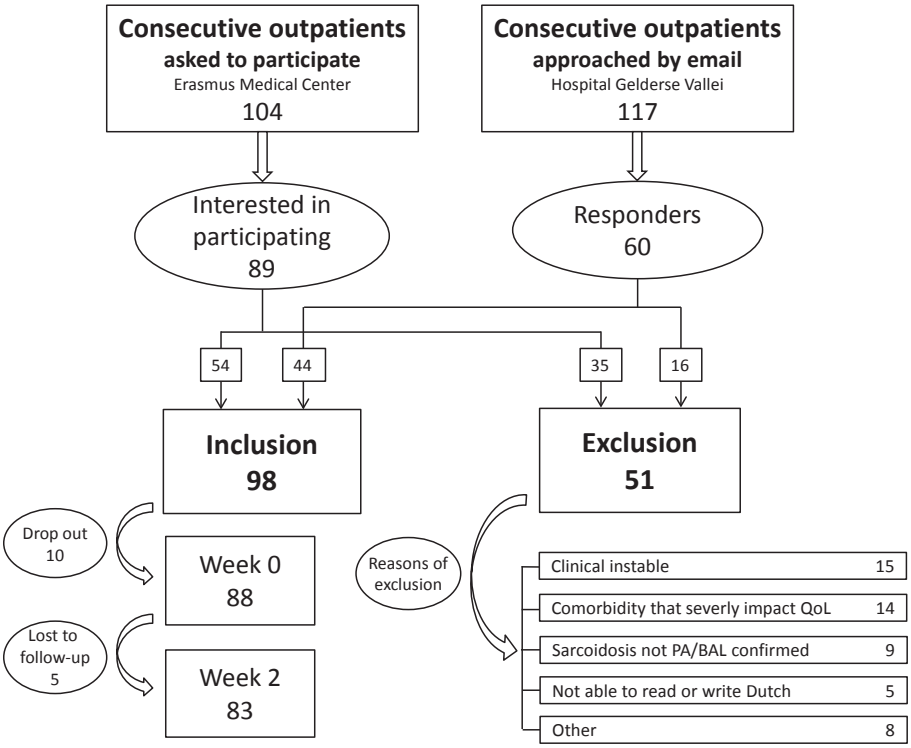

Figure 1. Study design

Demographics

Table 1 shows the demographics of the patients included. Patients with two or more organs involved showed a significantly worse health status than patients with single-organ disease: mean (SEM) KSQ GHS score 53(1.6) versus 68(3.7); mean difference 15; 95% Confidence Interval (CI) 7-23; p = 0.001. No significant difference was found between the KSQ GHS score for females compared with males: mean (SEM) 54 (2.5) versus 60 (2.3); mean difference 5; 95% CI 1-12, p = 0.115. Patients with more complaints of fatigue (FAS score ≥ 22) have a significantly worse health status (mean (SEM) KSQ GHS

52(1.5)), than those with lower FAS scores (mean (SEM) 76(3.2); mean difference KSQ GHS -24; 95% CI -30 to -17, p = 0.000).

Construct validity

The correlations between the KSQ GHS domain and all generic questionnaires (WHOQOL-BREF and EQ-5D-5L) were strong (r= 0.50 – 0.84). KSQ organ modules combined with the GHS module all showed a moderate to strong correlation with the WHOQOL-BREF and EQ-5D-5L (r= 0.44 – 0.85). The Medication module showed a weak to moderate correlation with the generic questionnaires (r= 0.26 – 0.47) (Table 2).

All KSQ modules correlated moderately to strongly with the FAS. The relationship between the KSQ organ-specific modules and their corresponding organ-specific questionnaires was also moderate to strong. The Lung module was weakly correlated with the FVC% predicted (r= 0.24) (Table 2).

Table 1. Patient demographics

		Organ involvement		
	All patients	Lung	Skin	Eyes
Number	88	85	22	24
Age, years, mean (SD)	52 (11)	51 (11)	52 (11)	52 (13)
Women, n (%)	36 (41)	35 (41)	10 (46)	11 (46)
Ethnicity, n (%)				
Caucasian	70 (80)	67 (79)	17 (77)	16 (67)
Afro-American	2 (2)	2 (2)	-	-
Surinamese-Hindi	13 (15)	13 (15)	4 (18)	5 (21)
Morrocan	2 (2)	2 (2)	1 (5)	2 (8)
Unknown	1 (1)	1 (1)	-	1 (4)
Smoking status, n (%)				
Current	3 (3)	3 (4)	-	1 (4)
Ex	15 (17)	15 (18)	5 (23)	8 (33)
Never	64 (73)	61 (72)	15 (68)	12 (50)
Unknown	6 (7)	6 (7)	2 (9)	3 (13)
Time since diagnosis, years, mean (SD)	8.0 (8.8)	8.1 (8.9)	7.4 (10.5)	8.4 (11.2)
Organs involved, n (%)				
Lungs	85 (97)			
Skin	22 (25)			
Eyes	24 (27)			
Small nerve fibers	26 (30)			
FVC % predicted, mean (SD), [n]	92 (20) [84]	91 (20) [81]		
FEV1/FVC ratio % predicted, mean, [n]	76 (13) [74]	76 (13) [72]		
TLCOc % predicted, mean (SD) , [n]	81 (21) [73]	81 (21) [70]		
TLC % predicted, mean (SD) , [n]	86 (18) [57]	86 (18) [56]		

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; TLCO, diffusing capacity of the lung for carbon monoxide, corrected for hemoglobin level; TLC, total lung capacity as % predicted.

Table 2. The relationship between KSQ and disease-specific outcome measures

	Generic QoL						Fatigue	Lung		Skin	Eye	SFN
	WHOQOL-BREF				EQ-5D-5L		FAS	FVC	MRC	DLQI	NEIVFQ-25	SFNSL
	DOM1	DOM2	DOM3	DOM4	Index Value	VAS	Total	%Pred	Breathlessness	Total	Total	Total
KSQ modules												
General Health Status	0.84	0.70	0.61	0.50	0.69	0.67	-0.81	-	-0.29	-0.43*	0.52	-0.60
Lung	0.55	0.52	0.47	0.44	0.55	0.39	-0.63	0.24*	-0.45	-	-	-0.56
Skin	0.37**	0.46*	0.35**	0.44*	0.48*	0.32**	-0.50*	-	-	-0.62	-	-0.37**
Eyes	0.36**	0.32**	0.51*	0.45*	0.49*	0.28**	-0.56	-	-	-	0.75	-0.59
Medication	0.47	0.31	0.28*	0.36	0.30	0.26*	-0.39	-	-0.19**	-0.45**	0.66	-0.33
Overall Health Status												
Lung + GHS	0.79	0.68	0.60	0.52	0.68	0.59	-0.79	0.15**	-0.40	-	-	-0.64
Skin + GHS	0.85	0.83	0.70	0.64	0.61	0.44*	-0.76	-	-	-0.51*	-	-0.63
Eyes + GHS	0.72	0.56	0.62	0.58	0.81	0.68	-0.74	-	-	-	0.75	-0.69
Lung + Skin + GHS	0.77	0.76	0.65	0.65	0.58	0.35**	-0.72	0.18**	-0.13**	-0.60	-	-0.64

Data shown are Pearson's correlation coefficients for organ-specific comparisons. All p<0.01 except *p<0.05 and >0.01 and **p>0.05 (not significant). WHOQOL-BREF, World Health Organization Quality of Life-Brief questionnaire; DOM1 = physical, DOM2 = psychological, DOM3 = social relationships, DOM4 = environment; EQ-5D-5L, Euroqol-5D-5 level; FAS, Fatigue Assessment Scale, FVC, forced vital capacity; MRC, Medical Research Council dyspnea scale; DLQI, Dermatology Life Quality Index; NEIVFQ-25, National Eye Institute Visual Function Questionnaire-25; SFN, small fiber neuropathy, SFNSL, Small Fiber Neuropathy Screening List.

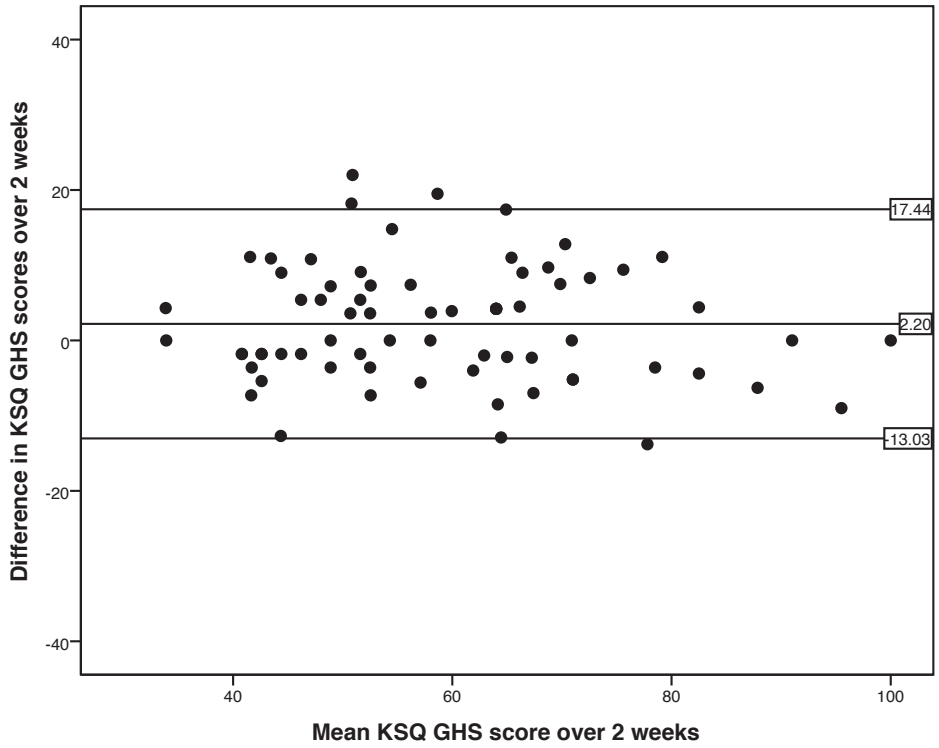

Figure 2. Bland Altman plot of repeatability of King's Sarcoidosis Questionnaire General Health Status module. Solid line represents mean difference and dashed lines represent 95% limits of agreement

Reliability

All domains of the KSQ had good internal consistency, Cronbach α; 0.90 (GHS), 0.91 (Lung), 0.72 (Medication), 0.84 (Skin), and 0.93 (Eyes). With regard to the repeatability (test-retest) 83 patients (lung n= 80, skin n= 20 and eyes n= 22) completed the KSQ twice. The following intraclass correlations were found: GHS 0.85, Lung 0.74, Medication 0.70, Skin 0.77, Eyes 0.90, suggesting a good reliability. Twelve patients in the GHS and 13 patients in the Lung module groups were excluded from the analysis for repeatability, because they did not show stability in their Punum scores. The Bland-Altman plots in figure 2 and 3 show the repeatability of the KSQ GHS and Lung module, respectively. Both plots have a few outliers (outside the 95% of limits of agreement). We found a mean difference between the first and second measurement of 2.20 in the KSQ GHS module and 2.45 in the Lung module.

DISCUSSION

The Dutch KSQ is the first health status questionnaire for sarcoidosis in the Netherlands. It is also the first non-English validation of the questionnaire. The KSQ is simple to ad-

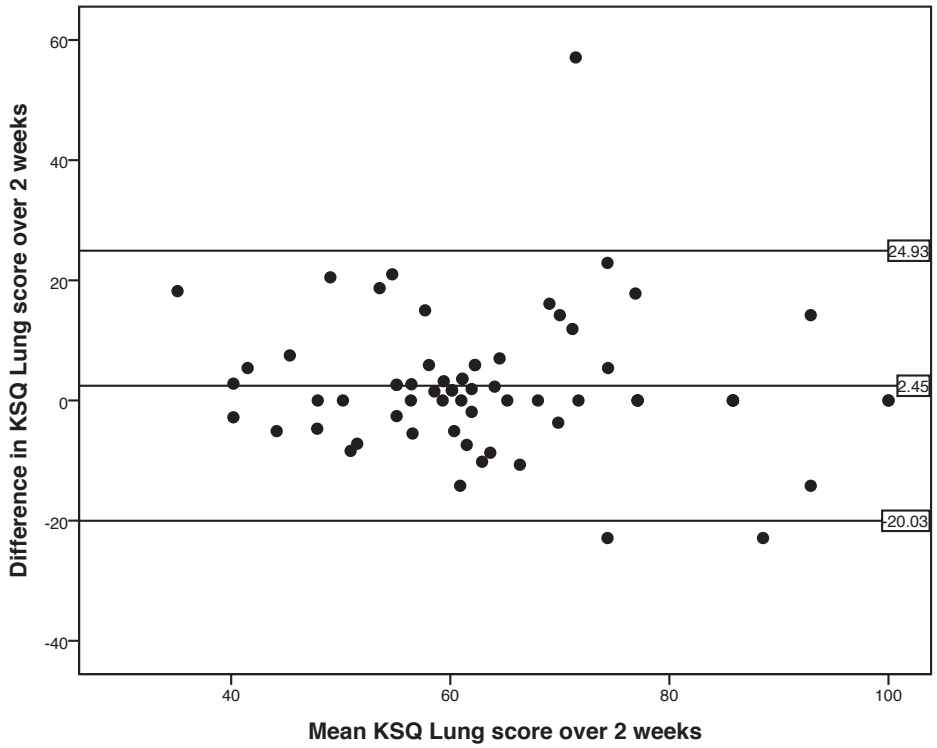

Figure 3. Bland Altman plot of repeatability of King's Sarcoidosis Questionnaire Lung module.
Solid line represents mean difference and dashed lines represent 95% limits of agreement

minister, adaptable to individual organ involvement and shown to be a valid and reliable health status measurement in Dutch patients with sarcoidosis.

PROMs are becoming more important in clinical trials and daily care.[6] Health status is nowadays a standard outcome measure. Most sarcoidosis studies use non-disease specific questionnaires such as the WHOQOL-BREF and the SF-36.[10-12] The KSQ is a self-administered sarcoidosis specific instrument. The KSQ questionnaire was originally developed in the UK and was not available in languages other than English. The availability of the KSQ in other languages could facilitate international collaboration aiming at measuring, comparing and improving health status in patients with sarcoidosis, which is often severely affected. During translation in Dutch and the patient interviews no major cultural difference was noted and the questionnaire was considered comprehensible and relevant by Dutch patients.

The patient demographics of the current Dutch study population were in line with the original study, though there were slightly more Caucasians in our study and lung function was less severely affected.[13] Quality of life was worse in females similar to Patel et al. but in contrast did not reach statistical significance.[13,28]

The following domains of health status are covered in the KSQ: General Health Status, Lung, Medication, Skin and Eyes. Construct validity of the organ-specific questionnaires with their corresponding modules is similar to the development paper.[13] The KSQ Lung module showed a weaker correlation with the MRC. In the original article from Patel et al. the MRC dyspnea scale as well as the St. George Respiratory Questionnaire (SGRQ) was used. They found a Pearson's correlation of -0.58 for the MRC dyspnea scale and -0.85 for the SGRQ. It therefore seems that the MRC dyspnea scale is a less reliable tool to assess construct validity in this population. We did not include the SGRQ, because of the high number of questionnaires patients had to complete for validation and we feared this would lead to 'questionnaire fatigue'. Moreover, the SGRQ is a disease-specific questionnaire developed for chronic obstructive pulmonary disease, with 50 items and no questions about skin or eye involvement.

We found a difference in study population between Patel et al. and ours; our population had less patients with a severe impairment of the lungs, which is shown in the difference in TLCOc% predicted (63 vs. 81 in our group).[13] This could also explain the weaker correlation found between the Lung module and FVC% predicted (r= 0.24). To date, this lack of correlation between health status questionnaires and lung function has often been reported in other pulmonary diseases as well.[29] This underlines the idea that health status questionnaires measure different aspects of disease severity and therefore are a very important additional outcome measures. When combined with the KSQ GHS module all organ-specific KSQ modules showed a better correlation with the generic questionnaires. This supports the use of organ-specific modules in combination with the GHS module.

Fatigue is a major problem in patients with sarcoidosis with an important impact on health status.[30] This was reflected by a strong correlation between the FAS and GHS. This confirms that the KSQ also captures the health status caused by fatigue.[13] Our results are in line with other studies showing the major effect of fatigue on the wellbeing of patients.[30]

Small fiber neuropathy related symptoms, which are disabling and difficult to control, can also significantly reduce health status.[31] We chose to include the SFNSL questionnaire to evaluate if the KSQ also captures this problem as this had not been evaluated before. Strong correlations with the SFNSL were found by combining the KSQ GHS and the organ-specific KSQ modules. This suggests the KSQ captures the small fiber neuropathy related influences on health status.

In line with Patel et al. findings, weak to moderate correlations were found between the optional Medication module and almost all questionnaires.[13] Therapy for sarcoidosis, as for instance corticosteroids, often causes burdensome side effects. It is tempting to speculate that these side effects may have affected health status more than the symptoms of sarcoidosis. In both Patel et al. and the present study the Medication module

does not contribute much. Longitudinal studies are needed with changes in medication to see if the KSQ captures influences of medication on health status.

According to the study of Patel and colleagues, we found that the KSQ has a good internal consistency.[13] Reliability was also assessed with Bland-Altman plots showing good repeatability (test-retest) in measurements.

At the time of this study, the Sarcoidosis Health Status Questionnaire (SHQ) was the only alternative sarcoidosis health status questionnaire.[32] In our view this 29-item instrument, developed in 2001, has some important limitations. It contains only few organ-specific questions, has not been validated for eye and skin disease and can, therefore, not be tailored to individual clinical phenotypes. Furthermore, the SHQ is mostly longer than the KSQ, because most patients do not have to fill in all the organ-specific KSQ modules. Recently, Judson et al. validated a new patient reported outcome measure, the Sarcoidosis Assessment Tool (SAT).[31,33] The SAT was constructed in a similar way as the KSQ and also consists of organ-specific modules. With 51 questions it is considerably longer than the KSQ. The SAT was validated in an interventional study giving the advantage that the MCID has been calculated.[5] However, to our knowledge repeatability has not yet fully been assessed making it difficult to conclude if a difference in scores indicates a low repeatability or a true change in health status. It would be valuable to compare the different sarcoidosis questionnaires prospectively.

In sarcoidosis any organ can be involved and it remains unclear if the KSQ will also capture the impact of more rare forms of sarcoidosis on health status. Another limitation of our study is the lack of follow-up after two weeks. Responsiveness of the questionnaire can thereby not be assessed. Further research, through longitudinal studies in larger patient cohorts, is warranted to determine the responsiveness, the influence of rarer disease forms and the value of the Medication module.

In conclusion, the Dutch KSQ is the first translation of the English KSQ, validated in a Dutch sarcoidosis population.

ACKNOWLEDGEMENT

The ild care foundation supported the translation procedure of the KSQ and granted the use of the FAS and SFNSL questionnaire for this study. We would like to thank Femke Muskens and Linda Kneppers - de Groot for their assistance in processing the data.

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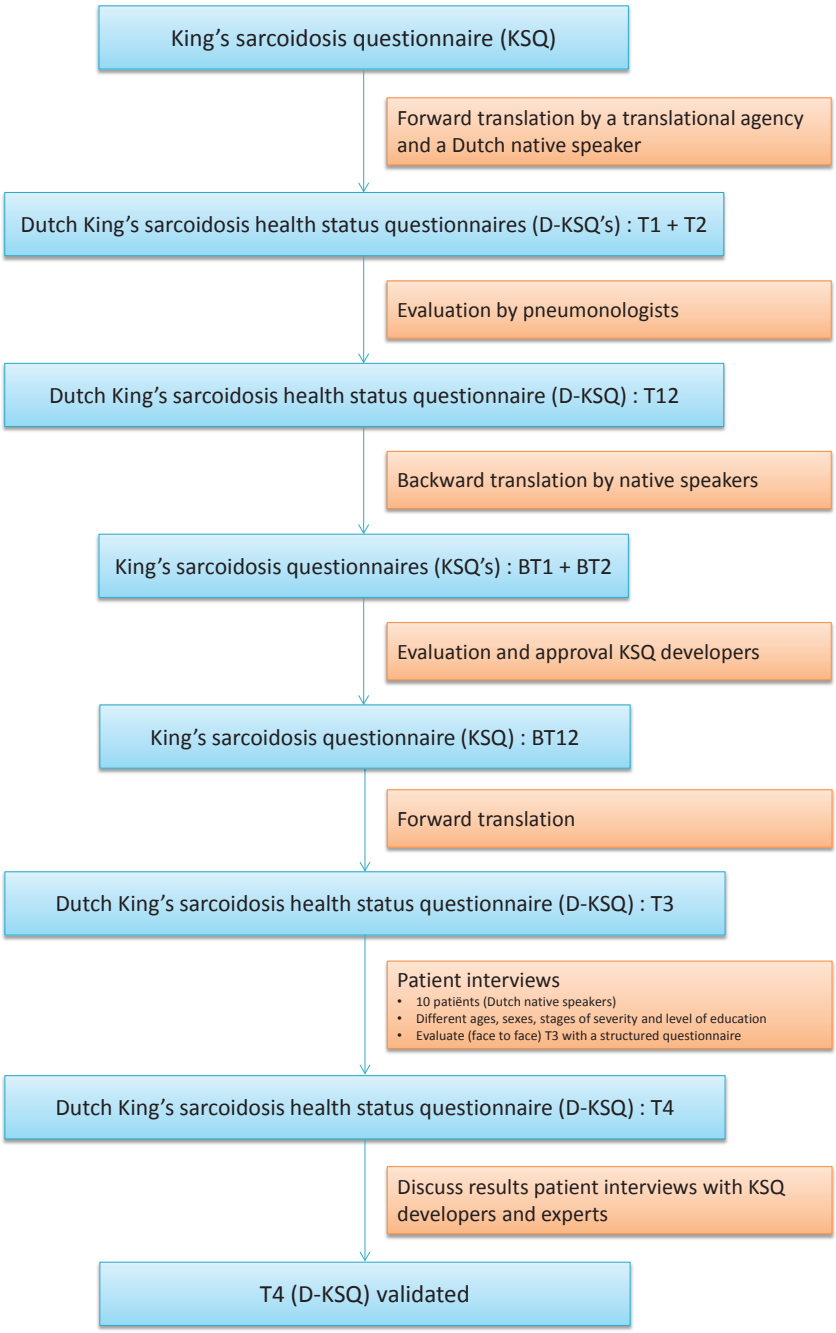
SUPPLEMENTAL



Online supplement 1. Translation procedure

Online Supplement 2. Depending on their organs affected patients will be asked to complete specific questionnaires

Questionnaire	KSQ (GHS + M)	KSQ (L)	KSQ (S)	KSQ (E)	MRC	DLQI	NEI-VFQ25
Organ(s) affected							
Lung	X	X			X		
Skin	X		X			X	
Eyes	X			X			X
Lung, Skin	X	X	X		X	X	
Lung, Eyes	X	X		X	X		X
Skin, Eyes	X		X	X		X	X
Lung, Skin, Eyes	X	X	X	X	X	X	X

KSQ, King's Sarcoidosis Questionnaire; GHS, General Health Status; M, Medication; L, Lung; E, Eyes; MRC, Medical Research Council; DLQI, Dermatology Life Quality Index; NEIVFQ-25, National Eye Institute Visual Function Questionnaire-25

.

Online supplement 3. The Dutch King's Sarcoidosis Questionnaire

King's Sarcoïdose Vragenlijst (KSQ)

Invuldatum: .....

Het doel van deze vragenlijst is het bepalen van de invloed van sarcoïdose op verschillende aspecten van uw leven. Lees elke vraag zorgvuldig door en omcirkel het antwoord dat het meest op u van toepassing is. Beantwoord ALLE vragen zo eerlijk mogelijk. Deze vragenlijst is vertrouwelijk. Alle vragen hebben betrekking op de manier waarop **SARCOIDOSE** uw gezondheid heeft beïnvloed.

ALGEMENE GEZONDHEIDSTOESTAND

	In de laatste 2 weken ...	De hele tijd	Het grootste deel van de tijd	Een flink deel van de tijd	Een deel van de tijd	Een klein deel van de tijd	Heel zelden	Helemaal niet
1	Heb ik me gefrustreerd gevoeld	1	2	3	4	5	6	7
2	Heb ik moeite gehad me te concentreren	1	2	3	4	5	6	7
3	Heb ik onvoldoende motivatie gehad	1	2	3	4	5	6	7
4	Heb ik me moe gevoeld	1	2	3	4	5	6	7
5	Heb ik me zorgen gemaakt	1	2	3	4	5	6	7
6	Heb ik last of pijn in mijn spieren/gewrichten gehad	1	2	3	4	5	6	7
7	Heb ik me geschaamd	1	2	3	4	5	6	7
8	Heb ik me zorgen gemaakt over mijn gewicht	1	2	3	4	5	6	7
9	Heb ik me zorgen gemaakt over mijn sarcoïdose	1	2	3	4	5	6	7
	In de laatste 2 weken ...	**Zeer sterk**	**Behoorlijk sterk**	**Matig sterk**	**Enigszins**	**Weinig**	**Zeer weinig**	**Niet**
10	Heeft vermoeidheid mij gehinderd bij mijn normale sociale activiteiten, zoals uitgaan met vrienden of familie	1	2	3	4	5	6	7

LONG

	In de laatste 2 weken …	De hele tijd	Het grootste deel van de tijd	Een flink deel van de tijd	Een deel van de tijd	Een klein deel van de tijd	Heel zelden	Helemaal niet
11	Heb ik pijn/ongemak gehad door het hoesten	1	2	3	4	5	6	7
12	Ben ik buiten adem geraakt als ik de trap op klom of een flauwe helling op liep	1	2	3	4	5	6	7
13	Heb ik diep moeten ademhalen, ook bekend als “snakken naar adem”	1	2	3	4	5	6	7
14	Heb ik me benauwd op de borst gevoeld	1	2	3	4	5	6	7
15	Heb ik perioden van benauwdheid gehad	1	2	3	4	5	6	7
16	Heb ik last gehad van pijn op de borst	1	2	3	4	5	6	7

MEDICATIE

Gebruikt u medicatie voor uw sarcoïdose?

JA O NEE O (ga naar het volgende onderdeel)

	In de laatste 2 weken …	Zeer sterk	Behoorlijk sterk	Matig sterk	Enigszins	Weinig	Zeer weinig	Niet
17	Heb ik me zorgen gemaakt over bijwerkingen van mijn medicijnen	1	2	3	4	5	6	7
18	Heb ik me slechter gevoeld door mijn medicijnen voor sarcoïdose	1	2	3	4	5	6	7
19	Ben ik aangekomen door mijn medicijnen voor sarcoïdose	1	2	3	4	5	6	7

HUID

	In de laatste 2 weken …	Zeer sterk	Behoorlijk sterk	Matig sterk	Enigszins	Weinig	Zeer weinig	Niet
20	Heb ik last gehad van mijn huidproblemen	1	2	3	4	5	6	7
21	Heb ik me zorgen gemaakt over veranderingen in de kleur van mijn huidafwijkingen	1	2	3	4	5	6	7
	In de laatste 2 weken …	**De hele tijd**	**Het grootste deel van de tijd**	**Een flink deel van de tijd**	**Een deel van de tijd**	**Een klein deel van de tijd**	**Heel zelden**	**Helemaal niet**
22	Heb ik mij geschaamd vanwege mijn huid	1	2	3	4	5	6	7

OGEN

	In de laatste 2 weken …	De hele tijd	Het grootste deel van de tijd	Een flink deel van de tijd	Een deel van de tijd	Een klein deel van de tijd	Heel zelden	Helemaal niet
23	Heb ik droge ogen gehad	1	2	3	4	5	6	7
24	Heb ik problemen gehad met fel licht	1	2	3	4	5	6	7
25	Zijn mijn ogen rood geweest	1	2	3	4	5	6	7
26	Heb ik pijn in of rond mijn ogen gehad	1	2	3	4	5	6	7
27	Heb ik moeite gehad met lezen	1	2	3	4	5	6	7
	In de laatste 2 weken …	**Zeer sterk**	**Behoorlijk sterk**	**Matig sterk**	**Enigszins**	**Weinig**	**Zeer weinig**	**Niet**
28	Heb ik last gehad van wazig zien	1	2	3	4	5	6	7
29	Heb ik me zorgen gemaakt over mijn gezichtsvermogen	1	2	3	4	5	6	7

Einde vragenlijst

Chapter 4

Scalp hair cortisol and testosterone as objective biomarkers for psychological distress and fatigue in patients with sarcoidosis

"When there is too much stress or worry, look within"
Dalai Lama

Under review

M.J.G. van Manen[1*], V.L. Wester[2*], E.F.C. van Rossum[2], L.M. van den Toorn[1], B. van den Blink[1], K.Y. Dorst[3], Y.B. de Rijke[3], H.C. Hoogsteden[1], M.S. Wijsenbeek[1]

[1] Department of Respiratory Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands

[2] Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands

[3] Department of Clinical Chemistry, Erasmus University Medical Center, Rotterdam, the Netherlands

[*] Both authors contributed equally

ABSTRACT

Background

Patients with sarcoidosis often experience fatigue and psychological distress, but little is known about the etiology of these conditions. While serum and saliva cortisol levels are used to monitor acute stress, scalp hair analysis is a new method enabling measurement of long-term steroid levels. We investigated whether scalp hair cortisol and testosterone levels differ between sarcoidosis patients both with and without fatigue and general population controls. Additionally, we studied if these hormones could serve as objective biomarkers for psychological distress in sarcoidosis.

Methods

We measured hair steroid levels using liquid chromatography-tandem mass spectrometry in glucocorticoid naïve sarcoidosis patients. Patients completed the Perceived Stress Scale, Fatigue Assessment Scale, Hospital Anxiety and Depression Scale and Short Form 36 (SF-36). Hair steroid levels from 293 participants of the Lifelines cohort study served as controls.

Results

Thirty-two patients (14 males) were included. Hair cortisol concentrations were significantly higher in sarcoidosis patients than in general population controls (mean 6.6 versus 2.7 pg/mg, $p<0.001$). No differences were found in hair cortisol and testosterone levels between fatigued and non-fatigued sarcoidosis patients. Hair cortisol of sarcoidosis patients correlated significantly with anxiety ($r=0.47$, $p=0.01$), depression ($r=0.46$, $p=0.01$), and SF-36 mental domain ($r=-0.38$, $p=0.03$), but not with fatigue.

Conclusions

Patients with sarcoidosis have chronically higher levels of the stress hormone cortisol than the normal population. Hair cortisol levels were positively related to subjective measures of psychological distress, but not fatigue. Our study shows that hair cortisol is a promising non-invasive biomarker for psychological distress in patients with sarcoidosis.

BACKGROUND

Sarcoidosis is a multi-organ disease of unknown etiology, characterized by non-caseating granulomas, which commonly occur in the lymph nodes, lungs, skin and eyes.[1] In patients with sarcoidosis, fatigue and psychological distress are frequently reported problems.[2-5] Fatigue has been reported in 50-70% of the sarcoidosis patients.[3] Even when sarcoidosis is in clinical remission, fatigue may persist chronically and cause impaired quality of life (QoL) and reduced socio-economical participation.[6] The exact mechanism for chronic fatigue in sarcoidosis is currently unknown.

Stress might be one of the factors contributing to the onset of fatigue. Chronic fatigue in sarcoidosis patients has been associated with increased levels of perceived stress and psychological stressors such as depression and anxiety.[4-6] Psychological and physical stressors lead to activation of the hypothalamus-pituitary-adrenal axis, resulting in an increase in circulating levels of the stress hormone cortisol.[7] Cortisol, in turn, influences a wide range of bodily functions including metabolism, behavior and immunity.[7] Stress can be assessed subjectively using validated questionnaires, but cortisol levels can also be used as a biomarker for stress.[8,9] Systemic inflammation in chronic diseases has been associated with fatigue, and may affect cortisol levels as well.[10,11] While stress and inflammation are both associated with increased levels of cortisol, there are also studies that show evidence of hypocortisolism in relation to chronic fatigue,[12,13] thereby leaving the relationship between cortisol and fatigue in sarcoidosis unclear.

In male patients with sarcoidosis, another potential factor contributing to fatigue may be hypogonadism, with its consequent low levels of testosterone. Serum testosterone has shown to be significantly decreased in patients with chronic lung disease,[14,15] and has also been inversely related to fatigue in patients with advanced cancer and obstructive sleep apnea.[15,16] In a study of 30 patients with sarcoidosis, almost half of the patients had lower circulating testosterone levels than healthy controls; however, this study did not assess the relationship with fatigue.[17]

Both cortisol and testosterone are commonly measured in blood, urine, or saliva. However, these tests reflect only short-term exposure, and levels of cortisol and testosterone can greatly fluctuate within and across days.[7,18] Moreover, the tests themselves can induce stress and increase cortisol levels.[19]

In this study, we use a relatively novel method: scalp hair analysis to measure long-term cortisol, cortisone, and testosterone levels. This method has been validated in other – non pulmonary - diseases and allows a retrospective measurement of the endogenous production of these hormones over months of time, based on an average hair growth of approximately 1 cm per month.[20] Previous studies have shown that hair cortisol can serve as a biomarker for chronic stress.[9,21]

To the best of our knowledge, no studies have investigated hair steroid biomarkers, such as cortisol, cortisone and testosterone, in sarcoidosis. This non-invasive method could potentially give new insights into the mechanism of fatigue and psychological distress in sarcoidosis. Moreover, it may be used as a screening and follow-up tool to objectively measure fatigue and psychological distress as an alternative to the currently used subjective patient-reported outcome measures.

In this explorative study, we aimed to investigate whether scalp hair cortisol, cortisone, and testosterone levels differ between sarcoidosis patients both with and without fatigue and general population controls. Additionally, we studied if these scalp hair steroid levels could serve as an objective biomarker for psychological distress, fatigue and/or other clinical outcomes in patients with sarcoidosis.

METHODS

Study design and population

We conducted a prospective observational study. Sarcoidosis patients were recruited during their regular follow-ups at the outpatient clinic of the pulmonary department of the Erasmus University Medical Center, Rotterdam, the Netherlands, from June till December 2014. Patients aged 18 or older were included if they had been diagnosed with sarcoidosis according to the latest ATS/ERS/WASOG statement on sarcoidosis,[1] and if they had sufficient knowledge of the Dutch language. We aimed to include 20 patients with fatigue and 10 without fatigue. Fatigue was defined as a score of 22 or higher on the Fatigue Assessment Scale (FAS).[22] Other causes of fatigue had to be excluded or, in the case of contributing comorbidities (e.g. obstructive sleep apnea syndrome, hypothyroidism or anemia), optimally treated. Patients were excluded if they had a hair length of less than 1 cm, had used systemic and/or inhalation steroids in the last year, or had taken methylphenidate less than 1 month before the study. Scalp hair steroid levels of participants of the Dutch population-based Lifelines cohort study were used as general population controls.[23,24] Formal consultation with the Medical Ethical Committee of the Erasmus Medical Center affirmed that, under the Dutch act for medical research involving human subjects (Wet Medisch Onderzoek), approval of this study by the Medical Ethical Committee was not required (MEC-2014-206). All patients gave written informed consent.

Procedures

Hair sample collection and processing

In each subject, a small hair sample of approximately 150 hairs was cut from the posterior vertex as close to the scalp as possible using small scissors. Hair samples were taped on paper and stored in envelopes at room temperature. The hair samples of all patients were analyzed in one batch at the diagnostic endocrine laboratory of the internal medicine department of the Erasmus MC, Rotterdam. For analyses, hair samples

were divided in segments of 1 cm, weighed, washed, and steroids were extracted with methanol. Subsequently, hair cortisol, cortisone, and testosterone were analyzed with liquid chromatography-tandem mass spectrometry (LC-MS/MS) (figure 1). A detailed description on scalp hair analysis is available in a previous publication by Noppe and de Rijke et al.[25]

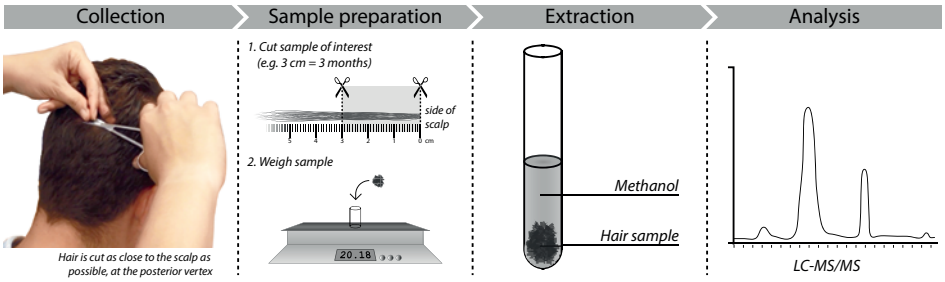


Figure 1. Scalp hair analysis: hair sample collection, pre-treatment and analysis
LC-MS/MS, liquid chromatography-tandem mass spectrometry. Modified from[20] with permission from the publisher.

Questionnaires

Patients filled in the FAS at the outpatient clinic. Other questionnaires were completed at home as soon as possible, but within a maximum of two weeks from the clinic visit. The 10-item FAS measures fatigue and has been well-validated in patients with sarcoidosis.[3,26] Scores range from 10 to 50, with higher scores indicating more fatigue, a FAS score of ≥22 is considered as significant fatigue.[27] Subjective health status was evaluated with standardized self-reported generic instruments, the Euroqol-5D 5-level (EQ5D5L), and the 36-item medical outcomes short form 36 (SF-36), with higher scores representing better health status.[28] The King's Sarcoidosis Questionnaire (KSQ) was used to measure disease-specific health status and consists of five modules: General health status, Lung, Medication, Skin, and Eye.[29,30] All domain scores range from 0 to 100, with a higher score representing a better disease-specific health status.[29] The 14-item Perceived Stress Scale (PSS) is a broad score to assess a person's perception of stress, with a higher score indicating a higher perceived stress.[8] The Hospital Anxiety and Depression Scale (HADS) has a 7-item anxiety and a 7-item depression domain. The scores for both domains range from 0-21, with a cut-off point of 8 for depression or anxiety.[31]

Clinical parameters

Weight, height and waist circumference were measured during the visit. The results of routinely measured pulmonary function outcomes (forced vital capacity (FVC) and transfer factor for carbon monoxide corrected for hemoglobin (TLCOc)) were used when available.

Outcomes

The primary outcome was the differences between scalp hair steroid levels of sarcoidosis patients both with and without fatigue and general population controls. Secondary outcomes were relationships between scalp hair steroid levels, fatigue and psychological distress scores, and clinical parameters.

Statistical analysis

Data is presented as median (range) when not stated differently. Scalp hair steroid levels are presented as geometric mean (95% confidence interval, CI) and expressed in pg/mg; data was log-transformed to achieve normal distribution. To determine differences in characteristics of sarcoidosis patients with and without fatigue, we used a Mann-Whitney U test for continuous variables and Fisher's exact test for binomial variables. Hair steroid levels were compared between the two groups of sarcoidosis patients using independent sample t-tests. Analysis of (co)variance (AN[C]OVA) was used to compare hair cortisol and testosterone levels of sarcoidosis patients with general population controls, corrected for age and gender. Mann Whitney U tests were used for analyzing differences in questionnaire scores of patients with and without fatigue. Correlations between hair steroid levels, questionnaire scores and clinical parameters were assessed using Pearson's correlation coefficients. All statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY). A p-value of <0.05 was considered statistically significant.

RESULTS

Of the 36 patients screened for the study, 32 were included. Patients were excluded for the following reasons: incomplete questionnaires (2), not enough hair for hair sample (1), and psychiatric problems (1). Based on the FAS score, 23 of the 32 sarcoidosis patients had significant fatigue. There were no significant differences in patients' characteristics between the fatigued and non-fatigued groups of patients (table 1).

Hair steroid levels

Scalp hair cortisol and cortisone levels were detected in all sarcoidosis patients, and testosterone levels in 13 of the 14 male patients with sarcoidosis. In the population-based controls from the Lifelines study cohort, there were 293 participants with scalp hair steroid samples (262 had both cortisol and cortisone levels available, 4 only cortisol level, and 27 only cortisone). In 62 male participants, testosterone levels were also available. Hair steroid levels in the sarcoidosis patients with fatigue did not significantly differ from those of sarcoidosis patients without fatigue (figure 2). Scalp hair cortisol and cortisone concentrations of the total group of sarcoidosis patients were significantly higher than those of the general population controls (hair cortisol: mean 6.6 (95% CI 5.1-8.4) versus 2.7 (95% CI 2.5-2.9) pg/mg, $p<0.001$, hair cortisone: mean 18.0 (95% CI 15.2-21.2) versus 8.3 (95% CI 7.9-8.8) pg/mg, $p<0.001$) (figure 3). No significant

Table 1. Characteristics of the groups of sarcoidosis patients

	All patients [n = 32]	**Fatigue** [n = 23]	**Non-fatigue** [n = 9]	**p-value***
Fatigue severity	32 (10-46)	33 (22-46)	16 (10-21)	<0.001
Age	47 (31-66)	45 (31-64)	55 (36-66)	0.15
Women	18 (56%)	13 (57%)	5 (56%)	1.00
Ethnicity				0.69[#]
Caucasian	23 (72%)	17 (74%)	6 (67%)	
Moroccan	3 (9%)	3 (13%)	0 (0%)	
Surinamese Hindi	6 (19%)	3 (13%)	3 (33%)	
BMI, kg/m^2	26 (20-39)	26 (20-39)	29 (23-36)	0.21
Waist circumference	93 (65-116)	91 (65-116)	95 (84-104)	0.48
Time since diagnosis, y	5 (0-24)	4 (0-24)	6 (0-18)	0.82
FVC % predicted	105 (55-123)	103 (81-123)	106 (55-121)	0.95
TLCOc % predicted	88 (50-162)	89 (50-131)	86 (60-162)	0.82

Data are presented as median (range) or n (%). BMI, body mass index; FVC, forced vital capacity; TLCOc transfer factor for carbon monoxide corrected for hemoglobin.

* Mann-Whitney U test was used for continuous variables and Fisher's exact test for binomial variables to compare fatigue and non-fatigue sarcoidosis patients

[#] Caucasian versus other

differences in testosterone levels were found between male patients with sarcoidosis and male general population controls (mean 1.0 (95% CI 0.7-1.3) pg/mg versus 1.0 (95% CI 0.9-1.2) pg/mg, p=0.78) (figure 3). Cortisol correlated significantly with cortisone (r=0.72, p<0.001), but not with testosterone (r=0.38, p=0.20); neither did cortisone correlate with testosterone (r=0.26, p=0.39).

Psychological distress and fatigue questionnaires

Mean questionnaires scores are shown in table 2. Sarcoidosis patients with fatigue had significantly higher stress, anxiety, depression and lower quality of life scores than sarcoidosis patients without fatigue (table 2).

A significant positive correlation was found between scalp hair cortisol levels and anxiety (r= 0.47, p=0.01) and depressive symptoms (r=0.46, p=0.01) (table 3). Additionally, higher hair cortisol levels significantly correlated with lower mental health scores measured by the SF-36 (r=-0.38, p=0.03), indicating worse health status (table 3). There was a trend observed between hair cortisol levels and the PSS (r=0.31, p=0.09), but no correlation existed with the FAS (r=0.14, p=0.45) (table 3). For scalp hair testosterone levels, in male sarcoidosis patients, no significant correlations were found with any of the psychological distress and fatigue scores. Figure 4 shows an interaction network between hair steroid levels, psychological distress and fatigue scores, and pulmonary function tests in the total group of sarcoidosis patients.

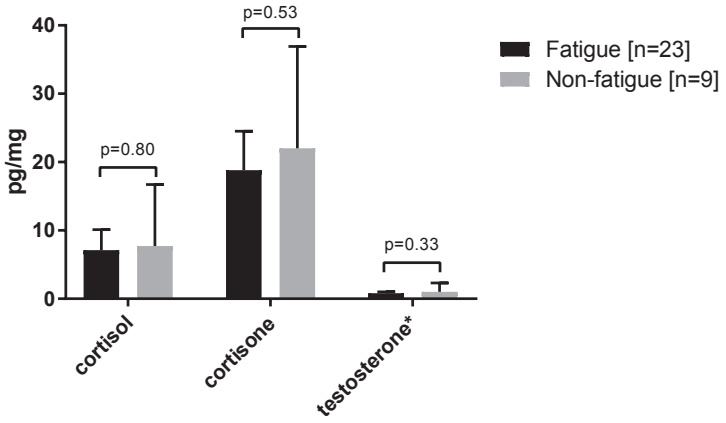


Figure 2. Hair cortisol, cortisone and testosterone levels in sarcoidosis patients with and without fatigue
* measured in 10 male sarcoidosis patients with fatigue and in 4 male patients without fatigue. Data are shown as geometric mean (95% CI). Independent sample t-test was used for analysis.

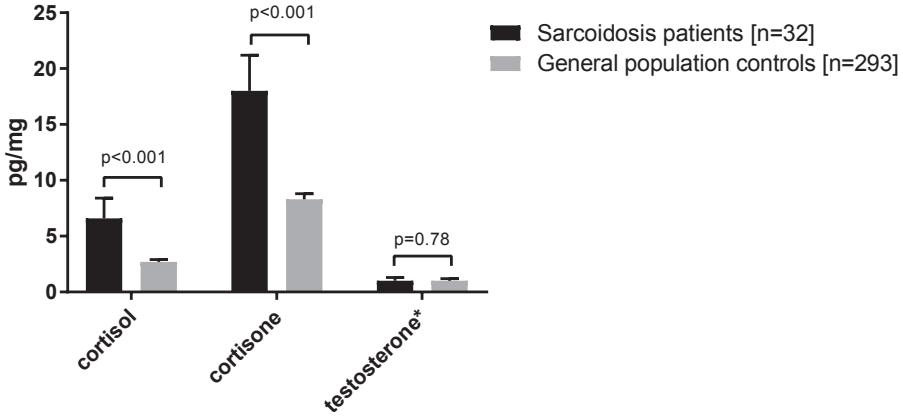


Figure 3. Hair cortisol, cortisone and testosterone levels in patients with sarcoidosis and general population controls[23,24]
* measured in 13 male sarcoidosis patients and in 62 male general population controls. Data are shown as geometric mean (95% CI), and corrected for age and gender. General Linear model – Univariate (ANCOVA) was used for analysis.

Clinical parameters

Scalp hair cortisol and cortisone did not correlate with clinical parameters. However, testosterone showed a significant positive correlation with weight (r=0.69, p=0.01), and a significant inverse correlation with waist circumference (r=-0.69, p=0.01) and FVC (r=-0.76, p=0.02).

Table 2. Questionnaire scores of patients with sarcoidosis

Questionnaire	Total [n=32]	Fatigue [n=23]	Non-fatigue [n=9]	p-value*
FAS	32 (10-46)	33 (22-46)	16 (10-21)	<0.001
PSS	26 (4-55)	29 (4-55)	14 (9-28)	<0.001
HADS anxiety	6 (0-19)	7 (0-19)	1 (0-2)	<0.001
HADS depression	6 (0-21)	8 (0-21)	0 (0-5)	<0.001
EQ5D5L	0.7 (-0.1-1.0)	0.7 (-0.1-0.9)	1.0 (0.6-1.0)	<0.001
SF-36 mental health	64 (36-75)	64 (36-75)	64 (60-64)	0.71
SF-36 general health	62 (30-87)	62 (47-87)	57 (30-77)	0.26
KSQ GHS	58 (2-100)	53 (2-83)	98 (75-100)	<0.001

Data are shown as median (range). * Mann-Whitney U was used for comparing questionnaire scores in fatigue and non-fatigue patients with sarcoidosis. FAS, Fatigue Assessment Scale; PSS, Perceived Stress Scale; HADS, Hospital Anxiety and Depression Scale; EQ5D5L, Euroqol-5D 5-level; SF-36, Short Form-36; KSQ, King's Sarcoidosis Questionnaire; GHS, General Health Status domain

Table 3. Correlations between scalp hair cortisol and cortisone and psychological distress and fatigue scores in all patients with sarcoidosis (n=32)

Questionnaires	Cortisol	Cortisone
FAS	0.14	-0.01
PSS	0.31#	<-0.01
HADS anxiety	0.47**	0.14
HADS depression	0.46**	0.18
EQ5D5L	-0.26	0.03
SF-36 mental health	-0.38*	-0.05
SF-36 general health	-0.28	-0.18
KSQ GHS	-0.25	-0.04

Pearson correlations, data are presented as R. FAS, Fatigue Assessment Scale; PSS, Perceived Stress Scale; HADS, Hospital Anxiety and Depression Scale; EQ5D5L, Euroqol-5D 5-level; SF-36, Short Form-36; KSQ, King's Sarcoidosis Questionnaire; GHS, General Health Status domain

$p \geq 0.05$ and <0.10, * $p<0.05$ and >0.01, ** $p \leq 0.01$

DISCUSSION

This study is the first to assess the feasibility of scalp hair steroid levels as a biomarker for psychological distress and fatigue in patients with sarcoidosis. Hair cortisol and cortisone levels were significantly higher in sarcoidosis patients than in general population controls. Hair cortisol levels were positively related to subjective measures of psychological distress. No differences were found in scalp hair steroid levels between sarcoidosis patients with and without fatigue.

In the current study, instead of the more conventional methods such as serum, urine or saliva measurements, we used scalp hair analysis to determine steroid levels. This method has several advantages. First, scalp hair analysis enables long-term steroid level determination as opposed to all methods using body fluids that only represent

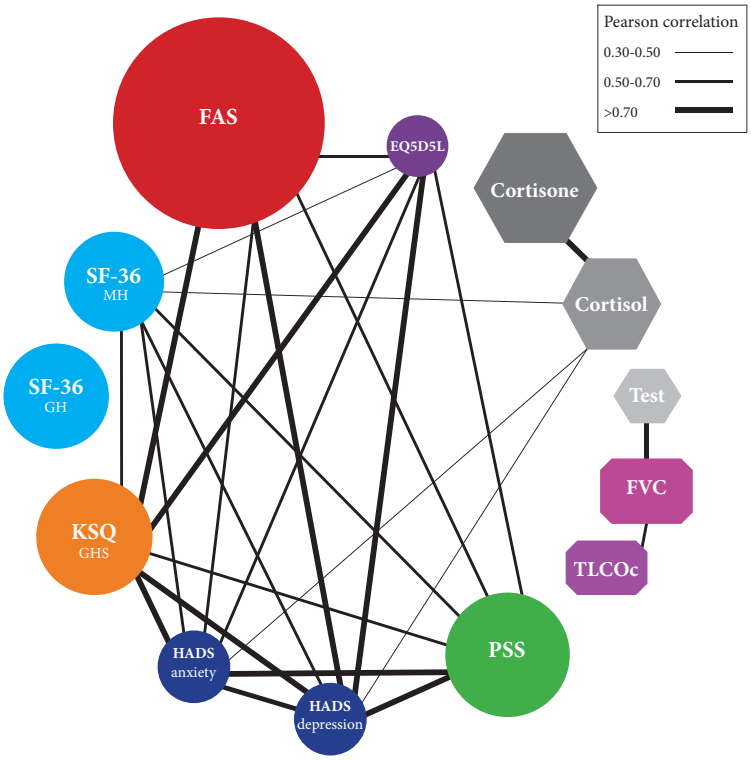


Figure 4. Interaction network showing all significant correlations between hair steroid levels, psychological distress and fatigue scores, and pulmonary function tests in sarcoidosis patients (n=32).
Each node of the network corresponds to a questionnaire score, and its size is proportional to the % of the total score of the questionnaire. Two nodes are linked if they significantly correlate, the wider the string the better the correlation. EQ5D5L; Euroqol-5D 5-level; FAS, Fatigue Assessment Scale; SF-36, Short Form-36; MH, mental health domain; GH, general health domain; KSQ; King's Sarcoidosis Questionnaire; GHS, General Health Status domain; HADS, Hospital Anxiety and Depression Scale; PSS, Perceived Stress Scale; TLCOc, transfer factor for carbon monoxide corrected for hemoglobin; FVC, forced vital capacity; Test, testosterone.

a momentarily steroid level and which can be influenced by acute stress, the diurnal rhythm, or pulsatile secretion of steroid hormones.[7,18,20] A recent study has shown that hair cortisol measurement provides a reliable measure of long-term integrated free cortisol production. It demonstrated that hair cortisol levels correlated well with 30-day average salivary cortisol area-under-the curve based on 3 samples collected during the day.[32] Second, scalp hair samples are easy to collect and store at room temperature.[33] In contrast, measuring steroid levels in body fluids, especially at multiple time-points, is invasive for patients, labour-intensive, and depends on patient instruction and cooperation.[20] Also, the measurement itself, as with blood sampling, can induce stress and thereby influence results.[19] Third, hair strings can be divided into segments of one or more centimeters to create retrospective timelines. In this way, scalp hair steroids could potentially be used in future trials to objectively measure the effect of interventions on psychological distress using only one or a few hair strings, thereby allowing easy data collection on a large scale.

Interestingly, hair cortisol and cortisone levels were significantly higher in patients with sarcoidosis than in the general population controls. Hair cortisol has previously been associated with both physical and mental health status and was found to be increased in patients with various diseases such as obesity, post-traumatic stress syndrome, and cardiovascular diseases, and was also associated with extreme exercise, shift work, life events and chronic pain.[20,21,34] Cortisol is the active form of glucocorticoid and can be converted into cortisone, which has almost no biological activity.[35] The balance between cortisol and cortisone makes it possible to regulate cortisol levels. In our study, cortisol and cortisone showed good correlations and were both increased. This makes a mechanistic cause in the conversion or balance between cortisol and cortisone in sarcoidosis patients unlikely as the underlying mechanism for the higher cortisol levels found.

Scalp hair steroid levels did not differ between sarcoidosis patients with and without fatigue. Korenromp et al. reported that, in a principal component analyses, serum ACTH and cortisol were significantly lower in patients with sarcoidosis-related fatigue than in patients without fatigue.[12] However, their baseline cortisol analysis showed no difference between fatigued and non-fatigued patients, which is in line with our findings. Different assessment methods can complicate comparisons between studies. Korenromp et al., for example, measured cortisol in blood serum, a momentarily measure of cortisol, while in our study, cortisol was analysed in scalp hair representing long-term cortisol levels. As previously shown by Sauve et al., hair cortisol levels are not affected by diurnal variations or acute stress, and serum cortisol levels do not seem to correlate well with scalp hair cortisol levels.[36]

Hair testosterone levels in men with sarcoidosis did not differ from those of the general population controls. This is contrary to findings of Spruit et al. which showed significantly lower serum testosterone levels in male sarcoidosis patients than in healthy controls.[17] This variance could be due to differences in measuring methods since hair testosterone is a long-term measure, whereas serum testosterone is a time-point measure. But the small sample size (13 testosterone samples) of our study might have also played a role in the findings. Nevertheless, both our study and the study of Spruit et al. found no correlation between psychological wellbeing scores and testosterone levels. We can therefore only conclude that the clinical relevance of testosterone levels in sarcoidosis is not yet clear, and ideally a larger cohort should be studied.

Currently, tools to measure fatigue and psychological distress in sarcoidosis are limited to subjective patient-reported outcome measures (PROMs). PROMs often comprise many questions, which may complicate use in clinical practice. Not only can completing PROMs be time consuming, but patients may also struggle to remember what they answered the previous time. This can lead to variations in scores and difficulties to evaluate a meaningful change. Previous studies have shown that scalp hair cortisol can serve as a biological marker for chronic stress.[9,21] In our study, scalp hair cortisol levels, indeed, positively correlated with psychological distress scores of depression

and anxiety. A trend was found in the correlation with perceived stress scores. These findings are in line with previous studies.[33,37] The underlying mechanism of the positive correlation between scalp hair cortisol levels and psychological distress in sarcoidosis patients could be bi-directional. Hence, sarcoidosis-associated inflammation may cause increased cortisol levels, and increased cortisol levels can lead to psychological distress. Studies in Cushing patients suggested a similar relationship.[38] On the other hand, having such a disease as sarcoidosis might also directly cause psychological distress, resulting in higher cortisol levels. We found that while stress scores differed significantly between fatigue and non-fatigue patients, no differences in cortisol levels were found. This might indicate that psychological stress is not the predominant underlying mechanism driving the increase in cortisol levels found in sarcoidosis patients.

Little is known about the etiology of fatigue in sarcoidosis. Fatigue is presumably multifactorial, and might be related to aspects in pathogenesis, comorbidities, and medication.[2,3] In the current study, no relationship could be found between cortisol and testosterone levels and fatigue. This is in line with clinical experience that, in sarcoidosis-associated fatigue, steroids treatment is often futile, or might even result in side-effects causing further deterioration. As can been seen in figure 4, fatigue is closely related to quality of life, anxiety, depression and stress scores, which, in turn, are also strongly interrelated. This underlines the major impact fatigue has on patients' lives and the need for studies to advance knowledge on its etiology and for effective treatment interventions for fatigue in sarcoidosis. Figure 4 also shows that scalp hair cortisol is the only objective clinical parameter correlating with subjective scores of psychological distress. No correlation is found between questionnaires and pulmonary function parameters. This is in line with previous findings that pulmonary function tests do not correlate with subjective questionnaire scores as they capture another dimension of disease.[29,30] Testosterone levels showed a correlation with FVC in sarcoidosis patients; however, sample size was limited and too small to draw conclusions about the clinical significance of this finding.

Our study has some limitations. Only patients without steroid use were included, whereas in daily practice, both systemic and topical corticosteroids are used by a fair number of patients with sarcoidosis. Previous studies have shown that endogenous cortisol production can be suppressed by exogenous corticosteroids.[39] In children with asthma using inhalation corticosteroid, serum and scalp hair cortisol levels were found to be lower than in healthy controls.[40] Likewise, studies in healthy adults showed significantly lower hair cortisol levels in participants using systemic corticosteroids than in non-users.[24,33] It needs to be studied if scalp hair cortisol analysis can be used to assess compliance and dosing of corticosteroid treatment in sarcoidosis. Currently, hair analysis can only be done on scalp hair, and the method is not validated for other types of bodily hair, thereby excluding patients with very short or no scalp hair. Another limitation is the small sample size, which might explain the lack of differences found in hair steroid

levels in fatigued and non-fatigued patients. Nevertheless, hair steroid levels of the total group of patients differed significantly from those of the general population controls.

CONCLUSIONS

Patients with sarcoidosis have significantly higher levels of scalp hair cortisol and cortisone than the general population controls. Scalp hair steroids levels did not differ in sarcoidosis patients with and without fatigue. Increased hair cortisol in sarcoidosis patients was associated with increased psychological distress, assessed by questionnaires. In male sarcoidosis patients, no significant correlations were found between hair testosterone and scores of psychological distress and fatigue. This study suggests that scalp hair cortisol analysis is a feasible, non-invasive biomarker for psychological distress, but not fatigue, in patients with sarcoidosis.

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Chapter 5

Clubbing in patients with fibrotic interstitial lung diseases

**"Not everything that can be counted counts,
and not everything that counts can be counted"**
William Bruce Cameron

Under review

M.J.G. van Manen[1], L.C. Vermeer[2], C.C. Moor[1], R. Vrijenhoeff[1], J.C. Grutters[2,3], M. Veltkamp[2,3], M.S. Wijsenbeek[1]

[1]Department of Respiratory Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands

[2]Department of Respiratory Medicine, ILD Center of Excellence, St. Antonius Hospital Nieuwegein, Nieuwegein, the Netherlands

[3]Department of Respiratory Medicine, University Medical Center, Utrecht, the Netherlands

ABSTRACT

Background

Clubbing is associated with poor prognosis and considered typical in idiopathic pulmonary fibrosis (IPF), but is also seen in other fibrotic interstitial lung diseases (ILDs). Little is known about the exact prevalence, clinical meaning, and the best method to assess clubbing in these ILDs. We aimed to evaluate the agreement between different clubbing assessment methods in patients with fibrotic ILDs. Additionally, we assessed the prevalence of clubbing in different fibrotic ILDs, and related clubbing to disease severity and quality of life.

Methods

Consecutive outpatients with fibrotic ILDs of two tertiary referral centers were included. Clubbing was assessed with the phalangeal depth ratio, the digital index, the Schamroth sign test, and by the treating physicians and investigator.

Results

We included 153 patients (100 men), mean age 65 (range 33-88), mean FVC 79% (25-145%), mean TLCOc 50% (16-104%). Kappa values between clubbing assessment methods ranged from -0.47 – 0.68. Prevalence of clubbing ranged from 7-42% in the total group of patients and 7-52% in IPF, depending on assessment method used. Clubbing did not correlate with FVC or TLCOc ($p>0.2$) or with quality of life scores.

Conclusion

Clubbing was present in 7-42% of our fibrotic ILD cohort, and showed no correlation with disease severity. Although considered an important clinical feature, assessment methods for clubbing showed no to poor agreement. Further studies are needed to gain more insight into measuring clubbing reliably, and the possible prognostic value and evolution of clubbing.

INTRODUCTION

Interstitial lung diseases (ILDs), also known as diffuse parenchymal lung diseases, contain a variety of disease affecting the pulmonary interstitium or alveoli.[1,2] A significant proportion of these diseases is characterized by progressive pulmonary fibrosis. The most common form is idiopathic pulmonary fibrosis (IPF), a deadly disease with a median survival of 3-5 years without treatment.[3] Patients with pulmonary fibrosis experience symptoms of breathlessness, cough and fatigue.[4] Physical examination often reveals fine bibasilar inspiratory crackles and finger clubbing.[5] Clubbing is a deformation of the nail base, resulting in a swollen and sponginess, convex distal phalanx, with loss of the nail-fold angle.[6,7] Severe clubbing can be bothersome and painful for patients. The exact underlying mechanism of clubbing is unknown; though it has been hypothesized that dysfunction of fragmentations of megakaryocytes into platelets in the lungs plays a role.[8]

In most studies the presence of clubbing is assessed by the treating physicians.[5,9,10] However, many other methods have been described to measure clubbing, such as the digital index, phalangeal depth ratio and the Schamroth sign test.[11-13] Little is known about the best method to quantify clubbing in fibrotic ILDs.

Digital clubbing is thought to be present in approximately 50 percent of patients with IPF and has been associated with poor prognosis of disease.[5,14] Yet, there is little knowledge on prevalence, and clinical meaning of clubbing in other fibrotic lung diseases, such as underlying collagen vascular disease (CVD) and chronic hypersensitivity pneumonitis (CHP). Currently, it is increasingly acknowledged that IPF and other fibrotic ILDs share common features and might also benefit from the same treatments. To our knowledge no good studies have been performed to look at clubbing and associated patients characteristics in these diseases.

The purpose of this study was to evaluate agreement between different clubbing assessment methods in patients with fibrotic ILDs. Secondary, we assessed the prevalence of clubbing in different fibrotic ILDs, and the relationship between clubbing, disease severity and quality of life.

METHODS

Study design and population

This study is a prospective, consecutive, cohort study at the outpatient clinic of the pulmonary department of the Erasmus MC, Rotterdam and the St. Antonius hospital, Nieuwegein. Patients were included from May till December 2016, when having pulmonary fibrosis, defined as: “the presence of reticulation and traction bronchiolectasis or traction bronchiectasis, with or without honeycombing” and one of the following

diagnoses: IPF, underlying CVD, CHP, fibrosing pulmonary sarcoidosis, unclassifiable pulmonary fibrosis (PF), or other fibrotic ILDs. The study was approved by the local medical ethical commission of both centers (METC 2016-214) and all patients completed informed consent.

Outcomes

The primary outcome was the agreement between different clubbing assessment methods in patients with fibrotic ILDs. Secondary outcomes were the prevalence of clubbing in these patients, and the relationship between clubbing and disease severity (measured by pulmonary function tests) and quality of life (QoL).

Measurements

Clubbing was measured at the outpatient clinic using the digital index, phalangeal depth ratio and Schamroth sign test, and rated at sight by the treating physician and investigator (figure 1).

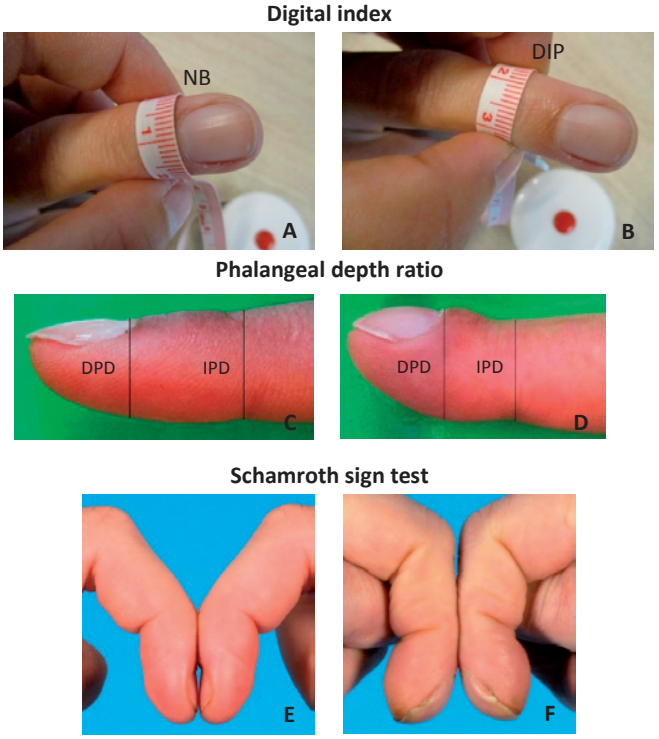

Figure 1. Clubbing measuring methods

A Measuring circumference of NB
B Measuring circumference of DIP
C Normal finger with DPD<IPD
D Clubbed finger with DPD>IPD
E Diamond-shaped window: negative
F No diamond-shaped window: positive

NB, nail bed; DIP, distal interphalangeal joint; DPD, distal phalangeal depth; IPD, interphalangeal depth. Digital index = NB:DIP ratios for all 10 fingers. Phalangeal depth ratio = DPD:IPD ratio.

Digital Index

The digital index was calculated by measuring the nailbed (NB) to the distal interphalangeal (DIP) ratio for each finger (figure 1).[11] A total score of the ten ratios above 10.2 is consistent with clubbing and a score ≤10.2 is considered normal.[6,11]

Phalangeal depth ratio

The phalangeal depth ratio is the ratio of the distal phalangeal depth (DPD) to the interphalangeal depth (IPD) (figure 1).[6,12] The ratio was measured with a digital caliper (150 mm) and determined for both index fingers. A ratio above 1.0 is indicative for clubbing.[7]

Schamroth sign test

For the Schamroth sign test, patients were asked to put the dorsal part of their nails of both index fingers together (figure 1). In patients without clubbing, a diamond shaped window is seen. The test is positive when this window disappears.[6,13]

At sight

Before starting the clubbing measurements, the treating physicians and investigator were asked to rate the patients' clubbing as present or not. They were blinded for each other's results.

Questionnaires

Patients completed several questionnaires at home, shortly after the visit. The 15-item King's Brief Interstitial Lung Disease health status questionnaire (K-BILD) is a validated, self-completed health status questionnaire with three domains: psychological, breathlessness and activities and chest symptoms.[15] Scores range from 0-100, with a higher score indicating a better health status.[15] The Euroqol-5D-5 level (EQ-5D-5L) is a self-administered generic measure of health-related QoL, and defines health in 5 dimensions: mobility, self-care, usual activities, pain and discomfort and anxiety and depression.[16] A higher score indicates better health-related QoL. The 5-item ICEpop CAPability measure for Older people (ICECAP-O) assesses capability in elderly people and focuses on five conceptual attributes of QoL: attachment, security, role, enjoyment and control.[17] The 15-item Groningen frailty indicator (GFI) is a short, self-administered screening questionnaire. It contains questions about psychological and physical frailty.[18] A 100 mm visual analogue scale (VAS) was used to assess cough, breathlessness, fatigue and general wellbeing.

Physiological measures

Results of routinely measured pulmonary function tests, forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) and the transfer factor for carbon monoxide corrected for haemoglobin (TLCOc)), were used when available.

Statistical analysis

Data is presented as mean (range) when not stated differently. To assess differences in demographics and questionnaire scores between patients with IPF and other diagnosis, we used an independent sample t-test for continuous variables and a Chi-Square test for categorical variables. The level of agreement between the different clubbing measuring methods was analyzed using Cohen's kappa.[19] Prevalences of clubbing were calculated as frequencies. Independent sample t-tests were used to compare clubbing measuring method, questionnaire and disease severity scores in patients with and without clubbing. Pearson correlation coefficients were used to assess the relationship between clubbing measuring methods, pulmonary function tests and questionnaire scores. SPSS version 21.0 was used for all statistical analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

Of the 167 patients approached for the study, 153 patients were included. Fourteen patients declined because they were not interested (5), too busy (8) or had difficulties understanding the questionnaires (1). Demographics are shown in table 1. The group "others" contains 19 (12%) underlying CVD, 12 (8%) CHP, 15 (10%) fibrosing pulmonary sarcoidosis, 17 (11%) unclassifiable pulmonary fibrosis, and 22 (14%) various fibrotic ILDs. A list of the various fibrotic ILDs can be found in supplementary table 1. In most patients, the dominant hand was right (right: 137 (90%), left: 10 (7%), no preference: 5 (3%) and unknown 1 (1%)).

Questionnaire scores are shown in table 2, and were missing in 16 patients (10%). No significant differences were found in questionnaire scores between IPF and other diseases, except for the K-BILD psychological (IPF: mean 50 (range 22-76), others: mean 57 (range 22-100), p<0.01) and total domain (IPF: mean 53 (range 27-72) others: mean 57 (range 34-91), p=0.04).

For the digital index the mean score was 9.72 (range 8.74-10.47, SD 0.31), for the phalangeal depth ratio left 0.97 (range 0.75-1.18, SD 0.07) and the phalangeal depth ratio right 0.96 (range 0.60-1.20, SD 0.08). Cohen's kappa values showed no to weak agreement on the presence of clubbing between the different clubbing methods, except for a moderate agreement between clubbing ratings of the physician and the investigator (0.62) (table 3).

Table 4 shows the prevalence of clubbing in fibrotic ILDs analyzed with the different clubbing measurement methods. Prevalences range from 7-42% in the total group of patients and 7-52% in patients with IPF. Interestingly the digital index and Schamroth sign test showed much lower prevalences in the total group of patients than the phalangeal depth ratio and ratings of the physician and investigator (7-8% versus 31-42%) (table 4).

Table 1. Demographics

	Patients (n=153)	**IPF** (n=68)	**Others** (n=85)	**p-value**[#]
Age (years)	65 [33-88]	69 [47-86]	62 [33-88]	**<0.001**
Male	100 (65)	55 (81)	45 (53)	**<0.001**
BMI	27 [19-42]	27 [20-39]	28 [19-42]	0.32
Smoking status				**<0.01***
Former	98 (64)	53 (78)	45 (53)	
Never	48 (31)	13 (19)	35 (41)	
Current	7 (5)	2 (3)	5 (6)	
Pack years	23 (18)	26 [1-85]	20 [0-64]	0.05
Comorbidity				0.84**
Pulmonary hypertension	6 (4)	4 (6)	2 (2)	
Cardiac	27 (18)	16 (24)	11 (13)	
Gastro-intestinal	2 (1)	0 (0)	2 (2)	
Thyroid	2 (1)	0 (0)	2 (2)	
Other	20 (13)	8 (12)	12 (14)	
Medication				0.69***
Nintedanib	17 (11)	17 (25)	0 (0)	
Pirfenidone	25 (16)	23 (34)	2 (2)	
Other	69 (45)	14 (21)	55 (65)	
None	48 (31)	20 (29)	28 (33)	
Lung function parameters				
FVC % predicted	79 [25-145]	78 [37-130]	79 [25-145]	0.78
FEV1 % predicted	77 [25-152]	79 [40-120]	76 [25-152]	0.44
TLCOc % predicted	50 [16-104]	46 [16-104]	55 [18-95]	**<0.01**

Data are presented as n (%) or mean [range]. IPF, idiopathic pulmonary fibrosis; FVC, forced vital capacity; FEV1, forced expiratory volume in the first second; TLCOc, transfer factor for carbon monoxide corrected for hemoglobin. [#]IPF versus others, analyzed with an independent sample t-test for continuous variables and a Chi-Square test for categorical variables * never versus former/current smoker ** comorbidity versus no comorbidity *** medication versus no medication

In supplementary table 2 questionnaire and pulmonary function test scores are shown for patients with and without clubbing according to the different clubbing measuring methods. TLCOc and, dependent on clubbing measuring method used, FVC were significantly lower in patients with clubbing than in those without clubbing. Yet, no correlation was found between pulmonary function tests and clubbing, measured with the digital index and phalangeal depth ratio (supplementary table 3). Pearson correlations ranged from -0.02 to -0.10 between TLCOc and the different clubbing measures. Questionnaire scores showed no to poor correlations with clubbing (supplementary table 3).

Table 2. Questionnaire and pulmonary function test scores for the total group of patients and patients with idiopathic pulmonary fibrosis

	Questionnaires	Total group (n=137)	IPF (n=62)	Others (n=75)	P-value*
	K-BILD psych	54 (22-100)	50 (22-76)	57 (32-100)	**<0.01**
	K-BILD BA	41 (0-100)	38 (0-80)	43 (0-100)	0.10
	K-BILD chest	68 (17-100)	69 (32-100)	68 (17-100)	0.51
	K-BILD total	55 (27-91)	53 (27-72)	57 (34-91)	**0.04**
	EQ-5D-5L VAS	65 (20-100)	63 (20-100)	66 (20-100)	0.40
	EQ-5D-5L index value	0.8 (-0.01-1.0)	0.7 (-0.01-1.0)	0.8 (0.2-1.0)	0.37
	VAS cough	40 (0-100)	43 (0-92)	38 (0-100)	0.46
	VAS breathlessness	48 (0-98)	51 (8-98)	46 (0-97)	0.38
	VAS fatigue	49 (0-98)	52 (3-97)	46 (0-98)	0.41
	VAS general health	41 (0-99)	44 (0-97)	39 (0-99)	0.41
	GFI	3.7 (0-11)	4.0 (0-10)	3.5 (0-11)	0.45
	ICECAP-O	0.8 (0.3-1.0)	0.8 (0.3-1.0)	0.8 (0.4-1.0)	0.31

Data is presented as mean (range). * Independent sample t-test: IPF versus others

K-BILD, King's Brief Interstitial Lung Disease health status questionnaire; psych, psychological domain; BA, breath and activities domain; EQ-5D-5L, euroqol-5D-5L; VAS, visual analogue scale; GFI, Groningen frailty indicator; ICECAP-O, ICEpop CAPability measure for Older people.

A higher score indicates better quality of life

A higher score indicates worse cough, breathlessness, fatigue, frailty and capability

Table 3. Cohen's kappa values of agreement for different clubbing measuring methods

	Digital index	Phalangeal depth ratio		Schamroth sign	At sight
		Left	Right		Physician
PDR – right	0.20	**0.68**			
PDR – left	0.21				
Schamroth sign test	0.02	0.01	-0.07		
Physician	-0.12	-0.30	-0.25	-0.07	
Investigator	-0.11	-0.47	-0.40	-0.12	**0.62**

Presence of clubbing is rated as yes or no, with a cut-off for digital index of ≥10.2 and for the phalangeal depth ratio of >1.0 indicating clubbing. IPF, idiopathic pulmonary fibrosis; CVD, collagen vascular disease, CHP, chronic hypersensitivity pneumonitis; PF, pulmonary fibrosis; ILDs, interstitial lung diseases

DISCUSSION

Digital clubbing is considered typical in IPF and has been associated with poor prognosis of disease. Yet, there is little knowledge on prevalence and clinical meaning of clubbing in other fibrotic lung diseases. This is the first study to assess multiple methods for measuring clubbing in a large fibrotic ILD cohort. Agreement between the different clubbing measuring methods was poor to moderate. Prevalence of clubbing ranged from 7-42% in the fibrotic ILD cohort and from 7-52% in patients with IPF. Clubbing did not correlate with disease severity or quality of life scores.

Table 4. Prevalence of clubbing in fibrotic ILDs according to the different clubbing measurements

N (%)	Digital index	Phalangeal depth ratio		Schamroth sign	At sight	
	≥10.2	Left	Right	Positive	Physician	Investigator
Total group	10 (7)	50 (33)	47 (31)	12 (8)	63 (41)	64 (42)
IPF	5 (7)	21 (31)	19 (28)	6 (9)	35 (52)	27 (40)
Underlying CVD	1 (5)	3 (16)	3 (16)	2 (11)	7 (37)	8 (42)
CHP	0 (0)	6 (50)	5 (42)	1 (8)	5 (42)	6 (50)
Fibrosing pulmonary sarcoïdose	0 (0)	4 (27)	3 (20)	0 (0)	3 (20)	5 (33)
Unclassifiable PF	0 (0)	6 (35)	7 (41)	1 (6)	6 (35)	8 (47)
Various fibrotic ILDs	4 (18)	10 (46)	10 (46)	2 (9)	7 (32)	10 (46)

IPF, idiopathic pulmonary fibrosis; CVD, collagen vascular disease, CHP, chronic hypersensitivity pneumonitis; PF, pulmonary fibrosis; ILDs, interstitial lung diseases

Etiology of clubbing

The exact cause of clubbing is unknown, though several theories have been proposed. The most plausible seems to be the "platelet" theory, which is supported by outcomes of various studies.[8,20-23] In this theory, clubbing is explained by a dysfunction of the fragmentation of megakaryocytes into platelets in the lungs. Normally, megakaryocytes enter the pulmonary circulation and are fragmented into platelets when going through the small calibre vessels of the pulmonary capillary bed.[21] Alterations of the lungs or systemic circulation, as caused by for instance lung tumours, pulmonary fibrosis or right-to-left intracardiac shunts, can cause entire or large fragments of megakaryocytes to enter the systemic circulation instead of the pulmonary circulation.[8,24] The megakaryocytes become impacted in the distal limbs circulation and release platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF).[23] The occlusion of the capillaries leads to a hypoxic environment which further promotes PDGF and VEGF release. PDGF and VEGF promote growth, vascular hyperplasia and permeability, oedema, chemotaxis, connective tissue changes and proliferation of fibroblasts and osteoblasts, characteristic for clubbing.

Clubbing measuring methods

In daily practice clubbing is assessed at sight, however changes are often subtle and presence of clubbing can be debated in those situations. Several more objective methods have been proposed to assess clubbing, but no "gold standard" exist. In the current study, clubbing was measured with the digital index, phalangeal depth ratio and Schamroth sign test, and rated at sight by the treating physician and investigator. Although clubbing is considered an important clinical feature, assessment methods for clubbing showed no to poor agreement in the current study. Only kappa values of agreement (0.62) for the physician and investigator were moderate (table 3), which corresponds with findings from previous studies, where kappa-values ranged from 0.39 to 0.90.[6] Apparently, the physician and investigator recognize something on sight that current measuring methods fail to detect. The poor agreement found between the clubbing

methods was surprising. We assessed both hands, as it might be that circulation differs in the dominant hand, but found no differences in clubbing. When using the phalangeal depth ratio's, a mean of 0.97 (SD 0.07) for the left index finger and 0.96 (SD 0.08) for the right was found, which corresponds with previous studies in COPD and bronchogenic carcinoma, and is higher than scores found in healthy subjects.[6]

Prevalence of clubbing

The poor agreement between the assessment methods leads to clubbing prevalences ranging from 7-42% in the total group of patients and 7-52% for IPF in our study. Previous literature also showed varieties of clubbing prevalences in fibrotic ILDs (table 5), which may be partly due to different assessment methods, though most of the assessments were done by a physician or investigator. The lower percentage of clubbing found with the Schamroth sign test and digital index compared to the phalangeal depth ratio and ratings at sight, suggest that these methods assess only the more severe clubbing. As there is no "gold standard" to assess clubbing, caution should be placed on putting too much emphasis on the diagnostic supportive role of the presence or absence of clubbing.

Table 5. Clubbing frequencies in previous literature

	Percentages of clubbing	Measuring method
IPF	13-73	1[5,9,14,25-31]
Underlying CVD	Unknown	
CHP	23-54	1[10,32]
Fibrosing pulmonary sarcoïdose	4-6	1[9,33]
Unclassifiable PF	Unknown	
Various fibrotic ILDs		
Asbestosis	32-43	1[34], 2[35,36]
NSIP	18-20	1[9,25]

1. Observed by the physician or investigator as present or absent

2. Estimated if hyponychial angle was ≥195°

IPF, idiopathic pulmonary fibrosis; CVD, collagen vascular disease, CHP, chronic hypersensitivity pneumonitis; PF, pulmonary fibrosis; ILDs, interstitial lung diseases; NSIP, non-specific interstitial pneumonia

Clubbing, disease severity and quality of life

In previous studies in IPF, clubbing was found to have a prognostic implication.[5,14] If this hold true for other fibrotic ILDs remains unclear to our knowledge. We found that TLCOc was significantly lower in patients with IPF than in patients with other fibrotic ILDs, and in patients with than without clubbing. However, symptoms and general QoL scores did not differ between patient with and without clubbing and, strikingly, also not between IPF and other fibrotic ILDs. Only the K-BILD psychological domain and total scores were significantly worse in patients with IPF, but they did not reach a minimal important difference (8 points).[37] This is in contrast to a previous study of Wapenaar et al. that showed a more impaired QoL in patients with IPF.[38] It might be explained by less difference found in lung function between our groups than in other studies.

Anti-fibrotic drugs

The clinical behaviour of clubbing is dependent on the underlying disease. In patients receiving a lung transplant, clubbing completely disappears after some time.[39,40] The same phenomenon has been observed in patients with clubbing associated with inflammatory bowel disease that were successfully treated.[41,43] If clubbing could be stabilised or reversed by successfully treating pulmonary fibrosis is not known. Neither is known if the underlying hypothesized pathway of clubbing itself could be influenced by anti-fibrotic treatment. One of the anti-fibrotic drugs, nintedanib, is a tyrosine-kinase inhibitor, that targets, among others the platelet derived growth factor receptor (PDGFR) and slows down lung function decline.[44] As the PDGF likely plays a role in the pathogenesis of clubbing,[42] nintedanib may hold properties to influence clubbing. If the presence of clubbing might be associated with a different phenotype of disease or a different response to therapy is unknown. Though the idea of clubbing being a potential easy physical marker of response to anti-fibrotic therapy is attractive, we first need to be able to assess and quantify clubbing in a reliable way.

CONCLUSION

Although clubbing is considered an important clinical feature in IPF and has been associated with poor prognosis, different methods to assess clubbing showed no to poor agreement. The prevalence of clubbing in fibrotic ILDs ranged from 7-42%. Further studies are needed to gain more insight into measuring clubbing reliably, and the possible prognostic value and evolution of clubbing.

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SUPPLEMENTARY TABLES

Supplementary table 1. Various fibrotic interstitial lung diseases

Diagnoses	N (%)
Non-specific interstitial pneumonia	5 (3)
Interstitial pneumonia with autoimmune features	3 (2)
Desquamative interstial pneumonia	3 (2)
Pleuroparenchymal fibroelastosis	2 (1)
Drug induced	1 (1)
Antisynthetase syndrome	1 (1)
Cryptogenic organizing pneumonia	1 (1)
Mixed dust pneumoconiosis	1 (1)
Follicular bronchiolitis	1 (1)
Hermansky Pudlak syndrome	1 (1)
Rheumatoid arthritis	1 (1)
ILD, exact diagnosis not yet known	1 (1)

ILD, interstitial lung disease

Supplementary table 2.
Next page

Supplementary table 3. Correlations between clubbing measurements and questionnaire scores and lung function parameters

	Digital index	Phalangeal depth ratio	
		Left index finger	Right index finger
K-BILD psych	0.12	0.04	0.04
K-BILD BA	0.11	<-0.01	0.05
K-BILD chest	0.02	-0.10	-0.09
K-BILD total	0.11	0.021	0.04
EQ-5D-5L VAS	0.19*	<0.01	0.03
EQ-5D-5L index value	0.15	<-0.01	0.03
VAS cough	-0.09	-0.12	-0.13
VAS breathlessness	-0.14	-0.01	-0.05
VAS fatigue	-0.23**	-0.13	-0.13
VAS general health	-0.07	-0.02	0.04
GFI	-0.06	0.03	-0.03
ICECAP-O	0.22*	0.12	0.14
FVC % predicted	<-0.01	-0.08	-0.07
FEV1 % predicted	0.12	<-0.01	-0.06
TLCOc % predicted	-0.10	-0.09	-0.02

* p<0.05 and ≥0.01, ** p<0.01

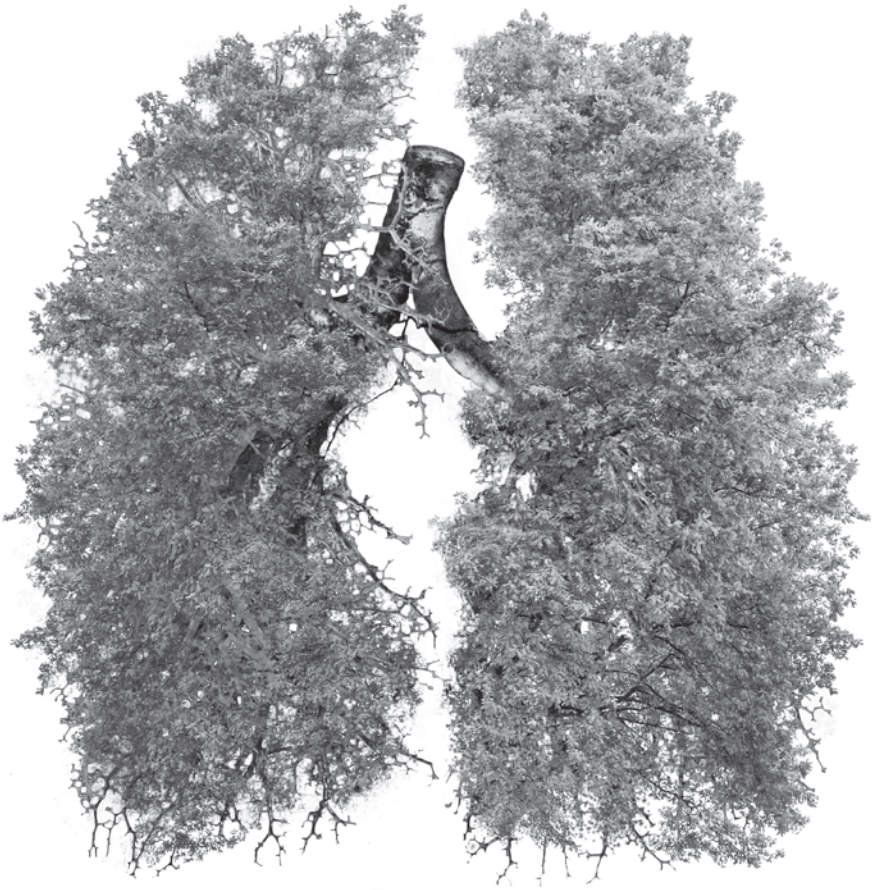
K-BILD, King's Brief Interstitial Lung Disease health status questionnaire; psych, psychological domain; BA, breath and activities domain; EQ-5D-5L, euroqol-5D-5L; VAS, visual analogue scale; GFI, Groningen frailty indicator; ICECAP-O, ICEpop CAPability measure for Older people; FVC, forced vital capacity; FEV1, forced expiratory volume in the first second; TLCOc, transfer factor for carbon monoxide corrected for hemoglobine

Supplementary table 2. Questionnaire and pulmonary function tests scores in patients with or without clubbing according to different clubbing measures

Scores	**Digital Index**		**Phalangeal depth ratio**				**Schamroth sign**		**At sight**			
Mean (SD)	≥10.2	<10.2	Left		Right		Positive	Negative	Physician		Investigator	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
K-BILD psych	60 (19)	54 (14)	57 (57)	53 (14)	56 (17)	54 (14)	47 (9)	55 (15)	52 (15)	56 (15)	55 (15)	54 (15)
K-BILD BA	51 (27)	40 (19)	42 (20)	40 (19)	42 (22)	40 (18)	35 (12)	41 (20)	39 (18)	43 (20)	39 (19)	42 (20)
K-BILD chest	72 (21)	68 (21)	67 (20)	69 (21)	67 (22)	69 (20)	56 (28)	69 (20)	67 (21)	68 (21)	68 (20)	68 (21)
K-BILD total	60 (17)	54 (11)	57 (12)	54 (11)	56 (13)	54 (11)	49 (8)	55 (12)	53 (11)	56 (12)	55 (11)	55 (12)
EQ-5D-5L VAS	69 (21)	64 (19)	65 (19)	64 (19)	68 (19)	63 (19)	56 (28)	65 (19)	63 (20)	65 (19)	66 (19)	63 (19)
EQ-5D-5L index value	0.8 (0.16)	0.7 (0.2)	0.8 (0.2)	0.7 (0.2)	0.8 (0.2)	0.8 (0.2)	0.7 (0.2)	0.8 (0.2)	0.8 (0.2)	0.7 (0.2)	0.8 (0.2)	0.7 (0.2)
VAS cough	35 (26)	40 (28)	37 (25)	42 (29)	38 (26)	41 (29)	51 (33)	69 (28)	39 (28)	40 (28)	42 (28)	39 (28)
VAS breathlessness	37 (26)	49 (28)	44 (26)	50 (29)	46 (30)	79 (27)	65 (24)	47 (28)	47 (27)	48 (28)	47 (27)	49 (29)
VAS fatigue	**31* (27)**	**51 (25)**	43 (26)	51 (26)	43 (27)	51 (26)	53 (29)	48 (26)	48 (26)	48 (25)	44 (26)	52 (26)
VAS general health	36 (29)	42 (24)	38 (24)	43 (24)	41 (27)	42 (24)	54 (27)	40 (24)	43 (24)	40 (23)	39 (25)	43 (25)
GFI	3 (3)	4 (3)	3 (3)	4 (3)	4 (3)	4 (3)	4 (3)	4 (3)	4 (3)	4 (3)	**3* (2)**	**4 (3)**
ICECAP-O	0.9 (0.1)	0.8 (0.2)	0.8 (0.1)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.1)	0.8 (0.2)	0.8 (0.1)	0.8 (0.2)	0.8 (0.1)	0.8 (0.2)
FVC % predicted	81 (21)	79 (22)	77 (22)	80 (22)	79 (20)	79 (23)	67 (19)	80 (22)	**75* (19)**	**83 (24)**	**75* (18)**	**82 (24)**
FEV1 % predicted	81 (18)	77 (21)	77 (20)	78 (22)	78 (18)	77 (22)	69 (18)	78 (21)	76 (18)	79 (23)	74 (18)	80 (22)
TLCOc % predicted	41 (19)	51 (20)	**45* (20)**	**53 (19)**	50 (19)	51 (20)	**34* (14)**	**52 (19)**	**45* (17)**	**55 (21)**	**44* (17)**	**56 (20)**

Independent sample t-tests were used to compare clubbing measuring method, questionnaire and disease severity scores in patients with and without clubbing, with yes versus no *p-value <0.05.

K-BILD, King's Brief Interstitial Lung Disease health status questionnaire; psych, psychological domain; BA, breath and activities domain; EQ-5D-5L, euroqol-5D-5L; VAS, visual analogue scale; GFI, Groningen frailty indicator; ICECAP-O, ICEpop CAPability measure for Older people; FVC, forced vital capacity; FEV1, forced expiratory volume in the first second; TLCOc, transfer factor for carbon monoxide corrected for hemoglobine



Part 2

Improving quality of life in interstitial lung diseases

Chapter 6

Optimizing quality of life in patients with idiopathic pulmonary fibrosis

"The outstanding doctor constantly emphasized the humanitarian aspect of medical care"
Ben Carson

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Mirjam J.G. van Manen*, J.J. Miranda Geelhoed*, Nelleke C. Tak, Marlies S. Wijsenbeek

Department of Respiratory Medicine, Erasmus Medical Center, University Hospital Rotterdam, the Netherlands

* Shared first authorship

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a devastating, progressive and ultimately fatal lung disease. The combination of poor prognosis, uncertainty of disease course and severe symptom burden heavily impacts patients' and their families' quality of life. Though new antifibrotic drugs have been shown to decrease disease progression, the effect on health-related quality of life (HRQOL) has not been convincingly demonstrated. In a relentless disease such as IPF, striving to optimize HRQOL should complement the endeavour to prolong life. Unfortunately, there is a paucity of interventions improving symptoms and functionality for patients with IPF, and research focusing on symptom improvement, and assessing and optimizing HRQOL, is limited.

This review summarizes the most recent insights into measuring and improving quality of life for patients with IPF, and discusses challenges in the management of this devastating disease. Moreover, we postulate a new model for continuous care in IPF – 'the ABCDE of IPF care': **Assessing** patients' needs; **Backing** patients by giving information and support; delivering **Comfort care** by focusing on treating symptoms and taking into account **Comorbidities**; striving to prolong life by **Disease modification;** helping and preparing patients and their caregivers for the eventual **End-of-life** events that are likely to occur.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a devastating, progressive, fibrotic lung disease. IPF is characterized by irreversible loss of lung function, ultimately resulting in most patients dying from respiratory failure within 3-5 years. The most common symptoms are dry cough, dyspnoea and fatigue.[1] Though the disease course may vary among patients and many patients experience periods of relative stability, disease progression and worsening of symptoms are inevitable for the majority of patients.[2,3] The combination of poor prognosis, uncertainty of disease course and severe symptom burden heavily impacts quality of life (QOL) both for patients and family members.[1,4,5] Recently, knowledge on the pathogenesis of the disease has improved and has led to the development of two antifibrotic drugs that slow down disease progression as measured by decline in pulmonary function. Though these drugs are major steps forward for patients, IPF still remains a devastating and deadly disease. It is encouraging that multiple new compounds are currently investigated in clinical trials, aiming at modifying the disease course. The majority of these trials are focused on disease modification measured by physiological parameters, such as lung function. However, in many patients with IPF, there is no clear correlation between physiological parameters and patient-reported outcome measures (PROMs), such as health-related QOL (HRQOL) scores, that strive to reflect how a patient feels or functions. In a relentless disease as IPF, striving to optimize HRQOL should complement the endeavour to prolong life. There is a paucity of interventions that convincingly improve symptoms and functionality for patient with IPF. This review summarizes the most recent insights into measuring and improving QOL in patients with IPF and postulates an ABCDE of IPF care to facilitate a systematic and comprehensive approach to care for patients with IPF.

HEALTH-RELATED QUALITY OF LIFE IN IPF PATIENTS

Health-related quality of life refers to a person's satisfaction with aspects of life that may be affected by health.[6] As clinicians, we focus primarily on HRQOL since QOL is also determined by such aspects of life as freedom, quality of environment and financial situation. Nevertheless, with a relentless disease as IPF, almost all aspects of life can become health-related.[6] Patients with IPF report an impaired HRQOL.[1] Symptoms as dyspnoea, decreased mobility and cough are often important determinants of HRQOL.[7,8] HRQOL is generally assessed by PROMs.[9] Often, there is a poor correlation between physiological assessments of disease severity by pulmonary function testing and patient reported outcomes of HRQOL and symptoms.[10] Drugs that may modify the disease by slowing down the pace of lung function decline, do not convincingly improve patients' overall symptoms or HRQOL.[11,12] Therefore, complementary disease management strategies are needed to improve HRQOL.

UNMET NEEDS OF IPF PATIENTS AND CAREGIVERS

Several recent initiatives have examined the needs of patients with IPF and their relatives.[1,5,13-18] Though identifying patient-specific needs is crucial in the individual treatment relationship between a patient and care provider, it should be recognized that many basic conditions for IPF care are still frequently unmet. An initiative by 11 European patient advocacy groups for pulmonary fibrosis identified five key themes of unmet needs: 1) better diagnosis, 2) better access to different treatment forms, 3) availability of emotional support, 4) improved information resources, and 5) equal availability of palliative and end-of-life care.[18] The European IPF Patients Charter was developed based on these outcomes (http://www.ipfcharter.org/call-to-action/).

An interesting study by Overgaard and colleagues not only looked at the the unmet needs of patients with IPF, but also included family caregivers.[5] They studied patients' and caregivers' experiences of living with IPF using extensive interviews of patients and their caregivers. In total, 25 patients and 24 family caregivers participated in the study. The main findings of their study showed a need for stepwise information and disclosure, and awareness of differences in reactions and wishes between patients and family caregivers.

A study by Russell and colleagues underscores the previous studies, pointing out a need for better diagnosis of IPF, access to high-quality information on IPF, and emotional support for both patients and family caregivers.[19] Additionally, they found a need for better access to interstitial lung disease (ILD) specialist nurses, and highlighted the meaningful position of physicians and ILD specialist nurses as main contact persons for patients.

Sampson et al. looked at the care needs of IPF patients and their carers in different phases of disease course.[17] Carers was defined as 'a person of the patient's choice who contributed most to their care or, in the early stages of disease, provided emotional support'. Their study shows that although patients and carers had adequate knowledge of the overall prognosis of IPF, it was difficult for them to translate this knowledge regarding their own disease course and the corresponding psychological and physical treatment possibilities. It also recommended that patients and carers needed a different approach to evaluating IPF in clinic, and that physicians should focus not only on lung function parameters, but also on overall health status, self-management, nutrition and explanation of disease progression.

An under recognized problem, but with great impact on QOL, is the presence of sexual dysfunction in some patients with IPF. Erectile dysfunction has been associated with chronic obstructive pulmonary disease (COPD) and was reported to be a common problem in ILD.[20,21]

As a part of the US Food and Drug Administration's (FDA) patient-focused drug development program, a meeting was conducted with patients to examine their perspectives in

treatment approaches. This meeting underscored the need for better medication and symptom relief, in particular for shortness of breath, severe cough and fatigue.[8]

Numerous other studies have evaluated the unmet needs of patients with IPF and their family caregivers.[13,14,16,22] All confirm the above-mentioned needs, and show the importance of holistic complementary care, focused on optimizing QOL in patients with IPF and their family caregivers.

PATIENT-REPORTED OUTCOME MEASURES

A variety of tools are used to assess the impact of disease on QOL in IPF; however, there is a paucity of specific well-validated PROMs and a lack of consensus on which tools to use for care and research.[9,23] Patient-reported outcomes (PROs) are defined as 'any report coming directly from the patient without interpretation by a third party about how they feel or function in relation to a health condition and given intervention'.[24] The most commonly used PROMs in IPF are questionnaires originally developed to assess HRQOL in other chronic (respiratory) diseases. These questionnaires have been modified and revalidated for the IPF population. Two of these questionnaires often used in IPF studies are the Saint George Respiratory Questionnaire (SGRQ) and the Medical Outcomes Study 36-item short-form health survey (SF-36).[25,26] Both are well validated and have proven to possess validity in assessing HRQOL in IPF.[27,28] Despite these qualities, they have failed to convincingly show changes in HRQOL in the major IPF trials. The SGRQ has only shown some significant positive changes in the STEP-IPF trial (using sildenafil) and the INPULSIS 2 trial (using nintedanib).

Since a few years, disease-specific PROMs have been developed and validated in IPF patients. A modified IPF version of the SGRQ (SGRQ-I) was created by statistical analysis (Rasch analysis) of the SGRQ data of a clinical trial in IPF.[29] The SGRQ-I holds validity and reliability comparable with the original SGRQ,[29] but the experience with the questionnaire is limited. The King's Brief Interstitial Lung Disease health status questionnaire (K-BILD) was developed in a population of 124 patients with mixed ILD's and 49 patients with IPF.[10,30] The questionnaire is short (15 questions) and holds good psychometric properties. A Tool to Assess Quality of Life in IPF (ATAQ-IPF) was developed in a group of 95 IPF patients.[31] The questionnaire contains 43 items and is validated in the UK and the US.[32] Longitudinal studies on the performance of the K-BILD and ATAQ-IPF are currently underway.

In addition, regarding IPF several symptom-specific questionnaires have been used. The most commonly used is the University of California San Diego Shortness of Breath Questionnaire (UCSD), which assesses dyspnoea.[33] One of the IPF trials using the USCD was the ASCEND trial (using pirfenidone). Though patients in this trial experienced a significant reduction in their decline of lung function, no effect in UCSD scores was found.[11] The Medical Research Council dyspnoea scale was found to be predictive of

disease progression, but its value to assess response to interventions in IPF is unclear.[34] The same limitation applies for other dyspnoea scoring tools, such as the Borg Rating of Perceived Exertion Scale and the Baseline Dyspnoea Index.[35,36] Though by some estimates, over 80% of IPF patient's experience cough, PROMs on cough in IPF are limited. Both the Leicester Cough Questionnaire (LCQ) and the Cough Quality of Life Questionnaire have been evaluated in IPF, but need further longitudinal validation.[37,38] Visual analogue scales are also used to assess the severity, frequency and impact of cough.[39] LCQ and cough-VAS show correlation with objective cough counts.[40,41] Though fatigue is often a problem in IPF, to our knowledge, no validated fatigue PROMs exist for IPF. Anxiety and depression are estimated to be present in around 25% of patients with IPF and are important to recognize.[4,42] Although no IPF specific tools exist to screen for anxiety and depression, in general practice common tools such as Hospital Anxiety and Depression Scale and the Centre for Epidemiologic Studies Depression are often used.[42,43] It is important to realize that though PROMs were initially mostly developed for use in clinical trials, their use is much broader. Using PROMs in routine care can improve communication, detect unrecognized needs and problems, and serve as outcome measures for interventions.[44-46]

OPTIMIZING QUALITY OF LIFE

Symptoms, perceptions and reactions all interact, and together they influence HRQOL for patients with IPF (Figure 1). This interacting balance wheel of symptoms, perception and reaction varies among patients, but also often changes within individual patients during the disease course (Figure1).

A synchronized comprehensive management strategy is vital to match patients' needs throughout the disease course.[47] Below, we focus on interventions and treatments that may have a positive effect on HRQOL in IPF. To facilitate a systematic and comprehensive approach to IPF care, we postulate to use an 'ABCDE of IPF care' (Figure 2).

Assess patients' needs and values

At time of diagnosis, careful discussion of preferences and needs of care should commence, allowing the patient and family caregivers time and space to cope with the diagnosis and information given. Not only will individual patients have different needs and preferences, the success of therapies and interventions will also depend on patient factors such as expectations, experiences and motivations. Continuous reassessment of the individual patient's wishes and adaptation of interventions is crucial. Good collaboration between patients and health care providers is the foundation for good care. Both need to trust and respect one another. The patient is obliged to inform the health care provider correctly, while the health carer is committed to provide the best care possible for this patient. Lee and colleagues elegantly modelled this patient-provider relationship as the foundation of care of the IPF patient.[47] Family caregivers should be

involved from the onset of the disease and supported as they are the main support for the patient.[5,48]

Figure 1. Balance wheel of symptoms, perception and reaction in patients with idiopathic pulmonary fibrosis.

Backing patients

Education is one of the crucial factors that empowers patients to make realistic choices and to play an active role in their care. The need for information is universal for patients with IPF and their families, and is iterated in all initiatives on identifying patient needs.[5,18,19] Nowadays, many patients diagnosed with IPF and their relatives turn to online sources of health information. Fisher and colleagues showed that these online sources are frequently of poor quality, outdated, or not available in the patients' native language.[49] In daily practise, clinicians and ILD specialist nurses play a central role in providing information and guiding patients to sources of information and support. Though information is such a crucial factor, research on best practices of educating patients and partners is scarce. Some recent studies underlined that information should be gradually paced, and dyssynchrony between patient and partners in coping with the disease should be taken into account.[5,50]

Over the last several years, support groups for patients with IPF have expanded (http://www.pulmonaryfibrosis.org/life-with-pf/support-groups). Support groups can decrease

ABCDE of IPF care

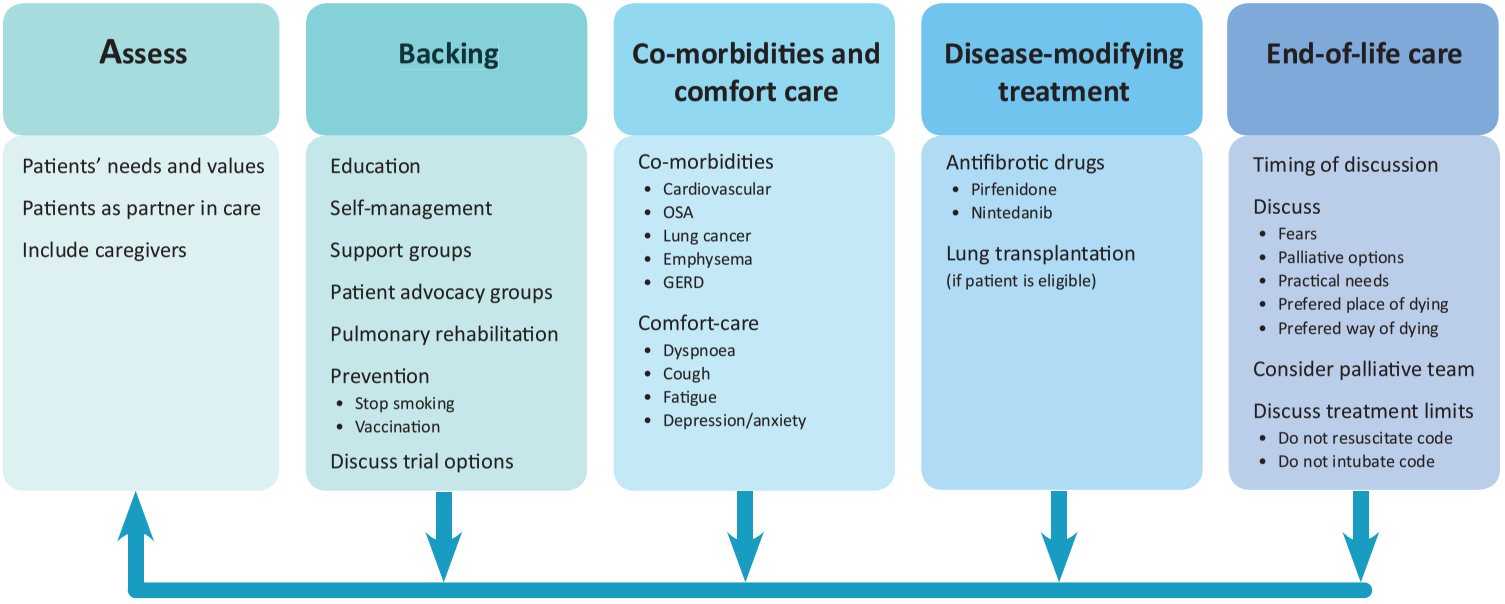

Figure 2. ABCDE of IPF care.
GERD, gastro-esophageal reflux disease; OSA, obstructive sleep apnoea.

anxiety and depression, are helpful in educating patients and family caregivers, and can improve wellbeing.[51] In oncology, support groups have shown their merits in improving QOL.[52,53] In IPF, unfortunately, only few studies have looked at the effect of support groups on the QOL of patients and family caregivers. Lindell and colleagues found that a 6-week disease-management program, surprisingly, decreased HRQOL and increased anxiety scores in IPF patients.[54] Nevertheless, stress scores declined in their partners, and all participants found participation beneficial. Contrary to the study of Lindell and colleagues, unpublished data shows that a 3-week multidisciplinary patient and partner empowerment program for IPF (PPEPP) improved QOL.[55] Patient advocacy groups can also play a role in providing information, support and contact with other patients to share experiences. Besides this, patients should be advised on preventative measures. Although no convincing evidence exists on the benefits of vaccination in IPF, influenza and pneumococcal vaccinations are generally advised. If patients still smoke they should be strongly encouraged to quit smoking.

Trials remain crucial to advancing mechanistic insights and stimulating the development of better therapies and intervention aimed at disease modification and improving HRQOL in IPF. A national survey of pulmonary fibrosis patients and family caregivers presented at the PFF Summit 2015 showed that healthcare providers discussed the trials that were currently being conducted with only 55% of their patients (http://www.viddler.com/v/197d1e49). Collaboration between patients, family caregivers and researchers is essential to advance care in IPF. Moreover, information about ongoing research projects and registries should be made available to enable patients to make choices on possible participation in clinical trials and registries.

Comorbidities and Comfort care

Adequate symptom relief is another crucial aspect in optimizing the QOL of patients and family caregivers.[47] IPF is a disease with a high symptom burden for patients. Symptoms often escalate due to the progressive nature of IPF. In patients with IPF comorbidities are frequent and may importantly contribute to symptom burden and QOL.[56] Identification and treatment of comorbidities may improve QOL and potentially influences prognosis.[57] In the next section, we will review measures that may positively influence the most common symptoms patients with IPF experience; dyspnoea, cough, fatigue/deconditioning and depression/anxiety.[8]

Dyspnoea

Dyspnoea is defined by the American Thoracic Society (ATS) as 'a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity'.[58] Almost all patients with IPF experience progressive dyspnoea, resulting in a major impact on their QOL; living with breathlessness impacts all aspects of daily life. Anxiety and avoidance of exertion lead to deterioration of functional impairment and social limitations.[59] Dyspnoea and change in dyspnoea is also an independent predictor of survival[34,60,61] and has a complex pathophysiology. Possibly, numerous factors – such

as mechanics related to the disease as well as psychological and neurological factors – play a role.[58] Hence, it is useful to understand that hypoxemia does not always result in dyspnoea sensations in patients with IPF.

Data on managing IPF-related dyspnoea is scarce. It is important to first rule out co-morbidities, such as pulmonary hypertension, cardiac disease, muscle weakness, sleep disorders and psychosocial factors. Although antifibrotic therapies have a disease modifying effect and slow down decline in lung function, they do not reduce dyspnoea. There are a few small scale studies suggesting a beneficial effect of supplemental oxygen on dyspnoea and exercise capacity in patients with IPF.[62-64] However, supplemental oxygen can also decrease patients' QOL as it may restrict daily activities, can be expensive, and makes the disease more visible.[65] Some patients regard the initiation of oxygen therapy as a negative landmark in their disease and, as such, often try to postpone start-up. To increase acceptability, compliance and efficacy of supplemental oxygen, careful attention should be paid to the delivery system (e.g. pulse versus continuous, portable versus home-based).

Pulmonary rehabilitation is widely used to improve exercise capacity in patients with chronic disease. In IPF, pulmonary rehabilitation programmes have also been shown to improve dyspnoea, QOL, physical activity and body composition.[66-68] Unfortunately, improvements seem to decrease after finishing the program. Therefore, patients should be encouraged to attend a pulmonary rehabilitation maintenance programme, which may prolong the positive effect of participating.

There is a lack of good quality studies on the effect of opioids on dyspnoea symptoms in patients with IPF. The few existing studies show systemic opioids may have a favourable effect on patients' experience of dyspnoea.[69] As opioids are often seen as end-of-life care and may also have unfavourable side effects, such as constipation and sleepiness, conscientious explanation on their use and anticipation of side effects is recommended. Colman and colleagues demonstrated in a small study that opioids can also be safely prescribed to those patients with ILD on the waiting list for lung transplants.[70] In a cohort of 38 patients taking chronic opioids for their dyspnoea, there was no respiratory depression and no clinically important opioid toxicity. Furthermore, they observed a trend toward increased exertion during exercise sessions with opioids versus pre-opioids. ATS, for example, recommends opioids as a treatment option for patients with chronic respiratory disease, but also, advises discussing drug choice and dosing with patient and family caregivers beforehand.[71]

There are some indications that sildenafil might decrease dyspnoea and improve QOL in patients with IPF.[72] However, debate on this exists and more research is needed.[73] A simple intervention that might be beneficial for patients with IPF is the use of a hand-held fan. Booth and colleagues studied the feasibility of this fan in patients with chronic refractory breathlessness and found a decrease of symptoms in half of the patients.[74]

Cough

No reliable data are available on the prevalence of cough in IPF. Almost 80% of patients with IPF experience some chronic cough, but the number of patients with severe disabling cough may be lower.[12,75] Nevertheless, cough is an invalidating symptom that can evoke spells of severe breathlessness and anxiety and may greatly impact patient's social participation. Cough in IPF has been associated with disease progression.[75] The exact underlying mechanism of cough in IPF patients is unknown, but is most probably 'multifactorial' and driven by mechanical, biochemical and neurosensory changes, with an important role for comorbidities as well.[76-78]

In the treatment of chronic cough in IPF, it is important to first exclude and treat underlying co-morbidities. Frequent comorbidities are gastro-esophageal reflux disease, obstructive sleep apnoea (OSA), chronic sinusitis, emphysema, lung cancer, infection and COPD associated chronic bronchitis. Angiotensin-converting-enzyme inhibitors can also cause chronic cough directly after starting the medication, or even months later.[79] IPF-related cough is frequently refractory to antitussive therapy, and the management of cough in IPF often consists of trying different treatment approaches and can thus be frustrating for both patients and clinicians. Low dose steroids are regularly tried for cough in IPF though there is little data to support their effect.[76] Considering the potential side effects and the fact that steroids as primary treatment for IPF have been associated with worse outcome, risk and benefits should be carefully balanced. In other respiratory diseases, opioids have been shown to decrease cough, although such evidence is absent in IPF data. Thalidomide has been shown to decrease cough in a small 24-week double blind study.[39] As only 20% of screened patients completed the study and thalidomide has a severe side effect profile, we would not recommend it as routine treatment. Recent findings suggest that the antifibrotic drug pirfenidone might have a positive effect on cough.[80] As for nintedanib, its effect on cough is still unknown. While there are no convincing data on over-the-counter cough suppressants in IPF, some patients do report relieve with these agents and the risks of trying them are negligible.

Fatigue and deconditioning

Many patients with IPF experience fatigue. The aetiology is multifactorial with factors such as deconditioning, reduction of skeletal muscle strength, cough, dyspnoea and hypoxemia likely to contribute. Additionally, comorbidities and psychological factors may play a role. Fatigue leads to fewer daily physical activities, resulting in a further decrease in exercise tolerance and muscle strength, which, in turn, increases the level of dependency and immobility, negatively affecting HRQOL and social participation. To objectively measure exercise capacity, a 6-minute walk test or cycle ergometry can be done.[81]

In the treatment of fatigue and deconditioning, it is again important to rule out comorbidities such as cardiac disease, depression and OSA. Referral to pulmonary rehabilitation is, as for dyspnoea, recommended as treatment for fatigue and deconditioning

in IPF patients. Treatment is difficult, as patients find it hard to exercise due to their fatigue and dyspnoea. A decrease in exercise then provokes a downward spiral where muscle strength declines and leads to even less exercise.[82] Early referral is advised as patients probably benefit most when there they are still able to exercise at full power.[83] In addition, oxygen supplementation can be given when hypoxemia limits exercise capacity; however, the exact benefits of oxygen therapy for fatigue in IPF patients are still unclear.[64] The effects of pharmacological therapy for fatigue symptoms in IPF patients is unknown.[47]

Anxiety and depression

In general, patients with chronic diseases are more susceptible to such symptoms as anxiety and depression. Also, many patients with IPF and their partners experience these symptoms.[48,84] In ILDs, percentages vary from 7% to 49 % for clinical meaningful depression, and 9% to 12% for clinical meaningful anxiety.[4,43,85,86] There is a known relationship between anxiety and breathlessness in other chronic diseases.[87,88] Breathlessness causes anxiety, as patients panic when they cannot breathe and fear the next attack. But anxiety can, on the other hand, increase the perception of breathlessness.[59] It is stressful for family caregivers that they cannot help their loved ones during these attacks.[22] Coughing can increase feelings of anxiety as it induces breathlessness as well. IPF patients also experience anxiety and depression due to the side effects of medication and the uncertainty about the disease course in the context of a poor prognosis. Depression and anxiety are not only essential in predicting the QOL for ILD patients, but can also aggravate breathlessness.[42,84] Therefore, screening for depression and other underlying symptoms that can increase psychological stress and may decrease the patients QOL, is needed.[42]

In the treatment of anxiety and depression, it is important to look at comorbidities such as OSA, fatigue and polypharmacy. Again, referral to pulmonary rehabilitation can be beneficial.[13,89] A valuable addition to pulmonary rehabilitation might be cognitive behavioural therapy (CBT).[90] CBT focuses on the relationship between thoughts, emotions, physical symptoms and behaviour, and enables people to cope with their negative thoughts.[91] CBT has been shown to decrease anxiety and depression symptoms in patients with COPD and might be beneficial for all chronic physical diseases.[42,91,92] In addition, ILD specialist nurses can play an important role in managing such symptoms as depression and anxiety. Since they are readily accessible and closely involved in the patient's disease path, it is easier for patients to talk to ILD specialists about their concerns and problems than doing so during their short visits to the doctor. Support groups can also help patients with their emotional struggles and are important for educating patients and their family caregivers.[51] The effect of pharmacologic treatment for anxiety and depression, such as anti-depressant medication, has not been studied in IPF; thus, the need to use such treatment should be considered thoroughly for each patient.

Disease-modifying treatment

The availability of two antifibrotic drugs with confirmed positive treatment effects has significantly changed the course of the disease and the hopes for patients.[11,12] Unfortunately, neither of these drugs cures IPF or completely halts disease progression, and lung transplantation remains the only curative treatment for the small minority of patients who are eligible for this major intervention. Although neither antifibrotic drug has convincingly demonstrated a positive effect on HRQOL, there is no evidence of negative reactions from side effects. It might well be that better tools are needed to detect changes in HRQOL. On the other hand, we should also consider the meaning of nonsignificant changes or stabilization of HRQOL for patients suffering from a disease that remains progressive. Furthermore, it might well be that disease modifying agents do not necessarily improve a patient's HRQOL. Since HRQOL is determined by many aspects of life and disease, it is evident that complementary treatment strategies are needed.

In the era before the availability of antifibrotic drugs, treatment goals gradually shifted during the course of the disease from more disease-centered management to more palliative measures.[47] Currently, this shift is less obvious as even when lung function declines, the effect of the antifibrotic drugs may still be present.[93] Furthermore, these drugs may prevent the development of acute exacerbation[12,94-96] and thereby protect the patient from a sudden decline in HRQOL or even death. In clinical practice, reassessing patients' wishes and expectations, as well as incorporating the balance between efficacy and the burden of side effects, will guide decisions on discontinuation of antifibrotic treatments.

End-of-life care

Despite the fact that IPF has a prognosis worse than most malignancies,[97] end-of-life care is far less developed in this area of medicine than in oncology. Experiences from oncology have taught us that early palliative care improves the QOL and the mood of patients with metastatic lung cancer, and this, in turn, has resulted in less aggressive care and better survival.[98] There are a few issues that complicate end-of-life care in IPF. The disease is rare and relatively unknown to patients and the community. In qualitative interviews, patients and their relatives frequently rated their situation worse than patients with cancer. They perceived that in cancer everybody understands the seriousness of the disease and patients with cancer have "help coming from every direction".[17] Another factor is the variable course of disease in IPF, in which sudden acute exacerbations can occur and prognosis is often unpredictable. Additionally, the timing of discussing end-of-life issues is difficult and should be tailored to the patients' needs and wishes. There can also be dyssynchrony between patient and partners in wishing for information on this issue. Interactive questioning of patients in the Netherlands and Germany established that the majority of patients and partners prefer talking about the end-of-life early in the disease course, though we acknowledge that cultural differences may exist.[48] It is useful, however, to realize that discussing end-of-life may be anxiety

provoking and can have a negative impact on HRQOL.[54] Sampson and colleagues found that patients with IPF clearly understand their prognosis but struggle to understand how their disease will progress.[17] Explaining the course of the disease, what to expect in the last phase, and palliative options may enable patients and families to make decisions in line with their values. In a recent study, only 13.7% were referred to palliative care services,[99] indicating that the use of palliative care teams is underutilised at the moment. Alternatively, Bajwah et al. showed that interdisciplinary community care conferences improved symptoms and QOL.[100]

Data from patients with other terminal diseases suggest that the majority of patients would prefer to die at home.[101] Lindell and colleagues showed that in a US cohort of patients more than half of the patients died in hospital, a third on the ICU, and the remaining patients died in a hospice.[99] European experiences showed that more patients died at home compared with the US study, but still the majority died in the hospital.[102] Hospital admission for respiratory-related causes in IPF is associated with high in-hospital mortality.[103] The limited options and devastating outcomes of hospital admission in the end-stage of the disease should be discussed with patients in an early phase to enable them to make decisions on limitations of care and allow them to choose the place of dying. At the patient's request – if this is legally possible in the country where the patient is seeking treatment – different options of dying should also be discussed. Currently, worldwide, euthanasia has been legalized under strict conditions in a few countries.[104] In these countries, patients should be able to receive information on euthanasia. It is important to also discuss a 'do not resuscitate' code and a 'do not intubate' code with patients and family to avoid medical futility or unwanted interventions.

CONCLUSION

In a relentless disease such as IPF, striving to optimize HRQOL should complement the endeavour to prolong life. As symptoms, perceptions and reactions interact and may change, a synchronized comprehensive management strategy is vital to match patients' needs throughout the disease course. To do so, we propose the ABCDE of IPF care: Assess patients' needs; give information and support to Back patients; deliver Comfort care by focusing on treating symptoms also taking into account Comorbidities; strive to prolong life by Disease modification; and help and prepare patient and family for the End-of-life. To optimize quality of life for patients with IPF, we need to provide patient-centered care that is comprehensive and not mainly focused on disease modification therapies.

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Chapter 7

Cough in idiopathic pulmonary fibrosis

"We all cough and cry with the same language"
adapted from Javad Alizadeh

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Mirjam J.G. van Manen[1], Surinder S. Birring[2], Carlo Vancheri[3], Vincent Cottin[4], Elisabetta A. Renzoni[5], Anne-Marie Russell[5, 6], Marlies S. Wijsenbeek[1]

[1]Department of Respiratory Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands.

[2]Division of Asthma, Allergy and Lung Biology, King's College London, London, UK.

[3]Department of Clinical and Experimental Medicine, Section of Respiratory Disease, University of Catania, Catania, Italy.

[4]Department of Respiratory Medicine, Louis Pradel Hospital, Hospices Civils de Lyon, Lyon 1 University, Lyon, France.

[5]Interstitial Lung Disease Unit, Royal Brompton Hospital, London, UK.

[6]National Heart and Lung Institute, Imperial College London, London, UK.

ABSTRACT

Many patients with idiopathic pulmonary fibrosis (IPF) complain of chronic refractory cough. Chronic cough is a distressing and disabling symptom with a major impact on quality of life. During recent years, progress has been made in gaining insight in the pathogenesis of cough in IPF, which is most probably “multifactorial” and influenced by mechanical, biochemical and neurosensory changes, with an important role for comorbidities as well. Clinical trials of cough treatment in IPF are emerging, and cough is increasingly included as a secondary endpoint in trials assessing new compounds for IPF. It is important that such studies include adequate end-points to assess cough both objectively and subjectively. This article summarizes the latest insights into chronic cough in IPF. It describes the different theories regarding the pathophysiology of cough, reviews the different methods to assess cough and deals with recent and future developments in the treatment of cough in IPF.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease of unknown cause with a median-survival of 3-5 years after diagnosis.[1] Treatment of IPF aims at slowing or stopping the disease progression, increasing survival, reducing symptoms and improving quality of life (QoL).[2] Currently, two anti-fibrotic drugs are available that slow down disease progression.[3,4] In a small minority of patients lung transplantation is an option which can increase survival and improve QoL. Alleviating symptoms and improving QoL in IPF is often a major challenge to treating clinicians. Patients report that the symptoms that have the greatest impact on daily life are cough, shortness of breath and fatigue or malaise.[2] Chronic cough in IPF is not only often refractory, but is also an independent predictor of disease progression.[5] Better understanding of the underlying mechanism(s) causing cough in IPF and better treatments are clearly needed. This review summarizes the latest insights on chronic cough in IPF.

CHARACTERISTICS AND DEMOGRAPHICS OF CHRONIC COUGH

Chronic cough is defined as a cough lasting for at least 8 weeks. In the general population it has a prevalence of 9 to 33% in the USA and Europe.[6] It is a frequent reason for seeking medical advice, with a high number of medical consultations.[7] The most important risk factor for chronic cough is cigarette smoking. Prevalence of chronic cough is three times higher in chronic smokers as in never- or ex-smokers.[6]

No reliable data on the prevalence of cough in IPF exist. Some studies report that up to 80% of patients experience chronic cough;[5,8] however, lower numbers are also reported.[4] This may be attributed to method of reporting and the definition of cough used (any cough *versus* disabling cough). When cough is present in IPF, it is severe and difficult to treat.[8] Cough is mostly nonproductive and dry, although some patients experience non-purulent sputum production, possibly related to traction bronchiectasis in advanced IPF or concomitant chronic obstructive pulmonary disease (COPD). The urge to cough cannot be relieved by coughing.[9]

Cough frequency is high in patients with IPF, with median (range) 24-h cough counts varying from 226 (36-946) to 520 (117-1493) depending on the population studied.[10,11] The cough frequency in IPF is similar to patients with chronic cough presenting to a cough specialist clinic, and higher than in patients with asthma or COPD (asthma median (range) 24-h cough rate 62.4 (0-341), COPD ex-smokers 117.6 (range 14.4-648)).[10,12] Strikingly, IPF patients experience more cough symptoms during daytime (median hourly cough rate 14.6 during the day *versus* 1.9 during the night), analogous with COPD and asthma patients.[10,12] Chronic cough in IPF is not related to age or gender, and is more common in "advanced" disease and in never-smokers,[5,10] the latter in contrast to chronic cough in the general population.[6] There is no clear explanation why IPF patients without a history of smoking cough more, but this may be related to the phenotype of IPF.[13]

EFFECT ON THE PATIENT

In general, chronic cough can impact severely on different aspects of life.[14] Problems with sleeping, raucous vocal sounds and musculoskeletal pain of the chest can occur.[9] Chronic cough can cause relationship difficulties, avoidance of public areas, decreased social interaction and work-related problems affecting physical, mental and social health.[14,15] In IPF, the limited studies about cough and QoL also show that cough is a very disabling and distressing symptom impacting QoL.[9,10] Some patients also experience cough-related urinary incontinence with dramatic impact on QoL.[16] Moreover, the social impact of chronic cough in IPF further compounds limited exercise ability, reduced walking distance and the need to use supplemental oxygen.

PATHOPHYSIOLOGY OF CHRONIC COUGH

A detailed overview of the pathophysiology of cough is beyond the scope of this review; however, a summary of the mechanisms that may play a role in cough in IPF[17] is shown in figure 1. Imbalance between stimuli and responses results in increased coughing. Minor stimuli such as laughing, talking, smoke, perfume and temperature changes already induce a cough reflex.[6,18] This has also been named cough hypersensitivity syndrome and can occur in patients with and without pulmonary disease.[19]

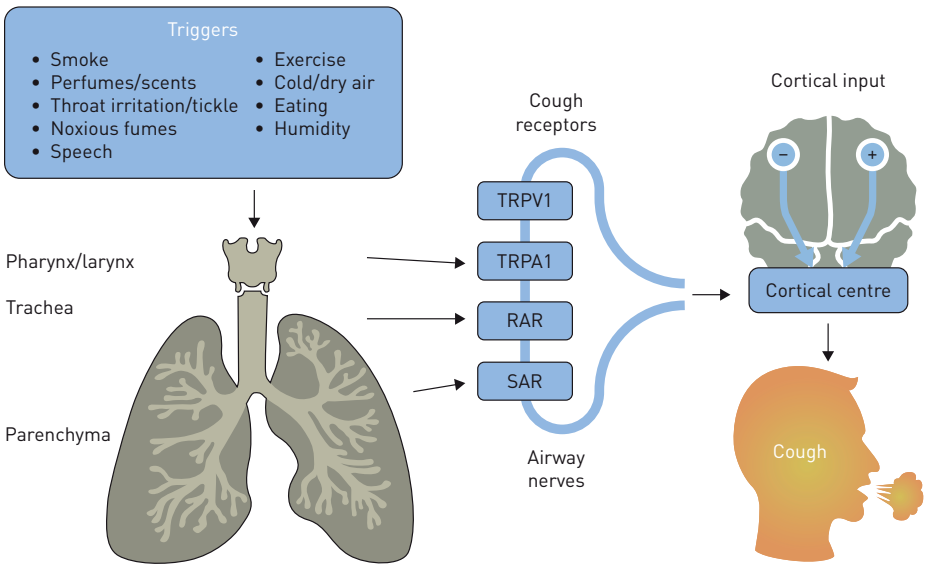

Figure 1. Pathophysiology of cough.
TRPV1: transient receptor potential vanilloid 1; TRPA1: transient receptor potential ankyrin 1; RAR: rapidly adapting receptor; SAR: slowly adapting receptor. Reproduced from[17] with permission from the publisher.

The cough reflex has an afferent pathway, with sensory nerve fibres of the vagus nerve located in the ciliated epithelium of the upper airways and cardiac and oesophageal branches from the diaphragm.[20] These afferent impulses go to the brain stem and cortical center, which are important in regulating the cough response. In response this activates the efferent motor pathway of the cough reflex, by sending impulses *via* the vagus, phrenic, and spinal motor nerves to the diaphragm, abdominal wall and muscles, resulting in cough.[17,18,20]

The afferent part of the cough reflex involves at least three broad classes of nerves: C-fibres, rapidly adapting receptors (RARs) and slowly adapting receptors (SARs).[20] 1) C-fibres are sensitive to thermal and chemical stimulation, such as capsaicin, citric acid and hypertonic saline. TRPV1 and TRPA1 are C-fibre receptors that are very responsive to chemicals.[20,21] 2) RARs are rapidly responsive to mechanical stimulation, such as changes in, for example, diameter, length, and compliance of the airways. RARs are also sensitive to changes in PH and osmolality but relatively insensitive to other chemical stimulation.[22,23] 3) SARs are highly sensitive to mechanical forces and are thought to be the afferent fibres involved in the Hering-Breuer reflex, which terminates inspiration and initiates expiration when the lungs are adequately inflated.[20]

Recently it has also been recognized that neuroplasticity, whereby nerves switch phenotype, can occur in different disease processes.[24] Voluntary cough and the sensation of an urge to cough have their origin in the cerebral cortex.[18]

PATHOPHYSIOLOGY OF COUGH IN IPF

The pathophysiology of chronic cough in IPF is still unknown and is complicated by the frequent confounding comorbidities in this population. Different concepts of the possible mechanisms of cough in IPF have been proposed.[25]

There is some evidence that the cough reflex sensitivity in patients with IPF is increased,[8,26] suggesting an upregulation of sensory fibres in the lungs.[8,26] However, the studies assessing cough sensitivity were performed before the publication of the current international guidelines for the diagnosis of IPF in 2011.[1] Assuming that increased cough reflex sensitivity may play a role in at least part of the IPF population, the question remains what causes this enhanced sensitivity.

A possible explanation could be that mechanical distortion of the lung, caused by the fibrosis, directly influences nerve fibres. As RARs and SARs are sensitive to mechanical changes they could be influenced in sensitivity or quantity by the traction forces of the fibrosis.[22,25] Nerves that inhibit cough might also be destroyed due to fibrosis.[22] This corresponds with the finding of increased cough reflex sensitivity by mechanical stimulation of the chest wall in IPF patients, compared with controls. An increased sensitivity

was especially found following low frequency stimulation of the posterior basal lung base, the area where lung fibrosis in IPF is typically most extensive.[22] This mechanism may also explain the observation that cough seemed to be more frequent in advanced IPF, although in another study this correlation was not found.[5,10] Moreover, this is in line with clinical findings that patients often report starting to cough when talking or not being able to stop coughing once they start. The transmission of vibration caused by talking or even coughing itself might lead to increased mechanical stimulation of the sensory receptors, perpetuating a cycle of more cough and more vibration.[27]

Another explanation of enhanced cough sensitivity could be the higher levels of neurotrophins that have been found in the sputum of patients with IPF than in controls.[8,25] Neurotrophins induce the survival and development of different subgroups of sensory neurones and can also cause increased capsaicin sensitivity, enhancing cough reflex.[8,25,26] Immunohistochemical studies have shown that non-neuronal cell types, such as bronchial and alveolar epithelial cells, mesenchymal cells, lymphocytes and macrophages can express neurotrophins.[28] In patients with idiopathic interstitial pneumonias, an increased expression of neurotrophins in the lung was shown, suggesting that they may potentially modulate sensory nerve proliferation and neuroplasticity.[29] Immunoblots revealed more neurotrophin expression in IPF/usual interstitial pneumonia than in nonspecific interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung disease.[29] The underlying drivers of increased neurotrophin expression in IPF are unknown, although in other diseases inflammation is related to increased neurotrophin expression.[30]

Interestingly, cough is an independent predictor of disease progression and the amount of coughing is not clearly related to the pulmonary function measurements.[10] Leslie[31] suggested that recurrent stretch injury caused by pressure changes during breathing may explain why fibrosis in IPF typically commences at the peripheral basal part of the lung. Leslie[31] argues that in these areas the traction forces and alveolar collapse are greatest, leading to sheer stress, lung injury and activation of fibrotic cascades. By analogy, mechanical ventilation in IPF can be a risk factor for acute exacerbations of the pulmonary fibrosis.[32] If pressure differences play a role in the pathogenesis of IPF, it could be speculated that the pressure differences caused by cough might influence disease behavior itself. One could hypothesise that cough is not only a symptom, but may also contribute to enhance activation of profibrotic mechanisms and disease worsening in IPF.

Furthermore, cough could be evoked centrally through cortical influences. The urge to cough, induced by capsaicin inhalation, activates many areas of the cerebral cortex.[33] Administration of a placebo prior to capsaicin testing can decrease activity in several brain regions.[34] This suggests that expectations of treatment can influence central processing of peripheral sensory input.[34] Suppression of cough by cortical influences could also explain why IPF patients cough less during their sleep.

COMORBIDITIES INFLUENCING COUGH

In patients with IPF, a number of potential causes of chronic cough must be excluded before chronic cough may be considered directly linked to the underlying disease. In at least half of the patient comorbidities may play a role (table 1).[35]

Table 1. Comorbidities influencing cough in idiopathic pulmonary fibrosis (IPF)

Comorbidity	Frequency in IPF (%)	Reference(s)
GORD	21 – 94	[36-38]
OSA	59 – 88[#]	[38-40]
Emphysema	30 – 55	[41]
ACE inhibitor use	9 – 15	[5, 42]
Chronic sinusitis/ UACS	17 – 34	[5, 42, 43]
Lung cancer	4.4 – 16	[41, 44]
Infection	11 – 20	[3]

GORD: gastro-oesophageal reflux disease; OSA: obstructive sleep apnoea; ACE: angiotensin converting enzyme; UACS: upper airway cough syndrome. [#]: with high mean body mass index of 28-32 $kg \cdot m^{-2}$.

Gastro-oesophageal reflux disease (GORD) is highly prevalent in IPF, yet classical symptoms are often absent.[37,38] GORD associated microaspiration of acid and non-acid reflux in the airway is thought to induce epithelial damage and may cause fibrosis.[45] Traction caused by lung fibrosis also can result in a weakened lower esophageal sphincter, leading to gastro-oesophageal reflux and microaspiration.[38,46] Cough receptors could be directly stimulated through aspiration of gastric secretion in the larynx and the upper airways.[6] Moreover, the presence of acid in the distal oesophagus may induce cough, probably through an oesophageal-tracheobronchial reflex.[47] Disappointingly, a study of Kilduff et al. showed no improvement of cough by anti-acid treatments, but a paradoxical increase in non-acid reflux. It might well be that non-acid reflux is influencing cough more than acidic reflux.[48] Unfortunately, cough itself may also increase trans-diaphragmatic pressure and promote GORD.[47]

Obstructive sleep apnea (OSA) is common in IPF.[39] OSA itself, with intermittent hypoxaemia may promote profibrotic mechanisms.[49] In the general population, chronic cough is more prevalent in OSA and can be improved by treatment with continuous positive airway pressure (CPAP).[50] A complicating factor is that obstruction of the upper airway in OSA could increase a trans-diaphragmatic pressure differential promoting GORD.[51,52] GORD, on the other hand, may promote OSA, through microaspiration of gastric substance, creating an inflammatory reaction blocking the airway.[53] GORD, chronic cough and, as recently shown, IPF can be improved by treatment of OSA.[49,51] Figure 2 shows the interplay between IPF, GORD, OSA and cough. Further research is needed to disentangle these interactions.

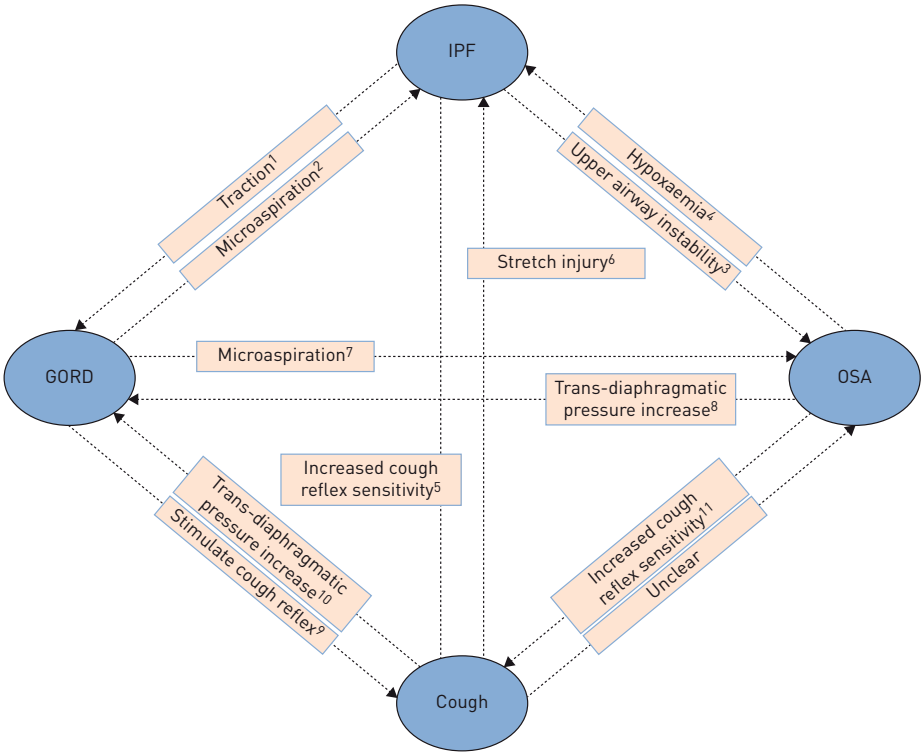

Figure 2. Interactions between idiopathic pulmonary fibrosis (IPF), gastro-oesophageal reflux disease (GORD), obstructive sleep apnoea (OSA) and cough.

1: traction leading to a weaker lower oesophageal sphincter tonus[45]; 2: microaspiration inducing epithelial damage[38, 46]; 3: restriction inducing instability of the upper airway[39]; 4: intermitted hypoxaemia promoting profibrotic mechanisms[49]; 5: increased cough reflex sensitivity[22–31]; 6: pressure causing stretch injury and activation of fibrotic mechanisms[31]; 7: microaspiration causing an inflammatory reaction blocking the airway[53]; 8: obstruction increasing trans-diaphragmatic pressure[51, 52]; 9: aspiration directly and acid reflux indirectly stimulate the cough reflex[6, 47]; 10: cough increasing trans-diaphragmatic pressure[47]; 11: less central inhibition and inflammation increasing cough reflex sensitivity[54].

Additional comorbidities not directly linked to IPF should also be evaluated, especially cardiovascular comorbidity and associated treatment. Left heart disease and the use of beta-blockers are possible causes of chronic cough. Angiotensin converting enzyme (ACE) inhibitor as a cause of chronic cough should always be checked. ACE inhibitors can cause enhanced cough receptor sensitivity leading to cough just after taking the drugs, but also even months later. Symptoms can improve days after drug removal, but can take longer to disappear completely.[6] In the work-up of cough in IPF, infections, chronic sinusitis, COPD-associated chronic bronchitis and pulmonary malignancies should also be excluded.

ASSESSMENT OF COUGH IN IPF

In recent years, many tools have been developed to assess different aspects of cough; subjectively with cough questionnaires or visual assessment scales, and objectively using cough recorders and cough challenge tests. All these instruments have been developed

Table 2. Cough measurements in idiopathic pulmonary fibrosis (IPF) patients

Cough measurement tool	Description	Validation studies and MCID	Advantages	Disadvantages
Subjective				
Visual Analogue Scale[56]	100 mm scale with extremes no cough to worst possible cough severity	Not validated in IPF	Easy to use Repeatable Responsive	Not validated in IPF or chronic cough
Cough Quality-of-Life Questionnaire[57]	28-item cough-specific quality-of-life questionnaire with six domains	Validated in IPF (n=23) MCID in IPF: change of five points on a 28-112 scale[57]	Comprehensive questionnaire Reliable Valid instrument for assessing impact of cough	Need more studies in IPF: MCID evaluated with a retrospective anchor scale
Leicester Cough Questionnaire[15]	19-item self-administered chronic cough quality-of-life questionnaire with three domains	Evaluated in IPF: high correlation found with cough visual analogue scale, cough symptom score and objective cough frequency in IPF[10,22] MCID in chronic cough: 1.3	High reliability Valid instrument for assessing impact of cough Ability to detect a response to change	Need more studies in IPF: MCID evaluated in chronic cough
Objective				
Cough challenge test[58]	Measurement of cough reflex sensitivity by inhalation of nebulised tussive agents (most common citric acid or capsaicin)	Not validated in IPF No MCID Standardized methodology published by ERS[14]	Useful for testing effect of new cough therapies on cough reflex sensitivity and for obtaining mechanistic insights	Doesn't measure efficacy of therapy or predict response in patients Limited availability
Cough monitor[59]	Microphone and recording device measuring cough in a pre-specified time slot	Validated cough monitors for chronic cough High correlation found with subjective cough measurements[10]	Measures cough frequency accurately	Currently limited to research and trails Benefit in routine clinic is not clear

MCID: minimal clinically important difference; ERS: European Respiratory Society.

for chronic cough in a general population and are reviewed elsewhere.[55] Experience and validation of these tools in patients with IPF are limited (table 2 provides an overview).

By analogy with chronic cough, we would recommend the visual analogue scale to measure the severity of IPF related cough in a clinical setting, as it is fast and easy to use.[60] When designing a clinical trial, validated subjective as well as objective cough outcome measures should be incorporated.

TREATMENT OF COUGH IN IPF

In clinical practice, cough in IPF is a major challenge for the treating physician and patient, as it is often refractory. The first step in the management of chronic cough in IPF consists in addressing possible comorbidities as described in table 1.

Conventional anti-tussive therapy is often not beneficial.[8] Oral corticosteroids have been shown to improve cough symptoms in IPF patients in one small nonrandomised study,[8] and low doses of prednisone are sometimes tried in daily practice to relieve cough, and later slowly tapered if beneficial. However, no effect on QoL and survival was found and possible side-effects should be taken into consideration. Although opiates are recommended in the palliative setting, their effect has not been proven in IPF.[1,27] Caution is warranted as opiates may influence the protective mechanism of cough, but might be a useful option for palliation of severe cough in patients with advanced IPF. With respect to GORD, no good evidence on the work-up and treatment of GORD-related cough in IPF exists, whilst the effect of proton pump inhibitors on cough is debated.[48,61]

A 24 week single center double-blind cross-over study with thalidomide for treatment of cough showed a positive effect on QoL measured with the Cough Quality of Life Questionnaire. However, only 20% of the screened subjects completed the study and the potential side-effects of thalidomide can be severe.[43] Thalidomide has anti-inflammatory and anti-angiogenic effects, similar to currently used anti-fibrotic drugs. Its side-effect profile with dizziness and neuropathy suggest that it might also have effects on sensory nerves. Although these results advocate the need for further investigations, thalidomide should not be considered a routine treatment of cough in IPF, even as a second-line therapy, until further evaluation of the benefit/risk ratio has been undertaken.

The majority of IPF patients are treated with one of the two new anti-fibrotic drugs, pirfenidone or nintedanib.[62] Although the effect of these drugs on cough has not yet been evaluated, there are some indications of a possible effect on cough. Azuma et al.[63] showed, in a subgroup analysis of the phase three trial in Japan, that pirfenidone seemed to reduce cough in patients with an forced vital capacity >70% and arterial oxygen saturation measured by pulse oximetry <90% predicted. Using a nonvalidated

cough score, a Dutch group also observed a reduction in cough with pirfenidone use.[64] In a guinea pig model, the capsaicin-induced cough reflex sensitivity was inhibited by pirfenidone in a dose-dependent manner.[65] This effect was accompanied by a reduction of bronchoalveolar lavage mediators promoting cough sensitivity.[65] No data currently exist on the effect of nintedanib on cough.

FUTURE TRIALS

Progress has been made in the treatment of "general" chronic cough. A combination of pregabalin and speech therapy has been found to improve cough and QoL more than speech therapy alone.[66] Gabapentin, a neuromodulator, was shown to improve cough severity, cough frequency and QoL of patients with chronic cough.[67] Physiotherapy aimed at suppressing cough improved sleep and cough frequency.[68] Very recently AF-219, a P2X3 receptor antagonist, showed very promising phase two results in chronic cough.[69]

Many trials in IPF are emerging that assess the effect of these treatments or other novel medications on cough as either a primary or exploratory end-point, illustrating the need for better cough treatment in patients with IPF. Amongst these trials are studies on pirfenidone, AF-219, azithromycin, PA101, GSK2126458, laparoscopic anti-reflux surgery, supplemental oxygen, omeprazole and cognitive behavioral therapy (clinicaltrials.gov; searched using the terms "cough" and "IPF"; date last accessed: August 17, 2015).

CONCLUSION

Chronic cough in IPF is a major problem for patients and treating physicians. The pathogenesis of cough is most likely "multifactorial" and influenced by mechanical, biochemical and neurosensory changes. Comorbidities also have an important role, in particular GORD. While progress has been made in gaining insight into the pathogenesis of cough in IPF, more research is needed to find effective therapies. Clinical trials of cough treatment in IPF have only recently started, with either compounds developed for "general" chronic cough or new compounds in development for IPF, which are also evaluated for their potential effect on cough. It is crucial that validated cough measurements are included in these trials. Hopefully these new studies will ultimately lead to adequate treatment of cough, thereby improving quality of life in patients with IPF.

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Chapter 8

Effect of pirfenidone on cough in patients with idiopathic pulmonary fibrosis

"Silence is sometimes the best answer"
Dalai Lama

Adapted version in press in Eur Respir J

Mirjam J.G. van Manen[1], Surinder S. Birring[2], Carlo Vancheri[3], Virginia Vindigni[3], Elisabetta Renzoni[4], Anne-Marie Russell[4,5], Monique Wapenaar[1], Vincent Cottin[6], Marlies S. Wijsenbeek[1]

[1]Department of Respiratory Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands
[2]Division of Asthma, Allergy and Lung Biology, King's College London, London, UK
[3]Department of Clinical and Experimental Medicine, Section of Respiratory Disease, University of Catania, Catania, Italy
[4]Interstitial Lung Disease Unit, Royal Brompton Hospital, London, UK
[5]National Heart and Lung Institute, Imperial College London, London, UK
[6]Department of Respiratory Medicine, Louis Pradel Hospital, Hospices Civils de Lyon, Claude Bernard Lyon 1 University, Lyon, France

ABSTRACT

Background

In patients with idiopathic pulmonary fibrosis (IPF), cough is a major unmet treatment need and independent predictor of disease progression. Clinical observations suggested that pirfenidone, an anti-fibrotic drug, decreased cough. We aimed to objectively assess the effect of pirfenidone on cough in patients with IPF.

Methods

In this multicenter, prospective, observational study, patients with IPF and a cough visual analogue scale (VAS) ≥40mm, about to start on pirfenidone, were recruited from four European centers. The primary endpoint was change in 24-h objective cough counts at 12 weeks compared to baseline, measured with the validated ambulatory Leicester Cough Monitor. Secondary endpoints included changes in subjective cough-related quality of life measured with the Leicester Cough Questionnaire (LCQ), cough severity with VAS, and quality of life with King's Brief Interstitial Lung Disease questionnaire.

Results

Of 46 patients screened for the study, 43 were included. Pirfenidone decreased objective 24-h cough by 34% (95% confidence interval (CI) -48 – -15; p=0.002) over 12 weeks. Subjective measurements were consistent; LCQ scores improved by 2.0 points, (CI 1.0-3.0; p<0.001), cough VAS improved by 19 mm (CI -28 – -10); p<0.0001) and urge-to-cough VAS improved by 18 mm (CI -26 – -10; p<0.0001). There were no significant changes in other quality of life scores.

Conclusions

In patients with idiopathic pulmonary fibrosis suffering from cough, pirfenidone reduced objective 24-h cough counts and improved subjective measures of cough. The magnitude of these changes was clinically meaningful to patients.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease with a median survival of 3-5 years. One of the most disabling symptoms reported by patients with IPF is cough.[1-3] A recent study reported that IPF patients cough on average 226 times per 24-hours (range 36-946).[4] Cough not only has a major impact on IPF patients' quality of life (QoL), but is also an independent predictor of disease progression.[2,4,5]

In patients with IPF, cough is often non-responsive to anti-tussive therapy.[6] Studies on cough in IPF are scarce and have unfortunately not yet resulted in effective treatments. Recently, pirfenidone, an anti-fibrotic drug which reduces disease decline measured by the forced vital capacity (FVC),[7] was approved for treatment of IPF. Several observations have suggested that pirfenidone might decrease cough. Pirfenidone seemed to reduce cough in a post-hoc subgroup analysis of a phase III trial in Japan.[8] Furthermore, pirfenidone inhibited cough reflex sensitivity in guinea pigs.[9] To date, there are no studies prospectively investigating the effect of pirfenidone on cough in IPF.

We aimed to objectively measure the effect of pirfenidone on cough in patients with IPF suffering from substantial cough. Additionally, we aimed to assess the effect of pirfenidone on subjective cough outcomes and QoL measures.

MATERIALS AND METHODS

Study design and population

This study was an international, multicentre, prospective, observational study at four sites (Netherlands, Italy, France and UK) between December 2013 and June 2016. The study was approved by the ethics committees of all participating centers (e-Appendix 1), and carried out according to the Declaration of Helsinki and good clinical practice. All patients provided written informed consent. An independent research organisation (Venn Life Science) monitored the study at all sites. The study was registered at clinical trials.gov, NCT02009293.

Treatment naïve IPF patients aged 40-85 years in whom pirfenidone therapy was about to be initiated according to regular practice, and who had daily cough related to IPF present for more than eight weeks with a cough score of ≥40 mm on a 0-100 mm visual analogue scale (VAS), were eligible for this study. Inclusion and exclusion criteria can be found in e-Table 1.

Outcomes

The primary outcome was the change in objective 24-h cough frequency at week 12 compared to baseline. Secondary outcomes were: 1. change in cough frequency at baseline versus week 4; 2. change in subjective cough-related QoL and cough severity

and urge-to-cough at week 12 versus baseline; 3. the impact of cough on QoL, anxiety and depression at baseline, week 4 and week 12; 4. the change in cough frequency in relation to lung function; and 5. identification of clinical characteristics predictive of 24-h cough.

Data collection

Leicester Cough Monitor (LCM) – objective measure

Patients underwent baseline 24-h ambulatory cough measurement with the LCM prior to starting with pirfenidone and after 4 weeks and 12 weeks of treatment. The LCM is a validated ambulatory cough monitoring system, which has been used in randomised controlled trials of therapy for patients with chronic cough.[10-12] The LCM consists of an MP3 recording device and a small microphone attached to the patient's clothes close to the neck. The cough monitor was set up in clinic and used by the patients at home for 24 hours. Afterwards, the recordings were extracted from the recorders and centrally analysed with automated cough software as described previously.[11]

Questionnaires – subjective measures

On the days of cough recording, participants completed the Leicester Cough Questionnaire (LCQ), the VAS cough, VAS urge-to-cough, King's Brief Interstitial Lung Disease health status questionnaire (K-BILD), the Hospital Anxiety and Depression Scale (HADS), the 7-item Generalized Anxiety Disorder screener (GAD-7) and Medical Research Council questionnaire (MRC).[13-17]

Physiological measures

Physical examination, symptom assessment, and pulmonary function tests were performed at baseline, at week 4, and at week 12.

Statistical analysis

Parametric data are shown as mean (SD) and nonparametric data as median (range). Analyses were done on the intention-to-treat population. Objective cough frequency data were log transformed. To assess the effect of pirfenidone on cough over time we used a linear mixed model. This model imputes missing data.[18,19] To determine the relationship between cough frequency, cough severity, cough-related QoL, QoL and pulmonary function tests, Pearson's correlation coefficients (r) were used. Sensitivity analyses were carried out on the per-protocol population with linear mixed models and paired t-tests. To identify clinical characteristics predictive of cough, a linear regression model was used. A two-sided p-value of less than 0.05 was considered statistically significant. SPSS Statistics version 21.0 and R version 3.2.2 were used for analysis.

RESULTS

Of 46 patients screened for the study, 43 patients were included (Figure 1). Thirty-one patients completed the study with a mean follow-up of 92 days (range 77-104). Two cough recording errors occurred at baseline, two at week 4, and three at week 12 (patients switched off recorder, incomplete recording, recording erased during transmission). Baseline patient characteristics are shown in Table 1. At baseline, 19% of participants reported having symptoms of gastroesophageal reflux disease (GERD). All of these patients were taking proton pump inhibitors (PPIs) for >4 weeks with no effect on their cough. Comorbidities and medications are shown in e-Table 2; none of the comorbidities were identified as causing the cough.

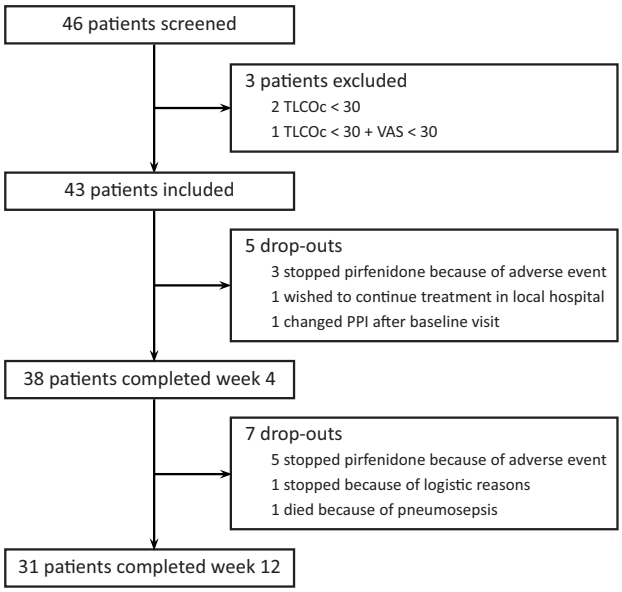

Figure 1. Flowchart cough study

Table 1. Patients characteristics (n=43)

	At baseline (n=43)
Age (years)	72 (7)
Male	33 (77%)
Smoking status	
Never	9 (21%)
Former	34 (79%)
FVC % predicted	78 (15)
TLCOc % predicted	51 (13)

Data are presented as mean (SD) or n (%). FVC, forced vital capacity; TLCOc, transfer capacity of the lung for carbon monoxide, corrected for hemoglobin.

Table 2. Objective and subjective cough and health status measures

	Baseline (n=43)	**At 4 weeks** (n=38)	**At 12 weeks** (n=31)
24-h cough	520 (91-3394)	511 (65-1947)	392 (75-1746)
Coughs per hour	23 (4-141)	22 (3-81)	17 (3-73)
Daytime	28 (5-171)	29 (4-106)	20 (4-121)
Nighttime	7.2 (0.7-101)	4.0 (0.3-45)	3.3 (0-54)
LCQ total	12 (4)	13 (3)	15 (4)
VAS cough	67 (15)	50 (20)	47 (27)
VAS urge-to-cough	68 (16)	53 (22)	49 (25)
MRC	3.1 (1)	2.9 (1)	2.8 (1)
K-BILD total	50 (22)	53 (22)	55 (23)
HADS anxiety	8.5 (4)	7.7 (4)	8.5 (4)
HADS depression	4.7 (3)	5.2 (3)	6.0 (3)
GAD-7	5.8 (6)	6.3 (6)	5.9 (6)

Data presented as median (range) or mean (SD). LCQ, Leicester Cough Questionnaire; VAS, visual analogue scale; MRC, Medical Research Council dyspnoea scale; K-BILD, King's Brief Interstitial Lung Disease health status questionnaire; HADS, Hospital Anxiety and Depression Scale; GAD-7, Generalized Anxiety Disorder 7-item screener

At baseline, median 24-h cough counts were 520 (range 91-3394), with a higher median cough per hour during daytime (28; range 5-171) than at night (7.2; range 0.7-101) (Table 2). Patients also scored high on subjective cough scores, LCQ mean 12 (SD 4) and VAS cough 67 (SD 15) (Table 2).

After 12 weeks of pirfenidone treatment, objective 24-h cough decreased by 34% (95% confidence interval (CI) -48% – -15%; p=0.002) (Table 3). Sensitivity analysis on the per-protocol population showed similar improvements in 24-h cough; 35% decrease with the linear mixed model (p=0.002), and 36% decrease with the paired t-test (p=0.003) (e-Table 3). At 12 weeks, 24-h cough frequency improved in 20/27 patients (74%), change per patient is shown in Figure 2.

Subjective cough measures showed consistent outcomes. The LCQ improved after 12 weeks by 2.0 points (CI 1.0-3.0, p<0.001) and the cough VAS by 19 points (CI -28 – -10, p<0.0001) (Table 3). No significant changes in disease-specific QoL measured with the K-BILD and anxiety, measured with the GAD-7 and HADS were found (Table 3).

At 4 weeks, a decrease of 14% in 24-h cough frequency was found (95% CI -22% – -6%; p=0.002), with 24/35 patients (69%) showing an improvement. Lung function remained stable throughout the study; at 4 weeks mean FVC % predicted was 78% (SD 18) and at 12 weeks FVC was 79% (SD 17). Also, TLCOc % predicted remained unchanged with a mean of 51% (SD 16) at 12 weeks.

At baseline, objective cough scores correlated moderately with the MRC, LCQ and VAS cough and strongly with VAS urge-to-cough (Table 4). Cough frequencies did not corre-

Table 3. Effect of 12 weeks pirfenidone treatment on cough and health status measures, analyzed with a linear mixed model – intention-to-treat analyses (n=43)

	Change (95% CI)	**P-value**
24-h cough**, %**	-34% (-48% – -15%)	0.002
Coughs per hour**, %**		
Daytime	-33% (-47% – -14%)	0.003
Nighttime	-34% (-54% – -5%)	0.029
LCQ, points	2.0 (1.0 – 3.0)*	<0.001
VAS cough, mm	-19 (-28 – -10)	<0.0001
VAS urge-to-cough, mm	-18 (-26 – -10)	<0.0001
K-BILD, points	3.4 (-2.3 – 9.1)	0.245
HADS anxiety, points	0.7 (-0.6 – 1.9)	0.291
HADS depression, points	1.6 (0.5 – 2.6)	0.004
GAD-7, points	0.7 (-0.9 – 2.3)	0.396

* Minimal clinical important difference for chronic cough is 1.3
LCQ, Leicester Cough Questionnaire; VAS, visual analogue scale; K-BILD, King's Brief Interstitial Lung Disease health status questionnaire; HADS, Hospital Anxiety and Depression Scale; GAD-7, Generalized Anxiety Disorder 7-item screener

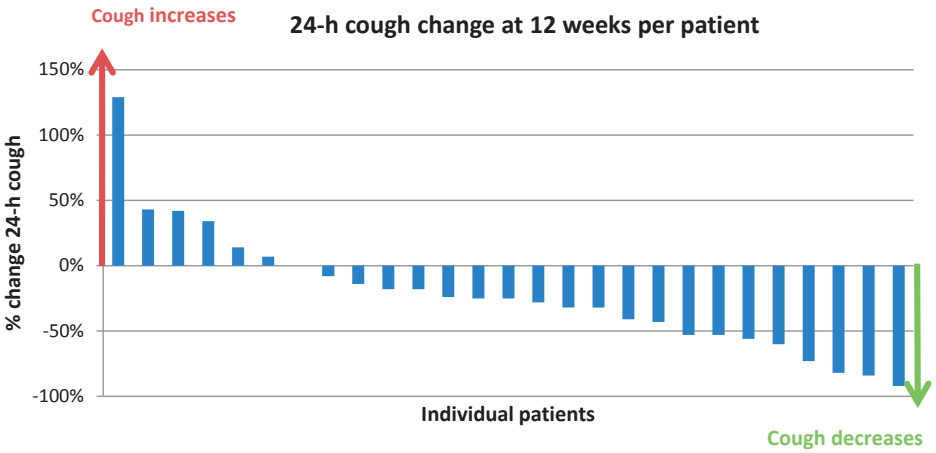

Figure 2. Change in 24-h cough at 12 weeks per patient

late with disease severity, measured with the FVC and TLCOc. There was no correlation between change in cough frequency and change in FVC (r=-0.03, p=0.897).

To identify clinical characteristics predictive of cough, we used linear regression model with bootstrap (1000 samples) for coefficients as the residuals were not normally distributed. We found that gender (relative difference (RD) women 2.24 (CI 1.09-4.44), p=0.037) and smoking status (RD never-smoker 2.15 (CI 1.21-3.86), p=0.008) were significant predictors of 24-h cough in univariable analyses (e-Table 4). In a multivariable model both variables remained significant (RD women 2.09 (CI 1.02-3.88), p=0.029, and

Table 4. Correlation of objective cough frequencies with questionnaires and lung function

	Cough per 24-h	Cough/h daytime	Cough/h nighttime
LCQ	-0.34*	-0.37*	-0.14
VAS cough	0.42**	0.44**	0.37*
VAS urge-to-cough	0.55**	0.52**	0.54**
MRC	0.38*	0.38*	0.42**
K-BILD	-0.19	-0.23	-0.05
HADS anxiety	<-0.01	-0.02	0.06
HADS depression	0.29	0.28	0.09
GAD-7	-0.22	-0.21	-0.28
FVC % predicted	-0.03	-0.03	-0.02
TLCOc % predicted	-0.20	-0.22	-0.41

Data shown are Pearson's correlation coefficients. All p≥0.05 except for *p<0.05 and ≥0.01, ** p<0.01
Cough data were not normally distributed and therefore log transformed.
LCQ, Leicester Cough Questionnaire; VAS, visual analogue scale; MRC, Medical Research Council dyspnoea scale; K-BILD, King's Brief Interstitial Lung Disease health status questionnaire; HADS, Hospital Anxiety and Depression Scale; GAD-7, Generalized Anxiety Disorder 7-item screener; FVC; forced vital capacity; TLCOc, transfer capacity of the lung for carbon monoxide, corrected for hemoglobin level.

RD never-smoker 1.97 (CI 1.27-3.26), p=0.008), predicting 26% of the variation in 24-h cough (p=0.004) (e-Table 4).

Adverse Events occurred in 30/43 patients (70%). Fatigue (23%), loss of appetite (19%), and nausea (16%) were the most frequent reported adverse events (e-Table 5). Two patients had a Serious Adverse Event; death because of pneumosepsis and an elective hospitalization (e-Table 5).

DISCUSSION

In this observational study, pirfenidone treatment reduced objective 24-h cough counts, cough severity and cough-related quality of life in patients with IPF. The magnitude of these changes was clinically meaningful to patients. Furthermore, this study provides insights into impact of cough and different methods to assess cough in IPF.

Cough is a major problem for patients with IPF, and their relatives.[1,4,20] No good therapies exist. This study is the first to show a significant improvement of a pharmacologic treatment both on objective as well as subjective measures of cough in patients with IPF.

As the study was not controlled, some placebo-effect should be questioned. When this study was designed, pirfenidone was just recently available and the only treatment possibility for patients with this deadly disease. This created high expectations for patients and physicians, and therefore patients, physicians and the ethics committee considered

it unethical to leave half the study population untreated for 12 weeks, a decision which might be viewed differently nowadays. Until now, there is only one placebo-controlled pharmacological study on cough in IPF completed that used objective cough as primary outcome. This recent phase 2 double-blind cross-over study, showed no placebo-effect at all in a similar group of IPF patients with chronic cough.[21] We therefore believe that the outcomes of our study are not influenced by a placebo-effect, which is further supported by the already significant, though smaller, effect on cough after 4 weeks of treatment.

Pirfenidone is an anti-fibrotic drug with pleiotropic effects. Its mechanisms of action are not completely understood, but in vitro studies have shown anti-fibrotic, anti-inflammatory, and anti-oxidant properties.[8] Given that the exact mechanism of chronic cough in IPF is also still unknown,[22] we can only speculate on the mode of action of pirfenidone in reducing cough. In IPF cough reflex sensitivity is thought to be increased.[6] Preliminary studies in guinea pigs show that pirfenidone decreases cough reflex sensitivity.[9] Future investigations are needed to see if pirfenidone alters cough reflex sensitivity in patients with IPF.

Recently, Froese et al. showed that mechanical tissue stretch activates TGF-beta1 and contributes to the development of pulmonary fibrosis in rodent and human.[23] This in line with Leslie et al., who proposed that recurrent stretch injury caused by pressure changes during breathing promotes fibrosis.[24] Cough might be an additional source of mechanical stress, and could theoretically contribute to a pro-fibrotic feedback loop. If this hypothesis is correct, this might explain why cough independently predicts disease progression.[5] More research is needed to investigate the potential role of cough as a potential driver of disease progression in IPF, as this might have therapeutic implications. In the current 12-weeks study there was no correlation between change in cough and FVC.

In the present study patients had high baseline cough frequencies, with median 24-h cough counts of 23 per hour. Key et al reported lower cough frequencies in 19 patients with IPF (9.4 per hour).[4] This is likely due to the selection of patients with a VAS cough score of ≥40 mm in the current study. The higher daytime cough frequencies we found corresponds with the diurnal pattern observed in patients with IPF and chronic cough.[4,25] Inhibition of cough by cortical pathways and higher thresholds of peripheral nerves at night might account for this pattern.[25] Also, less exposure to stimuli that might induce cough, such as talking, exercise, and fumes might play a role.[25]

Comorbidities and co-medication use are frequent in IPF,[26,27] and may cause cough. In our study we excluded patients with other reasons for cough. Patients with GERD had to be on PPI and remain on a stable dose, even though previous studies did not show a correlation with the presence of treatment for GERD and cough in IPF.[5,28] As comorbid

conditions and co-medication remained unchanged during the study, we believe that these did not influence the study outcomes.

Cough-related QoL, measured with the LCQ, also improved significantly after 12 weeks of pirfenidone treatment. The LCQs' MCID in chronic cough is 1.3 points, so we consider the 2.0 point change found in our population as clinically meaningful to the patients.[14]

There have been few studies evaluating anti-tussive treatment in IPF. A study by Horton et al. found that in patients with IPF thalidomide improved cough-specific QoL, though no objective cough measurements were done, and only 20% of the screened patients completed the trial.[29] Thalidomide has a toxic side-effect profile including neuropathy and may increase risk for thrombotic diseases.[30] Oral corticosteroids 40 to 60 mg/day for at least four weeks improved cough in six IPF patients in a non-randomized trial.[6] Yet, they found no effect on cough-related QoL, and, furthermore, immunosuppression has been associated with deleterious effects in IPF.[31] Currently, two medications are available for the treatment of IPF: nintedanib and pirfenidone. To date, there are no studies on the effect of nintedanib on cough. Our study results might imply that pirfenidone is preferable for treatment of IPF patients with severe cough; however, it would be valuable to compare the effects of both nintedanib and pirfenidone on cough prospectively.

In line with previous findings, we found that objective cough counts correlated moderately with subjective cough measures.[4] In our study we newly included a VAS on urge-to-cough in IPF, which showed the best correlation with objective cough counts. This could be an interesting tool to easily assess cough in future IPF trials, and might be better related to the underlying cough reflex hypersensitivity described in patients with IPF. No correlations were found with measures of disease severity, such as FVC and TLCOc. This confirms that cough can be a troublesome symptom at all stages of disease, and is in line with previous findings.[4]

Gender and smoking status were the only predictors of cough in the current study. Women in the study had twice as many cough counts as men; this is in line with findings in chronic cough patients, but not with other IPF studies.[4,5,32] In contrast to chronic coughers and COPD patients, but in line with findings of Ryerson et al., we found that IPF patients who had no history of smoking coughed more than former smokers. It is unknown why some IPF patients cough more, but it might be connected to different IPF phenotypes.[5]

Our study has some limitations. Firstly, we included IPF patients with a VAS score of ≥40 mm. Therefore, we do not know the effect of pirfenidone on IPF patients with mild cough. Nonetheless, patients with severe cough should benefit the most from reduction of their cough. Secondly, our study had a substantial drop-out rate, which is a known limitation of an observational study. By using the linear mixed model analyses we accounted for these missing data.[18] Moreover, the sensitivity analysis on the per-protocol

population showed similar results as the analysis on the intention-to-treat population. Lastly, our study had a short follow-up period of 12 weeks. The long-term effect of pirfenidone on cough in IPF patients is therefore unknown; however, our results suggest that the effect of treatment on IPF cough may be explored in 12-week trials.

CONCLUSIONS

In patients with IPF, pirfenidone treatment significantly reduced objective 24-h cough counts by 34%, and improved subjective measures of cough. These results are clinically meaningful to patients. More research is warranted into the mechanisms and management of cough in IPF and other fibrotic diseases.

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APPENDIX

E-Appendix 1 Ethics approval

Ethics approval

- Medical Ethics Review Committee (METC) of the Erasmus Medical Center, Rotterdam, the Netherlands (METC-2013-306).
- Comité de protection des personnes sud-est IV, Lyon, France (number L13-155).
- Comitato Etico, Aziende Ospedaliero-Universitaria, Catania, Italy (n 698).
- National Research Ethics Service (NRES) committee London, United Kingdom (NL44729.078.13).

E-Table 1. Inclusion and exclusion criteria

Inclusion criteria
- Diagnosis of definite or probable IPF according to ATS/ERS criteria[1]
- Daily cough related to IPF (exclusion of other causes) present more than eight weeks
- Cough score on the VAS of ≥40 mm
- FVC ≥50% and TLCOc ≥30%*
- Use of PPI more than four weeks, when patient had a history positive for GERD
Exclusion criteria
- Use of opiates, antitussive medication, antihistamines, steroids more than an equivalent of 10 mg prednisone or NAC within two weeks before the study
- Change in steroid dose if using <10 mg or inhalation steroids within two weeks before the study
- History of bronchial hyper responsiveness, asthma or relevant airway obstruction (FEV1/FVC <0.7)
- Within six weeks of the start of the study signs of respiratory tract infection, change of sputum production and fever

[1] Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824.

* Except for Italy were a TLCOc ≥35% is required for treatment reimbursement

IPF, idiopathic pulmonary fibrosis; ATS; American Thoracic Society; ERS, European Respiratory Society; VAS, visual analogue scale; FVC, forced vital capacity; TLCOc, transfer capacity of the lung for carbon monoxide, corrected for hemoglobin level; PPI, proton pump inhibitor; GERD, gastroesophageal reflux; NAC, N-acetylcysteine

E-Table 2. Comorbidities and medications

Comorbidities	**n (%)**
GERD*	8 (19%)
Emphysema	3 (7%)
Pulmonary hypertension	1 (2%)
Cardio vascular disease	20 (47%)
Endocrine disease	8 (19%)
Medications	**n (%)**
PPI	34 (79%)
Antibiotics	0 (0%)
ACE-inhibitors	0 (0%)
Steroids**	9 (21%)
Statins	19 (44%)
Anticoagulants	2 (5%)

*Reported by patients

** All patients had an equivalent dose ≤10 mg

There were no missing data. GERD, gastroesophageal reflux; PPI, proton pump inhibitor; ACE, angiotensin-converting-enzyme

E-Table 3. Sensitivity analyses

A. Effect of 12 weeks pirfenidone treatment on cough measures, analyzed with a linear mixed model – patient with data complete (n=27)

	Change (95% CI)	**P-value**
24-h cough**, %**	-35% (-50% – -16%)*	0.002
Coughs per hour**, %**		
Daytime	-34% (-49% – -14%)	0.003
Nighttime	-34% (-55% – -2%)	0.043
LCQ, points	1.9 (0.9 – 2.9)**	<0.001
VAS cough, mm	-16 (-26 – -6)	0.003
VAS urge-to-cough, mm	-18 (-27 – -9)	<0.001
K-BILD, points	3.0 (-2.8 – 8.8)	0.309
HADS anxiety, points	1.1 (-0.3 – 2.6)	0.124
HADS depression, points	1.5 (0.3 – 2.6)	0.016
GAD7, points	0.9 (-0.8 – 2.5)	0.291

* A decrease of 15% in 24-h cough was achieved at 4 weeks (95% CI -22% – -6%-; p=0.002)

** Minimal clinical important difference for chronic cough is 1.3

LCQ, Leicester Cough Questionnaire; VAS, visual analogue scale; MRC, Medical Research Council dyspnoea scale; K-BILD, King's Brief Interstitial Lung Disease health status questionnaire; HADS, Hospital Anxiety and Depression Scale; GAD-7, Generalized Anxiety Disorder 7-item screener

B. Effect of 12 weeks pirfenidone treatment on cough measures, analyzed with a paired t-test (n=27)

	Baseline	**Week 12**	**Change**	**P-value**
24-h cough	758 (91-3394)	484 (75-1746)	-36%	0.003
Coughs per hour				
Daytime	41 (6-171)	26 (4-121)	-36%	0.004
Nighttime	13 (1-101)	8 (0-54)	-37%	0.039
LCQ, points	13 (3)	15 (4)	2.1	0.004
VAS cough, mm	66 (14)	49 (28)	-18	0.002
VAS urge-to-cough, mm	68 (16)	49 (26)	-19	<0.001
K-BILD, points	52 (22)	56 (24)	3.9	0.258
HADS anxiety, points	7.6 (4)	8.7 (4)	1.2	0.174
HADS depression, points	4.7 (3)	6.1 (3)	1.4	0.035
GAD7, points	4.9 (6)	5.8 (7)	0.8	0.386

Data are presented as mean (range) or (SD). LCQ, Leicester Cough Questionnaire; VAS, visual analogue scale; K-BILD, King's Brief Interstitial Lung Disease health status questionnaire; HADS, Hospital Anxiety and Depression Scale; GAD-7, Generalized Anxiety Disorder 7-item screener

E-Table 4. Predictors of 24-h objective cough frequency (n=41)

Predictors of 24-h cough	**β**	**Relative difference** (95% CI)[#]	**P-value**[#]
Univariable analysis			
Age (per year)	0.02	1.02 (0.98-1.06)	0.191
Gender (female)	0.81	2.24 (1.09-4.44)	0.037*
FVC % predicted (per 1%)	<-0.01	1.00 (0.98-1.02)	0.824
TLCOc % predicted (per 1%)	-0.01	0.99 (0.96-1.00)	0.195
Smoking status (never)	0.76	2.15 (1.21-3.86)	0.008*
Packyears (per year)	0.01	1.01 (1.00-1.04)	0.296
CT finding (possible UIP)	0.37	1.44 (0.78-2.68)	0.267
Clubbing (yes)	0.06	1.07 (0.59-2.08)	0.865
Reflux (yes)	0.16	1.17 (0.71-1.78)	0.515
Appetite (yes)	0.19	1.21 (0.45-3.22)	0.706
Multivariable analysis			
Model		R^2 = 26%	0.004*
Gender (female)	0.74	2.09 (1.02 – 3.88)	0.029*
Smoking status (never)	0.68	1.97 (1.27 – 3.26)	0.008*

[#] Linear regression on log-transformed number of coughs per 24 hours, bootstrapping (1.000 samples) was used to construct 95% confidence intervals. Coefficients of the linear regression model were anti-logged to interpret the coefficients as relative difference

* Statistically significant

FVC, forced vital capacity; TLCOc, transfer capacity of the lung for carbon monoxide, corrected for hemoglobin level

E-Table 5. Adverse Events and Serious Adverse Events

Adverse Events*	**n (%)**
Fatigue	10 (23)
Loss of appetite	9 (19)
Nausea	8 (16)
Dizziness	6 (12)
Phototoxicity	4 (9)
Rash	4 (9)
Gastroesophageal reflux	4 (9)
Flu-like symptoms	4 (9)
Pneumonia	4 (5)
Change of mood/mood disturbance	3 (7)
Pruritus	3 (7)
Dyspepsia	3 (7)
Constipation	3 (7)
Diarrhea	2 (5)
Burning and dry eyes	2 (5)
Serious Adverse Events	
Death because of pneumosepsis	1 (2)
Elective hospitalization	1 (2)

* Listed are all adverse events that were reported in at least 2 patients

Chapter 9

What patients with pulmonary fibrosis and their partners think: a live, educative survey in the Netherlands and Germany

"Tell me and I forget, teach me and I may remember, involve me and I learn"
Benjamin Franklin

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Mirjam J.G. van Manen[1], Michael Kreuter[2,3], Bernt van den Blink[1], Ute Oltmanns[2,3], Karin Palmowski[2,3], Eva Brunnemer[2,3], Simone Hummler[2], Nelleke C. Tak[1], Leon van den Toorn[1], Jelle Miedema[1], Henk C. Hoogsteden[1], Marlies S. Wijsenbeek[1]

[1]Department of Respiratory Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands.
[2]Center for Interstitial and Rare Lung Diseases, Pneumology and Respiratory Critical Care Medicine, Thoraxklinik, University of Heidelberg, Heidelberg, Germany.
[3]Translational Lung Research Center Heidelberg, Member of the German Center for Lung Research, Heidelberg, Germany.

ABSTRACT

Pulmonary fibrosis greatly impacts patients and their partners. Unmet needs of patients are increasingly acknowledged; the needs of partners often remain unnoticed. Little is known about the best way to educate patients and partners. We investigated pulmonary fibrosis patients' and partners' perspectives and preferences in care, and the differences in these between the Netherlands and Germany. Additionally, we evaluated if interactive interviewing could be a novel education method in this population.

Patients and partners were interviewed during pulmonary fibrosis patient information meetings. In the Netherlands, voting boxes were used and results were projected directly. In Germany, questionnaires were used.

In the Netherlands, 278 patients and partners participated; in Germany, 51. Many participants experienced anxiety. Almost all experienced misunderstanding, because people do not know what pulmonary fibrosis is. All expressed a need for information, psychological support and care for partners. Use of interactive voting system is found to be pleasant (70%) and informative (94%).

This study improves the knowledge about care needs of patients with pulmonary fibrosis and their partners. There were no major differences between the Netherlands and Germany. Interactive interviewing could be an attractive method to acquire insights into the needs and preferences of patients and partners, while providing them information at the same time.

INTRODUCTION

Pulmonary fibrosis is a respiratory disease characterised by scarring of the lungs, resulting in a reduced oxygen transport.[1] Different forms of pulmonary fibrosis exist, with different disease courses and prognosis; however, in the majority of patients the disease is progressive. The main symptoms experienced by patients are cough, fatigue and breathlessness.[2] Pulmonary fibrosis impacts the social and emotional wellbeing of patients, partners and other family caregivers, in addition to its physical impact.[3-6]

In recent years, several studies have been conducted to generate more information on the needs of patients with pulmonary fibrosis, especially in idiopathic pulmonary fibrosis (IPF).[3-11] However, the needs of partners often remain unnoticed. Previous studies show the need for better disease related education, earlier diagnosis, support groups and better access to specialist centres and interstitial lung disease (ILD) specialist nurses. One of the crucial factors that empower patients to play a more active role in their care is education. However, the best way of educating pulmonary fibrosis patients and their partners needs to be established.

A pulmonary fibrosis patient information meeting is organised annually in the Erasmus University Medical Center (Rotterdam, the Netherlands) and at the Thoraxklinik (Heidelberg, Germany) to provide additional information about pulmonary fibrosis. During these meetings we use an interactive voting system, which enables us to gather information about participants' disease experiences and learn from their perspectives and preferences in care. These findings can be used to improve care for patients with fibrosis and their partners.

An interactive voting system, in addition, creates an environment where patients and partners can learn from each other's experiences. Outcomes of surveys are not always shared with patients. However, information on problems that patients and partners encounter could be very informative and might generate a feeling of relief, as people learn that others are facing the same difficulties.

Studies on cultural differences in preferences and perspectives in care are limited in pulmonary fibrosis patients.[9,12] By using the same survey at the pulmonary fibrosis patient information meetings in the Netherlands and in Germany, we could learn more about possible cultural differences.

The purpose of our study was to determine pulmonary fibrosis patients' and their partners' perspectives and preferences in care. In addition, we studied whether directly projecting survey answers, via an interactively voting system, is informative and wanted by pulmonary fibrosis patients and their partners. We also studied whether cultural differences exist in care needs between pulmonary fibrosis patients and their partners from the Netherlands and Germany.

METHODS

Patients and partners were interviewed during pulmonary fibrosis information meetings at two tertiary ILD centres: the Erasmus University Medical Center and the Thoraxklinik, Heidelberg University Hospital. The three information meetings in the Netherlands took place in 2013, 2014 and 2015 and the meeting in Germany in 2014. The content of the programme is shown in online supplementary table S1. We use the terminology "partners", but this term also includes other family members or nearest and dearest when applicable. We avoided the word caregiver, as we think that a relationship between patient and partner (or other nearest and dearest) comprises more than caregiving alone. In the Netherlands, patients and partners answered questions anonymously via interactive voting boxes (TurningPoint 2008; Keepad Interactive, Sydney, Australia). The questions were projected on a wide screen. Questions and answers were first read aloud, then a clock countdown of 10 s was started. The system recorded the number of votes and results were projected directly. In Germany, questionnaires were handed out to all participants and questions were discussed afterwards. Questions were derived by literature search and input of patients, ILD physicians, ILD specialist nurses an ILD research nurses. The Generalised Anxiety Disorder-single item (GAD-SI) questionnaire was administered before the lectures started, to avoid the influence of information presented during the meeting.[13] We asked participants 37 questions. In this article we present a selection of the questions asked. An overview of all questions is presented in online supplementary table S2.

Permission to use the data was obtained beforehand. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Patient permissions for data collection and usage were granted according to specific local requirements of the medical ethical committee at each participating centre. Data were collected and analysed using Microsoft Excel 2010 (Redmond, WA, USA). All data are presented as % (n), as the number of responders could vary per question.

RESULTS

278 patients and their partners participated in the Netherlands and 51 in Germany. Demographics are shown in table 1.

In Germany, 17% (8) of patients and partners attended the pulmonary fibrosis information meeting the previous year. In the Netherlands, 24% (15) in 2014 and 18% (10) in 2015 attended the previous meeting.

Table 1. Demographics of patients and partners

	The Netherlands (2013+2014+2015)	**Germany** (2014)
Patients	134 [48]	27 [53]
Partners	144 [52]	24 [47]
Diagnoses*		
IPF	88 [70]	20 [80]
CTD-PF	14 [11]	2 [8]
Exposure related	14 [11]	3 [12]
Unknown	10 [8]	0 [0]

Data are presented as n (%). IPF, idiopathic pulmonary fibrosis; CTD-PF, connective tissue disease-associated pulmonary fibrosis

* Based on survey question

Figure 1 shows that approximately two-thirds of patients and partners experience anxiety as assessed by the validated GAD-SI.[13] The fast majority of participants experienced misunderstanding because people do not know what pulmonary fibrosis is (figure 2). Patients in the Netherlands prefer to talk about matters concerning end-of-life early in the course of the disease, while in Germany this is less explicit (figure 3). In all groups, there is great need for information on the disease (figure 4).

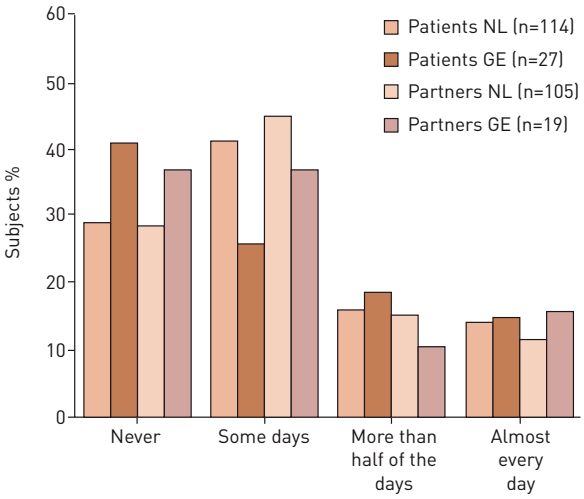

Figure 1. Patients' and partners' experience of anxiety in the Netherlands (NL) and Germany (GE), based on the Generalised Anxiety Disorder-single item questionnaire [13]. Subject responses to the question "How often in the past 2 weeks did you have problems relaxing?"

Other questions revealed that 88% (21) of the German and 61% (38) of the Dutch partners would like to have more care for partners. Psychological support was wanted by more than half of the German partners (55%, n=12). In addition, the majority of patients in the Netherlands and Germany would appreciate the possibility of psychological support: 80% (107) and 79% (19), respectively. Twenty-three percent (21) of patients think that psychological support is actually lacking in current care.

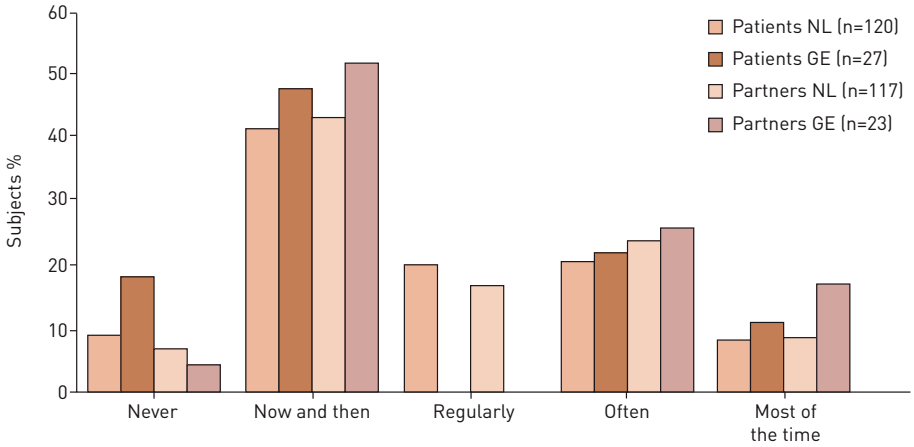

Figure 2. Experience of misunderstanding by patients and partners in the Netherlands (NL) and Germany (GE).
Subject responses to the question "How often do you feel misunderstood because people do not know what pulmonary fibrosis is?"

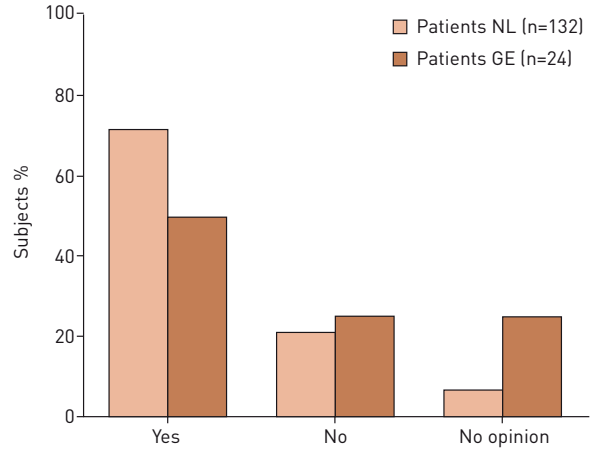

Figure 3. Preference of talking about matters concerning the end of life in patients from the Netherlands (NL) and Germany (GE).
Responses to the statement "I would prefer to talk about matters concerning end of life at an early stage of my disease".

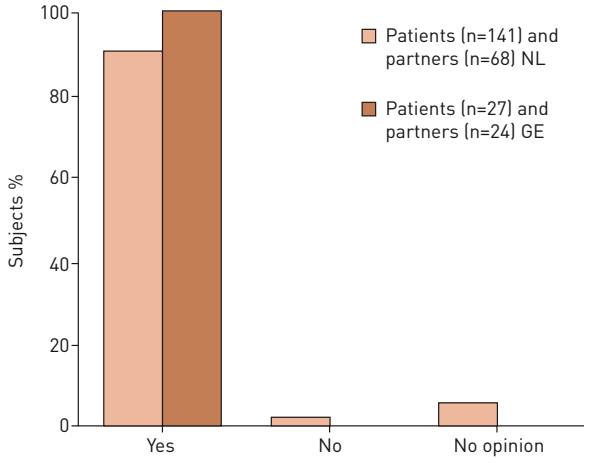

Figure 4. Need for information on disease and prospects in patients and partners from the Netherlands (NL) and Germany (GE).
Responses to the statement "I would like to know everything about my disease and its prospects".

In the Netherlands, patients and partners priorities in care are information on their disease (47% , n=62); access to an expertise centre (27%, n=35); and practical support (18%, n=23). Many Dutch patients desire treatment and follow-up in a hospital with the most expertise (58%, n=67), but a third of the patients (30%, n=34) prefer shared care between the expertise centre and a pulmonologist nearby. In Germany, the same percentage of patients favour shared care between the expertise centre and a pulmonologist nearby (29%, n=7), while only a third of patients prefer treatment only at an expertise centre (33%, n=8). Additionally, a minority (17%, n=4) of German patients prefer a combination of care at their general practitioner and pulmonologist nearby, whereas in the Netherlands only 4% (5) of patients prefer this option. Specialised centres offer access to clinical trials. Many patients desire active involvement in the development of clinical trials: 77% (20) of German and 68% (77) of Dutch patients.

At the Erasmus University Medical Center, ILD specialist nurses provide general care. They give additional information about disease, care options, medication and oxygen supply and are easily accessible by phone and email. Most (88%, n=36) Dutch patients think seeing an ILD specialist nurse is beneficial. At the time of the survey, there was no ILD specialist nurse in Germany, though 55% (12) of patients asked for such services. Twenty-one percent (30) of patients and partners from both countries would like to see the ILD specialist nurse every time when visiting their doctor. However, the majority of patients prefer to see the ILD specialist nurse only when asked for (67%, n=94).

The interactive voting system was well appreciated and considered informative by patients and partners (figure 5). Patients and partners in both countries considered the meetings to be very useful and the majority felt more secure after attending them (figure 6 and 7).

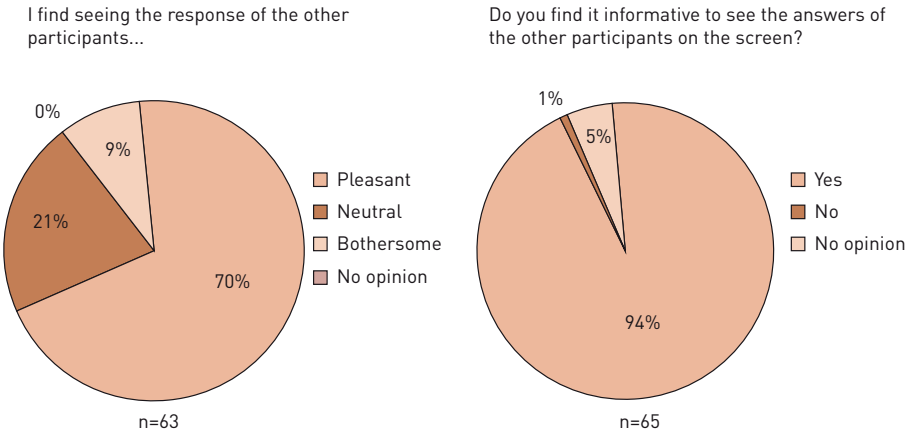

Figure 5. Feedback on interactive voting system in the Netherlands.

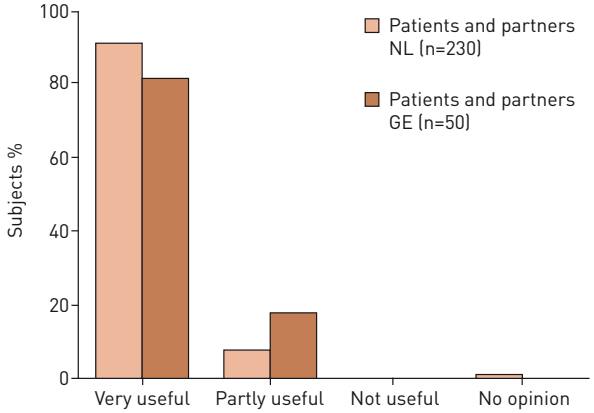

Figure 6. Perception of patients and partners from the Netherlands (NL) and Germany (GE) of the usefulness of the information meeting.

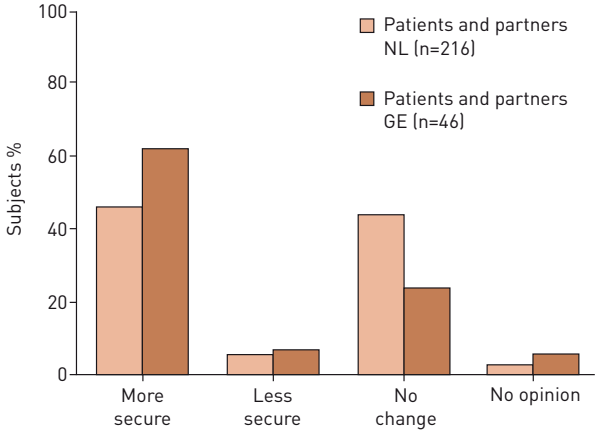

Figure 7. General feeling of patients and partners from the Netherlands (NL) and Germany (GE) after the information meeting.

DISCUSSION

This study improves the current knowledge of the needs of patients with pulmonary fibrosis and their partners. It emphasises the major impact pulmonary fibrosis has on the emotional wellbeing of patients and partners and the need for better education on all aspects of disease and psychological and practical support. Treatment is preferred in expertise centres with access to ILD specialist nurses and involvement in the development of clinical trials is wanted. Moreover, this study demonstrates a new way of questioning and educating patients and partners, by using an interactive voting system which projected answers directly. Patients and partners found this method pleasant and informative. No major cultural differences existed between the findings in the Netherlands and Germany.

Anxiety

In our study, many patients and partners reported some level of anxiety. Kreuter et al.[14] showed that depression and anxiety are common comorbidities in IPF. In another study of 502 IPF patients, anxiety was found in 9.4% at baseline.[15] This is comparable with the number of patients and partners in our group experiencing anxiety almost every day (11-16%). Multiple factors could contribute to the high prevalence of anxiety in this population. Anxiety is a known emotional response in breathless patients, but a background of anxiety can also increase the perception of breathlessness.[16] Partners feel helpless because they cannot relief the breathlessness.[2,17] The relationship between breathlessness and anxiety in patients and partners is also seen in chronic obstructive pulmonary disease (COPD) and chronic heart failure.[18,19] In COPD, anxiety is one of the comorbidities with the greatest influence on self-reported health status.[20] The progressive nature of the disease, especially in IPF, could also cause anxiety. Furthermore, the coughing attacks, suffered by many pulmonary fibrosis patients increases anxiety of partners, as they fear the next attack could be fatal.[5] Additionally, for certain patients, decisions about screening and being on the waiting list for lung transplantation might play a role.[7,21]

Misunderstanding

Patients and their partners both feel misunderstood by society, as people often do not know what pulmonary fibrosis is. This corresponds with findings of the study of Russell et al.[12], where IPF patients report feeling angry and frustrated because society has little knowledge of the disease. Moreover, patients often do not look sick to start with, which makes it difficult for family and friends to understand the devastating impact of the disease, troubling patients to talk about their condition.[2,7]

Psychological support

Many patients and partners in the Netherlands and Germany wish to receive psychological support, consistent with the findings of previous studies.[3,4,9,12] The progressive nature of the disease forces patients to adapt to growing restrictions in things they love to do and limits them in the activities of everyday life, impacting not only physical, but also emotional wellbeing. Patients become dependent on their loved ones and relationships with friends and family change.[2,4] Financial problems can occur when patients have to stop working.[22] Additionally, psychological distress can increase when patients start on supplemental oxygen. Besides loss of independency due to logistical difficulties, oxygen also makes the disease more visible.[22] For partners, the disease changes their lives and the relationship as well.[17] They become the main support in patients' lives and often feel they have to be the "strong one", allowing themselves no time to deal with their own grief. The high number of requests for more care and psychological support for partners found in our study illustrates the impact pulmonary fibrosis has on partners and corresponds with previous findings.[4,17] In both centres, the survey data helped to improve the level of psychological care and the tailoring this care to the needs of the patients and partners.

End-of-life

The majority of pulmonary fibrosis patients in our study prefer to talk about matters concerning end-of-life in an early stage of disease, but cultural differences exist. The study by Overgaard et al.[5] shows that reactional dyssynchrony can occur in coping with the disease. National Institute for Health and Care Excellence (NICE) guidelines on IPF state that discussion about end-of-life should start at diagnosis, and prior studies show patients' need for information on end-of-life issues.[23-25] In addition, the American Thoracic Society recommends advances care planning for patient with severe lung diseases.[26] However, it must be realised that these conversations could be distressing to patients and partners.[27] As mentioned by Thickett et al.[8], it is important to talk about disease progression and management so patients can prepare for the future, but this process should be personalised and develop over time. This corresponds with the wishes of patients and partners to receive paced information on disease and being able to plan care in advance.[5]

Education

Patients and partners, have a consistent wish to receive more information on the disease and its prospects.[3,12,25,27-29] Patient often consult the internet, but information found is frequently incomplete, inaccurate and not up to date.[11] Although the need for information is well known in pulmonary fibrosis, studies to improve education and care are scarce.[27] Lindell et al.[27] studied whether a 6-week disease-management programme would improve disease symptoms and health-related quality of life (HRQoL) in patients with IPF. Strikingly, patients' anxiety and HRQoL scores deteriorated, while the stress levels of partners improved. Post-intervention interviews showed that the course was perceived to be beneficial by all participants. In the current study, we used an interactive voting system with direct projection to improve patients' and partners' knowledge of the disease. Although this method cannot be compared to a disease-management program, we found that after the meeting most patients felt more secure. The majority of participants found the interactive voting system pleasant and informative. Studies on using interactive response systems in teaching have shown to improve learning, cognitive performance and student test scores.[30-32] This method could therefore not only be a good and efficient way to inform patients and partners, but also enhance the information patients and partners can absorb.

Expertise centres

The majority of Dutch patients in this study wishes to be treated and followed-up in a centre of expertise. This result could be biased, because the pulmonary fibrosis information meetings were held in expertise centres; however, similar findings were reported by Schoenheit et al.[3] They found that patients treated in expertise centres were more satisfied on disease information and quality of care. Yet, the German patients in the present study preferred a combination of treatment and follow-up at an expertise centre and pulmonologist nearby in equal numbers those preferring treatment at an expertise centre only. Geographical reasons may explain this difference, as in the

Netherlands an expertise centre is usually within les <2 h range due to the small size of the country. The British Lung foundation states that a considerable amount of ongoing care must be available and provided at local hospitals. The current study underlines the importance of this, as patients should be given the option of shared care, although in some countries reimbursement rules may unfortunately complicate such collaborative care options.

Research

In expertise centres, patients generally get more access to information about and enrolment in clinical trials. According to the British Lung Foundation, only 42% of patients currently receive information on clinical trials.[33] A study of diabetic patients attending an ongoing trial shows that attending clinical trials improves quality of care, patients interest and engagement in their overall health services and reduces healthcare costs.[34] Moreover, patients were more motivated, informed and aware of their disease and how to deal with their condition. Our study shows that patients not only want to receive information about and participate in clinical trials, but also wish to be involved in the development of trials. Involvement of patients in designing clinical trials could not only help identifying which outcomes are most relevant to patients, but could also improve feasibility and patient participation in trials and tailored dissemination of outcomes.[12,35]

ILD specialist nurse

ILD specialist nurses manage symptoms, treatment and possible side effects, coordinate care and involve other healthcare services where necessary. They also teach patients how to cope with their disease and create a comfortable environment were patients can discuss their fears and problems.[7,8,29] In the Netherlands, most patients find access to an ILD specialist nurse beneficial. The NICE guideline states that all patients and their partners should have access to an ILD specialist nurse in all phases of the care pathway.[23] Yet, currently, as seen in Germany, not all pulmonary fibrosis patients have access to ILD specialist nurses, although the demand for such services is high.[12,33] We agree on the NICE guidelines that all patients and their partners should have access to ILD specialist nurses. However, appointments with ILD specialist nurses should be individually tailored, as our study shows that patients and partners prefer to see the ILD specialist nurse only when required.

Cultural differences

We found no major cultural differences between Germany and the Netherlands. This in line with previous studies, showing that the emotional impact of disease is similar in different countries.[9,12,28] Practical care preferences might vary due to differences in organisation of care, geography, reimbursement criteria and local habits.[9,12,27,36] Cultural differences should be taken into consideration when trying to optimise guidelines for care.

Limitations

The interactive voting system used in the current study carries some limitations. Patients can potentially respond to questions aimed at partners and vice versa, resulting in higher numbers of answers and biased scores. In addition, participants might have responded too late or chosen not to respond, and a few participants left during the meeting for various reasons (fatigue, transport and unknown reasons), resulting in missing data. We therefore report in our results the absolute numbers of responders as well as percentages. Furthermore, patients and partners attending the pulmonary fibrosis information meeting in the Netherlands could have attend previous meetings. However, we found that only 24% in 2014 and 18% in 2015 had attended the information meeting the previous year, indicating only a small overlap in the data. As the total number of participants (278 in the Netherlands and 51 in Germany) is high compared to other studies assessing preferences of pulmonary fibrosis patients and partners,[3-5,12,17] this probably dilutes the potential voting errors and overlap in data. In the current study, questions were generated by healthcare providers of different backgrounds and patients. Although these questions were not validated (except for the GAD-SI), they were considered informative and useful by the participants and were used by the centres to improve care.

CONCLUSION

This study in a large cohort of patients with pulmonary fibrosis and their partners confirms the major impact pulmonary fibrosis has on emotional wellbeing and improves the current knowledge of their needs. There is need for better education on all aspects of disease, psychological and practical support and the need for ILD specialist nurses. No major cultural differences were found between Germany and the Netherlands. The method of interactively educating and interviewing could be a good and efficient way to generate new insights into pulmonary fibrosis care and is informative for patients and their partners. However, further research into the best method of education and on tailored support programmes is needed, as these are essential to improve care for pulmonary fibrosis patients and their partners.

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SUPPLEMENT

Table S1. Content of pulmonary fibrosis patient information meetings in the Netherlands and Germany

The Netherlands	Germany
Presentations	**Presentations**
- What is pulmonary fibrosis?	- Current therapy of different interstitial lung diseases
- Types of pulmonary fibrosis	- Clinical trials in interstitial lung diseases
- IPF - current state of affairs	- Registries in interstitial lung diseases and role of ILD specialist nurses
- Non-drug treatment for IPF	- Lung transplant
- Role of ILD specialist nurse and research nurses	- The role of patient support groups - a patients´ perspective
- Additional problems in pulmonary fibrosis	
- What did we learn from you?	
- How to coop with pulmonary fibrosis?	
- Future treatments for pulmonary fibrosis	
Information market	
- Dutch pulmonary fibrosis patient association	
- Meet the researches	
- Physiotherapy	
- Oxygen supplier	
- Lung transplantation	
- Pulmonary function	

IPF, Idiopathic Pulmonary Fibrosis; ILD, Interstitial Lung Disease.
In cooperation with the pulmonary fibrosis patient association.

Table S2. Questions asked during pulmonary fibrosis patient information meetings in the Netherlands and Germany

1 *[Everyone]* **Are you a patient or a partner?**
   1. I am patient
   2. I am a partner

2 *[Everyone]* **Have you been to the patient information meeting in this center last year?**
   1. Yes
   2. No

3 *[Patients]* **I mainly came for …**
   1. More information
   2. To meet other people with pulmonary fibrosis
   3. The information market
   4. My nearest and dearest and/or partner
   5. Contact with the doctors and nurses outside the consultation room

4 *[Partners]* **I mainly came for …**
   1. More information
   2. To meet other people with pulmonary fibrosis
   3. The information market
   4. My nearest and dearest and/or partner
   5. Contact with the doctors and nurses outside the consultation room

5 *[Patients]* **How often do you feel misunderstood because people do not know what pulmonary fibrosis is?**
   1. Never
   2. Now and then
   3. Regularly
   4. Often
   5. Most of the time

6 *[Partners]* **How often do you feel misunderstood because people do not know what pulmonary fibrosis is?**
   1. Never
   2. Now and then
   3. Regularly
   4. Often
   5. Most of the time

20 *[Patients]* **I aspire active involvement in the development of clinical trials on pulmonary fibrosis**
   1. Yes
   2. No
   3. Maybe

21 *[Patients]* **I would like to participate in medical trials because …**
   1. I might get better of it
   2. It could help other people
   3. It gives my hope
   4. I do not want to participate in medical trials
   5. No opinion

22 *[Patients]* **I find filling in questionnaires for research …**
   1. Annoying
   2. Neutral
   3. Fine
   4. Nice
   5. I do not want to fill in questionnaires

23 *[Patients]* **I would like to see and keep up with my own data online …**
   1. Yes
   2. No
   3. Maybe

24 *[Patients]* **I would find an ILD specialist nurse, who would take care of me during the whole course of my disease, very helpful in addition to the pulmonologist's treatment …**
   1. Yes
   2. No
   3. Unknown

25 *[Partners]* **I find a visit to an ILD specialist nurse, who cares for me my through the who disease course, a good addition to the general visit by the pulmonologist …**
   1. Yes
   2. No
   3. Unknown

Table S2. Questions asked during pulmonary fibrosis patient information meetings in the Netherlands and Germany (continued)

7 *[Patients]* **How often in the past two weeks did you have problems to relax?**
1. Never
2. Some days
3. More than halve of the days
4. Almost every day

8 *[Partners]* **How often in the past two weeks did you have problems to relax?**
1. Never
2. Some days
3. More than halve of the days
4. Almost every day

9 *[Everyone]* **What is pulmonary fibrosis?**
1. Inflammation of the lungs
2. Celluloses
3. Connective tissue
4. Thrombosis
5. It is unclear to me

10 *[Everyone]* **What causes pulmonary fibrosis?**
1. Exposure to harmful dusts
2. Underlying rheumatic diseases
3. Certain medication
4. Genetic predisposition
5. Unknown cause
6. All above mentioned causes
7. I have no idea

11 *[Patients]* **What type of pulmonary fibrosis do you have?**
1. Idiopathic Pulmonary Fibrosis (IPF)
2. Connective Tissue Disease associated Pulmonary Fibrosis (CTD-PF)
3. Exposure related pulmonary fibrosis
4. Lymphangioleiomyomatosis (LAM)
5. Sarcoidosis
6. Unknown

12 *[Patients]* **Most occurring symptom …**
1. Breathlessness
2. Cough
3. Dullness
4. Physical limitations
5. Worries
6. Other symptoms

26 *[Patients]* **During the past period, I found seeing an ILD specialist nurse in addition to the out clinic visit to the pulmonologist beneficial …**
1. Agree
2. Disagree
3. Neutral

27 *[Everyone]* **I see the ILD specialist nurse mainly as someone who …**
1. Is accessible for questions on my disease
2. Helps me with my oxygen applies
3. Gives support
4. Does all the above mentioned
5. No idea

28 *[Everyone]* **I wish to see the ILD specialist nurse …**
1. Always when I visit the pulmonologist
2. Only when asked for
3. I only want to see the pulmonologist

29 *[Patients]* **Next to support for my physical problems, I would like to have support for my psychological problems**
1. Yes
2. Yes, I think that is lacking in current care
3. No
4. I have no psychological problems, I do not need it

30 *[Partners]* **Next to support for my physical problems, I would like to have support for my psychological problems**
1. Yes
2. Yes, I think that is lacking in current care
3. No
4. I have no psychological problems, I do not need it

31 *[Patients]* **After this meeting I feel …**
1. More secure
2. Less secure
3. Nothing changed
4. No opinion

Table S2. Questions asked during pulmonary fibrosis patient information meetings in the Netherlands and Germany (continued)

13 *[Patients]* **I desire treatment and follow-up by …**
1. A pulmonologist nearby
2. In an expertise center
3. A pulmonologist nearby and in an expertise center combined
4. A general practitioner and in an expertise center combined
5. A general practitioner and pulmonologist combined
6. No preference

14 *[Patients]* **In the care for my lung fibrosis I mainly need …**
1. Access to an expertise center
2. Information on my disease
3. Contact with peers
4. Practical support (e.g. medical devices)
5. Emotional (psychological) support

15 *[Partners]* **In the care for my lung fibrosis I mainly need …**
1. Access to an expertise center
2. Information on my disease
3. Contact with peers
4. Practical support (e.g. medical devices)
5. Emotional (psychological) support

16 *[Patients]* **I would like to know everything about my disease and its prospects …**
1. Yes
2. No
3. No opinion

17 *[Partners]* **I would like to know everything about the disease of my partner and its prospects …**
1. Yes
2. No
3. No opinion

18 *[Patients]* **I would prefer talking about matters concerning end-of-life in an early stage of my disease**
1. Yes
2. No
3. No opinion

19 *[Partners]* **I would like to have more care for partners of patients with pulmonary fibrosis**
1. Yes
2. No
3. Maybe

32 *[Partners]* **After this meeting I feel …**
1. More secure
2. Less secure
3. Nothing changed
4. No opinion

33 *[Patients]* **This meeting was …**
1. Very useful
2. Partly useful
3. Not useful
4. No opinion

34 *[Partners]* **This meeting was …**
1. Very useful
2. Partly useful
3. Not useful
4. No opinion

35 *[Patients]* **I find current care …**
1. Excellent
2. Good
3. Sufficient
4. moderate
5. Poor

36 *[Everyone]* **I find seeing the response of the other participants …**
1. Pleasant
2. Neutral
3. Bothersome
4. No opinion

37 *[Everyone]* **Do you find it informative to see the answers of the other participants on the screen?**
1. Yes
2. No
3. No opinion

ILD, Interstitial Lung Disease

Chapter 10

Patient and partner empowerment programme for idiopathic pulmonary fibrosis

"Alone we can do so little; together we can do so much"
Helen Keller

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Mirjam J.G. van Manen[1], Adriaan van 't Spijker[2], Nelleke C. Tak[1], Carla T. Baars[3], Sandra. M. Jongenotter[3], Liesbeth R. van Roon[4], Jitske Kraan[1], Henk C. Hoogsteden[1], Marlies S. Wijsenbeek[1]

[1]Department of Respiratory Medicine, Erasmus Medical Center, University Hospital Rotterdam, Rotterdam, the Netherlands

[2]Department of Psychiatry, Section Medical Psychology and Psychotherapy, Erasmus Medical Center, University Hospital Rotterdam, Rotterdam, the Netherlands

[3]Unit Physiotherapy, Erasmus Medical Center, University Hospital Rotterdam, Rotterdam, the Netherlands

[4]Unit Psychosocial Care, Erasmus Medical Center, University Hospital Rotterdam, Rotterdam, the Netherlands

To the Editor:

Idiopathic pulmonary fibrosis (IPF) is a progressive, deadly disease with devastating impact on patients' and their partners' quality of life (QoL).[1] Many studies have shown the need for support groups, better information resources and disease education in IPF.[2-6] Although these needs have been identified, few studies currently exist concerning interventions that can fulfill them and possibly improve QoL for patients and their partners.[7] In our study, we determined the effect of a short multi-disciplinary empowerment programme on the QoL for patients with IPF and their partners.

In 2014 and 2015, consecutive IPF outpatients and their partners at the Erasmus MC, in Rotterdam, were asked to participate in a Patient and Partner Empowerment Programme for IPF, called PPEPP. "Partner" was broadly defined as spouse, partner, family member or close friend. PPEPP consisted of three afternoon meetings, divided over three consecutive weeks and focuses on coping with IPF. A psychologist who is experienced in group therapy leads PPEPP. A pulmonologist, specialized interstitial lung disease nurse, oxygen supplier, social worker and physiotherapists also contribute to the sessions. The protocol and content were designed by the participating disciplines. Moreover, two patients with IPF, a former physiotherapist and a vicar, gave their input on the protocol and content of the programme. A comprehensive description of the programme and contribution of each discipline can be found in the supplementary material.

Patients and partners were included in three blocks: two intervention groups and one control group. Patients were included if they had been diagnosed with IPF according to the guidelines of 2011,[8] had a life expectancy of ≥1 year, had a lung function with a forced vital capacity (FVC) ≥45% of predicted, and had a diffusion capacity for carbon monoxide (DLCO) ≥25% of predicted. Participants were asked to fill in questionnaires at baseline, after 3 weeks and after 3 months. All participants filled in the Hospital Anxiety and Depression Scale (HADS), Perceived Stress Scale (PSS) and a knowledge quiz about IPF.[9] Furthermore, patients completed the King's Brief Interstitial Lung Disease health status questionnaire (K-BILD), the Euroqol5D5L (EQ5D5L) and the Medical Research Council (MRC) dyspnoea scale, while their partners completed the Carer Quality of Life instrument (CarerQoL).[10-12] We also asked participants to complete an evaluation form after PPEPP. The Wilcoxon signed rank test was used to compare baseline scores with follow-up scores, because the data were not normally distributed. Medical ethics committee approval was obtained, and all participants gave written informed consent.

In total, 46 participants were included, 15 couples in the intervention group (eight couples in the first, seven couples in the second) and eight in the control group. In the intervention group, two couples were excluded. One couple could not participate because of clinical worsening of IPF, and the other couple did not complete baseline questionnaires and missed the first meeting due to an influenza infection. In the control

group, one patient died of heart failure after 3 weeks, thereby excluding this couple from analysis.

In the intervention group, most patients were men (10, 77%) and most partners were women (10, 77%); patients had a median age of 63 (range 54-74) years and partners of 64 (47-74) years; the median FVC in patients was 80% (50-100%) of predicted and DLCO was 46% (25-60%) of predicted. In the control group, all patients were men and all partners were women; patients had a median age of 76 (63-82) years and partners of 74 (22-84) years; the median FVC in patients was 78% (53-96%) of predicted and DLCO was 48% (30-82%) of predicted.

Both groups matched on disease severity defined by pulmonary function. However, baseline questionnaire scores differed except for HADS depression, PSS and CarerQoL (table 1). Questionnaire scores significantly improved after 3 weeks of PPEPP (table 1) in the intervention group only.

Table 1. Wilcoxon signed rank test intervention and control group - baseline versus week 3

Questionnaires	**Intervention group** (n=26)			**Control group** (n=14)		
	Baseline	Week 3	p-value	Baseline	Week 3	p-value
K-BILD total	43 (28-69)	46 (32-81)	0.06	72 (45-82)	61 (34-79)	0.17
K-BILD psych	49 (22-72)	52 (30-78)	**0.03**	65 (38-73)	63 (17-80)	0.87
EQ5D5L	0.6 (0.4-1.0)	0.7 (0.6-0.9)	0.07	0.9 (0.7-1.0)	0.9 (0.6-1.0)	0.40
MRC	3 (2-5)	3 (2-5)	0.32	2 (0-3)	2 (2-4)	0.18
HADS total	11 (3-26)	9 (0-27)	**0.04**	6 (0-22)	7 (1-23)	0.31
HADS anxiety	6 (1-15)	5 (0-14)	0.06	4 (0-13)	5 (0-12)	0.14
HADS depression	5 (0-15)	4 (0-13)	**0.04**	3 (0-10)	2 (1-12)	0.52
PSS total	20 (5-40)	21 (5-33)	0.94	23 (11-33)	23 (4-34)	0.48
CarerQoL	3 (0-10)	3 (0-6)	0.25	2 (0-3)	2 (0-3)	0.71
CarerQoL VAS	7 (5-9)	7 (5-10)	0.86	8 (7-9)	8 (6-9)	0.45
IPFquiz	6 (3-9)	7 (3-9)	0.27	4 (2-6)	4 (1-9)	0.86

Data are presented as median (range). K-BILD, King's Brief Interstitial Lung Disease health status questionnaire; psych, psychological domain; EQ5D5L, Euroqol5D5L; MRC, Medical Research Council dyspnoea scale; HADS, Hospital Anxiety and Depression Scale; PSS, Perceived Stress Scale; CarerQoL, Carer Quality of Life instrument; VAS, visual analogue scale; IPF, Idiopathic Pulmonary Fibrosis

A higher score indicates better quality of life/ knowledge on disease

A higher score indicates worse breathlessness/ anxiety/ depression/ stress/ quality of life

Bold indicates statistically significant p-values.

After a 3-month follow-up, no significant changes in questionnaire scores compared with baseline were found in the intervention group. In the control group, QoL measures were lower at 3 months than at baseline: K-BILD total median of 72 (range 45-82) versus 46 (31-86), p=0.03; K-BILD psychological domain 65 (38-73) versus 47 (15-72), p=0.03; EQ5D5L 0.9 (0.7-1.0) versus 0.8 (0.3-0.8), p=0.03; and HADS total 6 (0-22) versus 7 (1-

28), p=0.04. After 3 months, FVC deteriorated ≥5% in one patient of the control group and in none of the intervention groups.

All participants considered PPEPP useful and would recommend it to others, while 25 participants (96%) found PPEPP fulfilled their expectations. The following quotes illustrate the participants' experiences with PPEPP: "informative, useful and supportive", "pleasant to share experience with and learn from peers", "comforting to know that you're not alone in your struggles".

This study showed that a short multidisciplinary empowerment programme improved QoL for patients with IPF and their partners. To our knowledge, ours is the first study in which the effect of a support programme, co-developed with patients and multidisciplinary experts, demonstrated a positive effect on the wellbeing of patients and their partners.

Currently, it is well acknowledged that there is a need for better information and support for patients with IPF and their partners. Many hospitals organize general IPF information meetings and support groups; however, studies on effective ways of supporting and educating patients and partners are scarce. A previous study by Lindell et al.[7] on the effect of a 6-week programme on disease management and symptom reduction showed, strikingly, a decline in patients' QoL and increased anxiety levels. Nevertheless, in partners, stress levels decreased, and interviews showed that participants found attending the programme helpful. It is useful to realise that information can be distressing to patients and should be tailored carefully. In our study, perceived stress scores showed no differences in stress levels. The co-development by two patient experts may have been a factor in helping to tailor our programme more effectively.

PPEPP consists of small groups, which stimulate personal interaction, and can be more patient-tailored than general information meetings, which are often made up of large groups. In our opinion, the experience of the psychologist with group therapy was crucial in stimulating discussion and promoting balanced participation for all. The extensive experience with group counseling in the field of oncology could also prove useful. With IPF bearing similarities in both prognosis and treatment options with oncology, we think we could learn from their experience.[13-15]

PPEPP improved short-term QoL but showed no effect long-term. Research into more chronic support is needed as different stages of disease often mandate adaptation of coping strategies for patients and partners.[1]

This study has some limitations. First, it consists of small groups of patients from a single center, and though the results are encouraging, further studies are needed. Another limitation is the difference in baseline QoL scores between the intervention and control groups. We lack a good explanation for this, as no significant differences existed in

disease severity defined by pulmonary function (FVC and DLCO). Including patients in blocks (for practical reasons) instead of randomizing them may have influenced results. Still, participants were not allowed to choose between groups, and the control group was offered the opportunity to attend a future PPEPP. For future studies, it would be worth exploring the effect of matching participants based on their QoL scores instead of pulmonary function.

In conclusion, PPEPP, a concise multidisciplinary empowerment programme, improves short-term quality of life for patients with IPF and their partners. Patients and partners were very satisfied with PPEPP. More research, however, is needed to develop structural support programmes for patients and partners throughout the disease course.

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ONLINE SUPPLEMENT

A. Overview of the PPEPP program (chaired by psychologist)

Meeting 1

- Introduction round and assessing patients' and partners' wishes and expectations of the program
- "What is idiopathic pulmonary fibrosis" by pulmonologist
- "Dealing with IPF – coping strategies" by psychologist
- "Physiotherapy and training" by physiotherapist

Meeting 2

- "Dealing with IPF" by psychologist
- "Dealing with IPF" patients (led by psychologist) and partners (led by social worker) separated
- "Support by specialized ILD nurse and oxygen possibilities" by specialized ILD nurse
- Information market on oxygen devices, by oxygen supplier
- "Breathing, cough and limitations" by physiotherapist

Meeting 3

- "Caring about, for and with each other" by psychologist
- "Practical problems at home" by social worker
- "Latest research developments and patient support groups" by pulmonologist
- Evaluation of the program and round-up

B. Content of PPEPP program and contribution of each discipline

Psychologist

The psychological content of the programme consists of three parts. In the first part, the psychologist explains theories concerning stress and coping. For stress, four domains are described and discussed with the participants; bodily, cognitive, emotional, and behavioural manifestations of stress. Coping is described in terms of emotion-focussed coping and problem-focussed coping. Stress and coping are discussed with the stress-coping model of Lazarus and Folkman in mind.[1] Another important topic is the different ways of setting goals, for this discussion the model of Problem Solving Therapy forms the basis.[2] In this model, ample attention is paid to the definition of the problem at hand, because a change in problem formulation (e.g. from 'I am too tired to do things' to 'I can no longer have long evenings with my friends because of my lack of energy') will lead to a change in goals (e.g. from 'getting more energy' to 'finding different ways to see my friends'). Patients are encouraged to formulate their problems more specifically, so that the goals they set are more specific and more attainable.

The second part of the programme concerns the quality of the partner relation. For this part of the program patients and partners are separated, so that they can discuss more freely changes they experience in the partner-relationship. Subjects that are discussed

concern for instance feelings of dependency versus independence, changes in reciprocity of the relationship and discussing complex emotions. After patients and partners have discussed separately, the subjects of the discussions are shared with the group in total, while the content of the separate discussions is not revealed. In this way, the confidentiality of the discussion remains intact, while both patients and partners know what subjects were discussed. The last part of the psychological intervention consists of a discussion of questions that arise within the groups. Important concerns were; the uncertainty regarding the future, dealing with diminished levels of energy and dealing with ignorance from bystanders regarding the nature of the disease.

Physiotherapist

The physiotherapist's contribution to the programme consists of two presentations. The first presentation is about physiotherapy and training. During this presentation, the physiotherapist explains the importance of exercise for patients with IPF. Exercise is necessary to maintain muscle strength and exercise capacity.[3,4] The level of exercise can be adjusted according to the severity of patient's disease, patient's oxygen need, and should be adapted when disease progresses.[5] Patients also get information on dyspnoea and desaturation, and the uses of pulse oximetry and Borg dyspnoea scales. Moreover, they receive tips and tricks on how to decrease their breathlessness by adapting their exercise and using tools. The physiotherapist also emphasizes, especially for partners, that dyspnoea is a subjective measure and that not all IPF patients experience the same severity of breathlessness.

The second presentation is about breathing techniques, cough and limitations. Breathing techniques are often used in other lung diseases, such as COPD, and can help patients with lung fibrosis to control their breathing.[5] Besides breathing difficulties, many patients with IPF experience a burdensome cough. Different types of cough are discussed and tips are shared as for instance on how to better cough up sputum or how to try to avoid the urge to cough sensation in the more dry type of cough, and how to deal with the dyspnoea caused by cough. Progressive lung function impairment and limitations in training abilities are discussed as well as the fact that oxygen therapy can be helpful for some patients to maintain their exercise capacity.[4,5] It is important that patients inform their physiotherapist on IPF as many physiotherapists are not familiar with the disease. All participants received an information folder on how to exercise and to control your breathing, and contact information of the physiotherapist.

Social worker

The social worker's contribution to the programme consists of a presentation explaining how they can provide practical and material support for patients. Questions regarding regulations and patient rights according to the national policy on disease are discussed. The social worker explains what patients can expect when they are not able to work, and called in sick or get disqualified for work. The impact of the patient's medical situation on their partner and nearest and dearest is discussed, when patients and partners

are separated. Together with the psychologist subjects of the discussions are shared with the group in total, while the content of the separate discussions is not revealed to maintain confidentiality.

Specialized ILD nurse / Oxygen supplier

The specialized ILD nurse is involved with the PPEPP program from the start and plays a vital role in the logistical part. The good relationship with the patients and their partners in the outpatient clinic enables her to contact patients for participation. She also organizes, together with the researcher, the room and catering, sends invitations and is a contact person for the participants. Moreover, the specialized ILD nurse gives a presentation on supplemental oxygen, and discusses the potential advantages and disadvantages with the group. One of the subjects discussed is the impact the use of supplemental oxygen may have on daily life by making the disease more visible and limiting freedom of being away from home.[6] The need for supplemental oxygen is also a sign of disease progression,[7] which can be frightening for patients. But also the benefits of oxygen use, for example during exercise and activities, are explained.[5,8] Participants receive general information about supplemental oxygen; when to start with oxygen, what kind of devices exist, and what are the advantages and disadvantages of these devices. The specialized ILD nurse invites an oxygen supplier to show the different oxygen devices during the 'oxygen information market'. Participants get the opportunity to explore the use of different oxygen devices.

Pulmonologist

The pulmonologist also recruits patients for the PPEPP program and is available to answer disease-related questions. During the first meeting, the pulmonologist explains about IPF in an interactive way. Aetiology, risk factors, symptoms, diagnosis, heterogeneity in disease and prognosis are discussed with the group.[9] The pulmonologist also discusses the current available anti-fibrotic treatments and supportive options as symptom relieve, quitting smoking, oxygen therapy, physiotherapy and psychological support. In the third meeting and update of the latest research developments is given. Furthermore, the concept of support groups lead by patients is explained. Experiences of support groups are discussed.[10] Together with the psychologist, an evaluation round is done and a summary of the meetings and experiences is given. The meeting is concluded with drinks with the whole group.

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Chapter 11

General discussion

“The good physician treats the disease; the great physician treats the patient who has the disease”
William Osler

GENERAL DISCUSSION

Interstitial lung diseases (ILDs) contain a wide variety of diseases, usually affecting both lungs. The two most common ILDs are sarcoidosis and idiopathic pulmonary fibrosis (IPF), both known to negatively impact patients' quality of life (QoL) (chapter 4, 6).[1-4] In IPF, major drivers of QoL are decline in lung function, depression, cough and dyspnea.[5] In sarcoidosis, multiple organs can be involved, with diverse symptom burden, prognosis and effect on QoL.[3,6] Furthermore, in sarcoidosis, medication can also have a negative impact on QoL[3], while in IPF the effect of medication on QoL is less clear.

QoL is a defined by the World Health Organization (WHO) as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment."[7] As QoL is a broad definition, studies often evaluate health-related QoL: the subset of QoL that is affected by health,[8,9] or health status defined as: "the impact of disease on patients' physical, psychological and social functioning."[10] Although these terms represent different concepts, they are often used exchangeably in research and daily care. In general, treatment of ILDs is focused on improving physiological outcomes, such as lung function parameters and 6-minute walk tests (6MWT). Some of these outcomes are also used as surrogate measures of survival.[11,12] Physiological outcome measures often do not reflect patients' QoL. In the recent years, it is increasingly acknowledged that QoL should be part of treatment goals and that the patient's "voice" should also be incorporated as an outcome measure in care and research.[13-15] In ILD, there is a paucity of good patient-reported outcome measures (PROMs) and studies on interventions that may improve symptoms and QoL.

The aim of the studies in this thesis was to measure and improve quality of life in interstitial lung diseases by 1. generating better clinical outcome measures for quality of life; 2. developing interventions focussed on improving quality of life.

Clinical outcome measures for quality of life

Patient-reported outcome measures

To improve patients' QoL you first need to be able to measure it properly. PROMs are often used to measure QoL, but can also evaluate symptoms, such as cough, fatigue, and dyspnoea, that may impact QoL (chapter 2).[14,16] PROMs are useful in research, but can also serve as outcome measure in daily clinical practise, to guide therapeutic decisions, and for evaluating interventions and quality of care by healthcare policy makers (chapter 2). Chapter 2 shows that though PROMs have gained more attention over the last years, well-developed and validated PROMs for ILDs are still lacking. Ideally PROMs are developed according to a systematic approach[14,15,17] and in collaboration with the target population. Subsequently, the PROM should be validated in this target popula-

tion. Validation is an iterative process and the more an instrument is used in studies and real life, the more solid the validation will be. The risk of these comprehensive validations is that often less ideal PROMs are used, as choice of PROM will be based on familiarity and number of trials used before. This strategy may obstruct development and validation of new outcome measures.

For the research in ILD in this thesis, we choose to primarily use PROMs that were developed in the target population, such as the King's brief interstitial lung disease health status (K-BILD) questionnaire. The K-BILD is an ILD-specific PROM consisting of 15 questions, and has been developed and validated in an ILD population in 2012.[18] Since then, the K-BILD has been translated and validated in Dutch, French, Italian, Swedish, and German.[19,20] By developing these multi-linguistic versions, the questionnaire can now widely be used for international collaboration. Until now, the SGRQ has most often been used in ILD research and is the best validated questionnaire in patients with IPF.[21] Yet, it failed to show an effect on QoL in drug trials that were positive.[22,23] Disadvantages of the 50-item SGRQ are the original development in COPD and asthma, and the numerous questions, with many of them irrelevant to ILD patients. The SGRQ correlates well with the much shorter K-BILD,[18] while the K-BILD is easier to use in daily practise. The K-BILD is currently used in several trials in ILDs,[24-26] and registries are embracing the questionnaire,[27,28] which will improve its validation. For IPF, other PROMs, as for example the Tool to Assess Quality of Life in IPF (ATAQ-IPF), and the COPD Assessment Test (CAT), are also being validated.[29-32] Moreover, new questionnaires are now being developed for IPF, such as the IPF-PROM, IPF-PREM and patient experiences and satisfaction with medication (PESaM) questionnaire, that not only focus on patients perception regarding their health status and a given intervention, but also assess patient expectations and experiences with healthcare.[33-35]

For sarcoidosis, we chose to use the King's Sarcoidosis Questionnaire (KSQ) as it was developed in a sarcoidosis cohort, is simple to administer, and takes into account multiple organ involvement.[36] In chapter 3 we translated and validated the KSQ in a Dutch cohort of sarcoidosis patients and thereby enabling use of the questionnaire in Dutch-speaking countries, and facilitating participation in international collaborations. The validation of the KSQ in Dutch has stimulated international collaborative projects, and the KSQ has been used in several international and Dutch clinical trials.[37-41] These studies will prospectively follow up large cohorts in multiple countries and enable better validation of the KSQ. The minimal important difference (MID) for the KSQ Lung-GHS domain has been determined, but no MID for the total list or separate modules exists.[42] By correlating clinical data and outcomes to the different modules of the KSQ, future studies will help determining these MID using different anchors meaningful for patients. A study by Baughman et al. showed a significant improvement in KSQ scores after 24 weeks of additional treatment with repository corticotrophin in patients with sarcoidosis. Interestingly, they found no significant changes in SGRQ scores. This might be because the SGRQ was originally developed for COPD and asthma, and may contain

questions irrelevant to sarcoidosis patients.[43] Moreover, the SGRQ is focussed on the lungs, while the KSQ contains multiple organ domains to capture the multi-systemic nature of sarcoidosis. At the time of the KSQ study, the SHQ was the only alternative sarcoidosis-specific QoL questionnaire.[44] We chose to validate the KSQ, as the SHQ contained only few organ-specific questions and was not validated in eye or skin disease. Another sarcoidosis-specific questionnaire, the Sarcoidosis Assessment Tool (SAT), was developed during our study.[45] The SAT includes questions on multiple-organ involvement, but is with its 51 items considerably longer than the KSQ.[45] Both the SAT and SHQ have also shown to be able to capture effect of treatment.[46,47]

PROMs may serve a broader purpose than only as outcome measures; they might also be used as predictor for prognosis. As shown in a study in 182 Japanese patients with IPF, were the SGRQ showed to be an independent prognostic factor for mortality.[48] A score above 30 corresponded with significant higher mortality than a score below 30. Interestingly, the study showed that both baseline forced vital capacity (FVC) and the SGRQ independently predicted mortality.[48] The authors postulate that the SGRQ might capture another dimension and more comprehensive aspect of disease. This corresponds with our and previous findings that lung function parameters poorly correlate with QoL scores (chapter 3, 8),[18,29,49] and underscores the importance of incorporating QoL PROMs as outcome measure in clinical trials. If more disease-specific PROMs as the K-BILD will even better relate to prognosis, still needs to be studied. The recent years it is increasingly acknowledged that comorbidities may affect prognosis and may also influence QoL.[50,51] It seems reasonable to assume that comorbidities influence outcomes of disease-specific PROMs, however, to our knowledge no good research exist on the influences of comorbidities on PROM scores.

One of the problems with PROMs is that they are often lengthy questionnaires. Completing of PROMs is not only time-consuming but can also yield recall bias. Furthermore, they often contain questions irrelevant to certain patients. One of the options to solve these problems, as described above, are shorter and more relevant questionnaires. Recall bias may be solved by enabling patient's access to their data captured by serial measures, so that they can relate to their previous answers. The clinical meaningfulness and research implications of such methods need further evaluation. Another option might be the use of computer-adapted tests (CATs). CATs are based on an item response theory model, and try to establish the optimal test for each participant by adapting the test to their ability level or based on individual relevances.[52,53] Items (questions) are derived from an item bank were they define a common domain.[52,54] The first domain-specific question a participant answers is believed to predict the domain score. The second question is selected based on the previous answer, and so one. After each questions the reliability of the predicted domain scores should become more convinced.[44] CATs have the advantage that they can be shortened and tailored-made, as irrelevant questions can be avoided.[52] The KSQ with its multi-domains could potentially benefit from a CAT strategy.

Especially when studying orphan diseases, international collaboration is important to increase the number of patients that can be studied. Though the multilingual validations and new developments on ILDs PROMs are encouraging, more research is still needed to determine if disease-specific questionnaires, as the K-BILD and KSQ, can better capture QoL and treatment effects than PROMs adapted from other lung diseases, such as the CAT and SGRQ. Also, many ILD PROMs still lack longitudinal data and need to be translated and validated in larger and prospective cohorts. Currently, registers pop-up worldwide to study the clinical course of ILDs, possible biomarkers and PROMs.[55-57] Hopefully, these registers will provide the longitudinal data on PROMs we are waiting for.

Patient-reported outcome measures as primary endpoint

PROMs are now increasingly used as secondary endpoint in clinical trials in ILDs, which raises the question if PROMs also could and should be used as primary endpoint. Clinical trials in ILDs can broadly be divided into three groups: 1. trials aiming at disease-modification, 2. trials aiming at improving symptoms, 3. trials aiming at improving QoL. In group one, FVC is commonly used as primary endpoint as it is reproducible, easy to test and associated with mortality.[11,58] Other primary endpoints often used are transfer factor for carbon monoxide (TLCO), 6MWT, hospitalization and mortality.[11,59] Currently, we do not have robust enough PROMs to serve as primary endpoint in trials aiming at disease-modification. Also, Food and Drug Administration (FDA) and European Medicine Agency requirements should be taken into account, especially in drug registration trials.[60,61] However, as PROMs seem to capture another aspect of disease they should at least be included as secondary endpoint.

For group two, objective symptoms scores or measurements, or subjective symptom-related QoL PROMs can be used as primary endpoint. Our and previous studies show that objective and subjective symptoms scores may vary in correlation from poor to good (chapter 8).[62,63] For example, a patient's cough frequency does not always defines how a patient experiences his or her cough. The effect of cough on a patients' QoL might be influenced by work, social activities, and relationship status.[64] In clinical trials aiming at improving symptoms, the main goal should be to improve patient's experience of the symptom; ideally a symptom-related QoL PROM should therefore be used as primary endpoint. However, as objective symptom scores seem to capture another aspect of disease, and the relationship between objective and subjective is often only moderate (chapter 8), a novel strategy could be to use composite endpoints of subjective and objective outcomes.

In the third group, a QoL PROM should be the primary endpoint. As shown by our "PPEPP study" in IPF patients, QoL-related PROMs scores are able to capture effects of interventions (chapter 10). Also, other studies in ILD/IPF have confirmed this.[65,66] Better development and validation of PROMs together with patients, may improve the ability of the instruments to detect changes that are meaningful to patients.

Objective patient-reported outcome measures

Current PROMs on QoL are subjective and sometimes of bothersome length for patients, and pose a burden on logistics in daily practise. An objective measure for QoL, that is easy to obtain and fit for longitudinal follow-up, may be an innovative step forward in outcome development. At first for use in clinical trials, but maybe in the future also in regular care. Previous studies showed that scalp hair cortisol could serve as an objective biological marker for chronic stress.[67,68] Patients with ILDs may experience chronic stress, due to progressive respiratory symptoms, decreased QoL, and a sometimes chronic or even fatal disease course. We choose to first assess the feasibility of scalp hair steroid analyses in sarcoidosis, as patients with sarcoidosis often experience psychological distress and we also wondered if cortisol levels might be related to fatigue (chapter 4). Our study showed that scalp hair cortisol can be used to assess psychological distress, but that scalp hair steroids were not related to fatigue in patients with sarcoidosis. It also showed that cortisol and cortisone levels are much higher in sarcoidosis patients than in general population controls, which could be due to disease inflammation, or direct psychological distress. Further studies are needed to elucidate the increased chronic steroid levels, and to determine the precise role of scalp hair cortisol in monitoring patients with sarcoidosis. As many patients with other types of ILDs also experience psychological distress it is evident to evaluate scalp hair steroids level in these patients as well. Though research on biomarkers in ILDs is increasing, no biomarkers currently exist that can objectively measure QoL in ILDs.

Clubbing as diagnostic feature

Clubbing is a diagnostic feature of fibrotic ILDs. It has shown to be an independent predictor of disease progression and might be used as objective measure for prognosis.[69,70] However, the predictive value of clubbing was based on physicians' ratings and only assessed in IPF. To study if clubbing can be used as outcome measure in treatment or as predictor of prognosis in fibrotic ILDs, it is important to measure clubbing reliably and preferable quantify it. Clubbing can be measured subjectively on sight or objectively with several clubbing measuring methods (chapter 5).[71-74] In chapter 5 we show that, in patients with fibrotic ILDs, assessment of clubbing by different measuring methods showed no to poor agreement. Also, PROM scores were not influenced by the presence or absence of clubbing. Yet, severity of disease, measured with TLCO, seemed worse in patients with clubbing than those without (chapter 5). Though the exact pathogenesis of clubbing is unclear, it has been proposed that platelet-derived growth factor (PDGF) and vascular endothelial growth factor play a central role in clubbing. Clubbing is known to disappear after lung transplantation or when underlying diseases are treated successfully.[75-79] However, the effect of successful anti-fibrotic treatment on clubbing in ILD is unknown, though interesting as the anti-fibrotic drug nintedanib targets, among others, the PDGF receptor, that is thought to be involved in the pathogenesis of clubbing.[23] Nor do we know if clubbing might be a marker of anti-fibrotic treatment response, and could even be associated with a certain phenotype of disease. Nevertheless, determination of a "gold standard" for clubbing should be established first, before longitudinal studies

can provide information on the predictive value of clubbing and its potential role as physical marker for treatment response.

Interventions focussed on improving quality of life

The interventions described in this thesis are mainly focussed on patients with IPF. Some of these might also be applicable for other ILDs, including sarcoidosis. In future research we not only wish to optimize the current interventions, but also include other ILDs.

Holistic approach

Disease modification is often the central focus of treatment in ILDs. However, modification of disease behaviour will not always lead to improvement of symptoms and/or QoL. In IPF, the only curative option is lung transplantation, which is possible in only a small group of patients. Fortunately, there are now two drugs that slow down disease decline.[22,23] In a deadly disease as IPF, most people want to live as long as possible, at the best possible quality. Treatment should therefore not only aim at slowing down lung function decline but also on improving patients' symptoms and QoL. As inspiringly formulated by a family caregiver and IPF patient "it's really about what's going to improve the quality versus the length of your life" and "if we can't solve this problem today, let's do something that improves patients symptoms, that improves their quality of life, that can help them to move forward, at least for a little bit of time with their families."[80,81] Chapter 6 focuses on how to optimize QoL in patients with IPF. We proposed a new model for continuous care – the "ABCDE of IPF care": **A**ssessing patient's and partner's needs, **B**acking patients by giving information and support, delivering **C**omfort care by focusing on treating symptoms and taking into account **C**omorbidities, striving to prolong life by **D**isease modification, and helping and preparing patients and their family for the **E**nd-of life (chapter 6). Reassessing the patient's situation should be done during the different phases of the disease, as needs may change when the disease progresses. The ABCDE model tries to capture all aspects of disease management, and can function as guide for optimizing QoL in IPF patients. As with all models, the ABCDE model is not watertight and new insights or treatment options should lead to adaptations in future. For example, many patients with IPF, like in other chronic respiratory diseases, lose weight.[81,82] Though no studies have been done on the clinical significance of nutritional status in IPF, one could argue that dieticians, who can play an important role in maintaining patients' weight, should be added to the ABCDE model as well. Also, new developments in disease modifying treatment and studies on genetics and different phenotypes of patients with IPF will probably lead to alterations of the model. This model together with new approaches to managing IPF, underline the importance of a holistic approach when treating patients with IPF.[83,84]

Symptom intervention

As described in chapter 6, there is a paucity of interventions to improve QoL. In IPF, one of the main symptoms impacting patients' QoL is cough.[62,81] Patients with IPF often have a refractory and dry chronic cough (>8 weeks). Although cough in IPF can be related

to comorbidities, such as gastro-esophageal reflux disease, obstructive sleep apnea, and emphysema, its exact underlying mechanism is largely unknown (chapter 7).[85] In chapter 7, we describe concepts that have been proposed as possible mechanism of cough in IPF. Cough in IPF is difficult to treat, no convincing studies on treatment in cough exist, and patients often do not respond to conventional anti-tussive therapies (chapter 7). A number of observations suggested that pirfenidone might decrease cough in IPF patients.[86,87] In chapter 8, we therefore analysed the effect of pirfenidone on objective and subjective cough in patients with IPF, and found that both improved significantly after 12 weeks of treatment. These improvements were clinical meaningful for patients. Recently, a small placebo-controlled trial showed that 14-day inhalation of PA101, a highly concentrated cromolyn sodium formulation, has an beneficial effect on cough in patients with IPF.[88] To our knowledge, this is the only other study on treatment for cough in IPF that used objective cough counts. No effect on cough was seen in the placebo group of the PA101 trial.[88] In our study, no placebo group was studied, as at that time it was considered unethical to leave a group of patients untreated for 12 weeks. However, the results of the PA101 study suggest that no major placebo effect is present when treating IPF patients for their cough, and strengthens our results. Nevertheless, it remains unsatisfying that the exact mechanism of pirfenidone on fibrosis remains unknown and that we can only hypothesize what the possible mechanism on cough might be. In our study, pirfenidone significantly improved cough-related QoL measured by the LCQ, but showed no effect on K-BILD scores (chapter 8). This might be because the K-BILD contains no question on cough and possibly measures a different aspect of QoL. As shown by Lindell et al., cough not only impacts patients, but also their environment and relationships.[89] A significant clinical meaningful improvement of cough can therefore have an enormous positive effect on both patients and family. We regret that we missed the opportunity in our study to also assess the families' perception of cough and the impact of chronic cough and effect of cough changes on the patients' nearest and dearest.

Cough is not only a major bothersome symptom, but also an independent predictor of disease progression in patients with IPF. IPF patients who cough might have a different phenotype of disease and could respond differently to therapy. To further explore this, cough should be included as outcome measure in clinical trials (chapter 7). Ideally in these trials both objective and subjective outcome measures are used, as is often the case in well-designed trials for chronic cough.[90,91] However, it might not always be feasible due to logistics and resource difficulties. In our study, we found that correlations between objective cough and subjective cough scores were moderate, with the urge-to-cough VAS having the best correlation ($r=0.55$, $p<0.01$) (chapter 8). If objective cough counts cannot be used as primary endpoint, the urge-to-cough VAS, possibly in combination with the LCQ, would then be the way forward. Currently, clinical trials on new agents in IPF are already increasingly including cough as endpoint, and general chronic cough trials now often contain a subgroup of IPF patients.[92-94] Most of these studies use subjective cough-specific QoL and severity scores as outcome measure, and some

also objective cough frequencies. Some of the chronic cough trials show encouraging results, such as the trial by Abdulqawi et al.[95] They show that two weeks treatment with AF-219, a P2X3 receptor antagonist, reduced cough frequency by 75% in patients with refractory chronic cough.[95] This agent is now studied in patients with IPF.[92,96]

Cough is also a common symptom in sarcoidosis and other ILDs.[97,98] The heterogeneity of ILDs complicates study design, but as cough is often also an unmet need in these diseases, they should not be forgotten. Hopefully positive developments in anti-tussive mediation in chronic cough and in IPF can be extrapolated to other diseases.[88,95] Also, studies on the use of pirfenidone in other fibrotic ILDs are now emerging,[84] and might show a beneficial effect on cough as well.[99] If the anti-fibrotic drug nintedanib also has an effect of cough needs to be evaluated.

Quality of life intervention

In chapter 9, we asked pulmonary fibrosis patients and their partner's questions regarding their needs and preferences in care. Consistent with previous studies, the study showed that pulmonary fibrosis has a major impact on patients' and partners' psychological wellbeing, and a need for comprehensive information, and psychological and practical support.[2,100-103] An interactive voting system was used, which projected answers of participants directly on a screen. Participants found the system pleasant and informative, and felt more secure after the meeting (chapter 9). If this kind of educational methods will have a positive effect on QoL, through improvement of knowledge on disease and by showing patients and their partners that they are not alone in their struggles, is still unclear. Yet, we decided to continue using this interactive voting system at the patient meetings in our centre, to be able to continuously evaluate and improve our service and to catch potential changes in needs in future.

The unmet needs revealed during the patient information meetings, prompted us to develop an empowerment program for IPF patients and their partners, the "PPEPP program" (chapter 10). The program focussed on disease education, psychological support and interaction with peers, and comprised multiple disciplines: a pulmonologist, ILD specialist nurse, oxygen supplier, social worker and physiotherapist. The "PPEPP program" is the first IPF support program that shows to improve short-term QoL scores in both patients and partners (chapter 10). We currently implemented the PPEPP program in our general care and are now studying if follow-up meetings can prolong the QoL improvements found after 3 weeks.

There are several challenges in patient education and support. Practical challenges, as limited resources and time, demand new methods to be sought in addition to the consultation with doctor and specialist nurses. Group sessions as PPEPP could help, but are not (yet) reimbursed by insurance companies. Engaging patient associations is of great benefit, but not all patients wish or are able to travel to their meetings, and some prefer local setting and teams, and a more personalized approach. To more

actively involve patients in peer education, is difficult in a progressive disease as IPF were patients have limited energy. In the PPEPP program, we gave patients and partners information on how to continue the group and form a "self-organized" support group, based on the American Pulmonary Fibrosis Foundation support group leader guide.[104] Although they exchanged emails/addresses, none of them arranged a support group meeting. Another challenge is the content of the information, which should be carefully tailored as information may lead to more anxiety. Meeting peers with more advanced disease might also increase anxiety. In a 6-weeks support program in IPF of Lindell et al., patients' QoL and anxiety scores deteriorated.[105] By involving patient advisors from the start of the project we believe that this may be prevented. The effectiveness of different methods for delivering information to patients and family, through paper or online, is a subject for further studies.

Role of partners in care process

Chapter 9 showed, in analogy with findings of other studies, that ILDs not only impacts QoL of patients, but also of their nearest and dearest.[89,101,106,107] Patients with a life-limiting, progressive disease as IPF do not have their disease alone, but "together" with their partners. In oncology, multiple support programs have been developed and incorporated in care,[108-110] while in ILD there is little experience with this. With the "PPEPP program" we tried to fulfil this need, by letting the partner join the meetings (chapter 10). They were pleased to be involved, so that they could support their loved-ones, learn more about the disease, and had the opportunity to talk with other partners of IPF patients. In both patients and their partners QoL improved after the PPEPP program (chapter 10). Partners play an important role in the care of IPF patients, especially in the end-stage of disease. Psychological support for partners can be beneficial for both, as it enables partners to continue caring for the patient, allowing the patient to stay at home till a later phase in the disease.[101] In sarcoidosis, numerous studies assessed QoL, but none studied the impact of the disease on partners and other nearest and dearest. Unpublished data of interactive voting, during sarcoidosis patient meetings in the Erasmus MC in Rotterdam, showed that sarcoidosis patients have similar needs for care and psychological support as IPF patients. A PPEPP program adapted for sarcoidosis seems therefore desired. But, as QoL has shown to be decreased in almost all ILDs (chapter 4, 5, 6, 9),[18] the PPEPP program might need to be adapted for a more diverse group of ILDs.

Patient as partner in care and research

Patients are, as shown in chapter 9, an important source of information. Much research has been done on the preferences, perspectives and needs of patients with IPF,[1,2,81,102,111,112] and patients are now increasingly becoming involved in the development of outcome measures.[18,31,33,44] Main topics of patients interests are obtained through focus groups and patient interviews during the translation process of PROMs (chapter 3).[19,31,33] However, patients should also be involved in the start-up of clinical trials and care programs. As shown in chapter 9, the fast majority of patients wish to be involved in the development of clinical trials. Many problems could be overcome when

involving patients in an early stage. Knowledge on patients' thresholds for participations, expected burden and therapy adherence beforehand might prevent delays in inclusion and disappointing drop-out rates. It is likely that one of the reason for success of the "PPEPP program" (chapter 10) was the fact that it was developed with input of patients, and was adapted after feedback of participants. In the one to one consultation, most doctors will strive to take treatment and care decisions together with patients. However, only patients that are well educated will be able to make realistic choices, and in daily practise discussion will be influenced by the doctors' preferences. This may lead to, for instance, a different approach on when to start anti-fibrotic treatment, or differences in treatment limitations between doctors and centres. Besides better education also simple tools, such as the supportive and palliative care indicator tool (SPICT) that assesses patients at risk to progress or die,[113] will stimulate more discussion on choices.

Clinical implications

ILDs will remain to have a high impact on patients' QoL. In this thesis, most studies are focused on patients with IPF and sarcoidosis. In the future, we hope that our findings can be extrapolated to other ILDs.

This thesis generates new outcome measures for QoL in sarcoidosis and lung fibrosis (chapter 3, 4, 8). Clinical outcome measures can help with identifying subgroups of patients that benefit the most of treatment, and can also guide treatment decisions for the individual patients, both leading to more personalized medicine. Also, our studies show that simple interventions can improve QoL, and that anti-fibrotic drug, besides reducing lung function decline, may improve the burdensome symptom cough (chapter 8, 10). This fits in the ABCDE model of holistic and personalized care we propose (chapter 6). The impact of wider implementation of this model on quality of care and on the QoL for patients and partners needs to be further explored.

Analysis of scalp hair steroids in a broader group of ILDs might provide new information on cortisol levels and the role of steroid levels in the psychological distress patients with ILDs experience. As prednisolone is a less common treatment for IPF and some other ILDs than for sarcoidosis, it will probably be easier to include larger groups of patients. For sarcoidosis, scalp hair cortisol could well serve as an objective outcome measure of an intervention (such as a patient and partner empowerment or pulmonary rehabilitation program) in patients that have no indication for steroid treatment. In patient needing steroid treatment, it would be interesting to look at scalp hair cortisol levels before start with prednisolone and after some months of treatment. As previous studies showed that exogenous corticosteroids, as inhalation and systemic corticosteroids, can suppress cortisol production,[114,115] scalp hair cortisol might have a role for the monitoring of compliance and dosing of corticosteroid treatment in sarcoidosis.

For clubbing, it should be sorted out first which measure is most reliable. As in daily clinical practice clubbing is often rated by physicians, it would be interesting to look at the

intra- and interobserver agreement on clubbing of several ILD physicians. Longitudinal studies are needed to unravel the possible effect of anti-fibrotic treatment on clubbing, its prognostic value, and if clubbing could be a feature in personalized medicine.

Future perspectives

PROMs

Validation of existing non-ILD and ILD-specific PROMs, and development of new ILD PROMs, together with CATs might result in an overgrowth of questionnaires, with a risk of fragmented use and validation, with negative effect on quality. In future, international collaboration between countries with different backgrounds, systems and religions is required to filter out the best PROMs for ILD. We see a role for international networks, such as the European Reference Network to coordinate and fund collaborative efforts to promote more universal PROM development.

Expectation management

Besides PROMs, also patient-reported experienced measures (PREMs), that focus on patients expectations and experience with medications and care, are gaining more attention. In England, a IPF-PREM is developed which focuses on the quality of services during the different stages of the disease.[34] In the Netherlands, the PESaM, a questionnaire that focuses on patients' experiences and satisfaction with medication, for patients with IPF has been developed.[35] Better expectation management and education could influence patients' experiences with medications, and potentially improve medication adherence and handling of side-effects, which could positively contribute to QoL. Moreover, understanding patients' experiences with medication and care generates insights in how to improve quality of care and treatment perception. Well-validated PREMs may possibly complement PROMs in a structural approach to improve care for IPF, and hopefully in future also for other ILDs.

E-health

E-health is an emerging field in medicine. A broad range of definitions of e-health exists[116], with the WHO defining e-health as: "the use of information and communication technologies (ICT) for health."[117] We developed an e-health self-management tool for patients with IPF in our centre: IPF online.[118] IPF online is a secured personal platform which provides information about IPF, lung function parameters, PROMs on symptoms and QoL, and has an e-consult possibility.[118] IPF online and other e-health tools could give patients a more active role in care and research and might optimize care by providing high quality information, increasing efficiency of care, and overcome geographic distances difficulties in (international) research and care services.[119] E-health has the potential to bring care from the hospitals to the patients' homes by even adding home-based spirometry to e-health platforms.[120] In future, home-spirometry may be used to prevent unnecessary hospital visits and can help to monitor treatment response.[120,121] Further studies are needed to discover the exact role of e-health and home-spirometry in precision medicine and care of patients with ILDs.

Personalized medicine

While in this thesis we have tried to personalize care by focusing on clinical needs and outcomes, for true personalized or precision medicine these data should be integrated with more basic data such as genomics and biomarkers.[122,123] The last decades, research on genetics in ILDs has been evolving.[124-127] For IPF, numerous gene mutations and polymorphisms have been found associated with the disease.[123,124,128] Some of them are associated with survival in IPF.[124,128,129] Differences in genotypes might also influence treatment decision. A first example of this in IPF is that patients with an rs3750920 TT genotype might have a favourable effect of N-acetylcysteine (NAC) therapy while for patients with an rs3750920 CC genotype NAC treatment seems harmful.[130] In the coming years, more genetic mutations and polymorphisms will probably be discovered in ILDs, enabling differentiation of the various types of IPF and other ILDs. Also, biomarkers may play a role in predicting therapy response and disease behaviour. Only by integrating data from biomedical research, clinical outcomes and patient-reported outcomes, we will be able to improve diagnosis, treatment and care for the individual patient with ILD.

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Summary

SUMMARY

Interstitial lung diseases (ILDs) contain a wide variety of disorders, usually affecting both lungs diffusely. The name is actually incorrect, as the interstitium is the space between the alveoli and blood vessels, but ILDs also affect alveoli, respiratory tract, pleura, and blood vessels. There are more than 200 diverse ILDs, with the most common idiopathic pulmonary fibrosis (IPF) and sarcoidosis.

IPF is a progressive fibrotic lung disease of unknown cause, with a median survival of 3-5 years without treatment. Besides lung transplantation, which is only available for a small group of patients, no curative treatment exists. Recently two anti-fibrotic drugs became available that slow down lung function decline and improve life expectancy; pirfenidone and nintedanib. IPF has a high symptom burden, with progressive dyspnea, fatigue and cough having the most impact on patients' quality of life (QoL).

Sarcoidosis is a granulomatous multisystem disease of unknown cause. It can affect every organ but is mostly seen in the lungs, skin, eyes, liver and peripheral lymph nodes. Sarcoidosis has multiple manifestations, ranging from asymptomatic to life-threatening pulmonary fibrosis or cardiac disease. Symptoms can vary and depend on organ involvement, but most frequent symptoms seen are cough, dyspnea, pain and fatigue, with fatigue having the most impact on patients' QoL.

Although it is well-known that QoL is impaired in ILDs, treatment is often mainly focused on improving physiological outcome measures, such as lung function parameters and six minute walking tests. These physiological outcomes often do not reflect the impact ILDs have on a patient's QoL. Patient-reported outcome measures (PROMs), mostly questionnaires, can be used for measuring QoL and symptom burden. Unfortunately, there is lack of well-developed and validated ILD-specific PROMs and other measures to assess these important aspects of disease. Also, interventions on improving QoL in ILDs are scarce and of poor benefit.

The aim of this thesis was to measure and improve QoL in ILDs by generating better clinical outcome measures for QoL (part 1) and developing interventions focussed on improving QoL (part 2).

Part 1: Outcome measures in interstitial lung diseases

Chapter 2 describes the recent advances in research on PROMs in IPF. PROMs can be used for multiple purposes: as outcome measure for daily care or for driving therapeutic decisions, as efficacy endpoints in clinical trials, or as tools to collect data for healthcare policy makers in order to improve access and quality of care. They hold great potential to reveal new aspects of IPF, which can help understanding the variable response to

treatment and reduce interpretation biases in clinical trials. Unfortunately, well-validated IPF-specific PROMs are still lacking and past IPF trials showed that generic PROMs correlate poor with established endpoints of treatment response, such as the forced vital capacity (FVC). Nonetheless, promising IPF-specific PROMs have been developed and are currently being validated in large cohorts. The next years are likely to bring new well-validated instruments, which will provide useful data for researchers, healthcare providers, patients and policy makers to improve quality and access to IPF care.

In **chapter 3**, we translated and validated a sarcoidosis PROM, as no sarcoidosis-specific questionnaire existed yet in Dutch. This sarcoidosis-specific questionnaire, the King's Sarcoidosis Questionnaire (KSQ), was developed in 2012 in the UK. The KSQ is a brief self-administered PROM, which assesses health status using five modules; General health status, Lung, Medication, Skin and Eye. We translated and validated the KSQ in a Dutch population. The KSQ was translated according to an international multi-step forward-backward procedure, and tested on its relevance and applicability in ten structured patient interviews. Subsequently, 98 consecutive outpatients (85 lung, 22 skin and 24 eye involvement) completed multiple PROMs twice, two weeks apart. Psychometric validation showed good construct validity between KSQ modules and corresponding questionnaires, except for the medication module. Internal consistency was good for all KSQ modules (Cronbach's α 0.70-0.90), and intraclass correlation coefficients and Bland-Altman plots showed good repeatability. The Dutch KSQ was shown to be a valid and reliable PROM for assessing health status in Dutch patients with sarcoidosis and facilitates international collaboration in clinical trials in sarcoidosis.

Patients with sarcoidosis often experience fatigue and psychological distress, but little is known about the etiology of these conditions. Factors that might play a role are stress, systemic inflammation, hypocortisolism and hypogonadism, which can influence cortisol and testosterone levels. While serum and saliva cortisol levels are used to monitor acute stress, scalp hair analysis is a new method that measures long-term steroid levels. In **chapter 4** we investigated whether scalp hair cortisol, cortisone, and testosterone levels differ between sarcoidosis patients both with and without fatigue and general population controls. Additionally, we studied if these hormones could serve as objective biomarkers for psychological distress in sarcoidosis. Hair steroid levels were measured using liquid chromatography-tandem mass spectrometry in glucocorticoid naïve sarcoidosis patients. Hair steroid levels from 293 participants of the Lifelines cohort study served as controls. We included 32 sarcoidosis patients; of them 23 were fatigued (FAS score ≥22). Strikingly, we found that scalp hair cortisol and cortisone levels were significantly higher in sarcoidosis patients than in general population controls. No significant differences in hair testosterone levels were found between male sarcoidosis patients and controls, and in hair steroid levels between fatigued and non-fatigued sarcoidosis patients. Increased hair cortisol levels of sarcoidosis patients were significantly associated with increased anxiety and depression, and decreased mental health, but not with fatigue. Our study is the first to assess scalp hair steroids in sarcoidosis, and to show

that scalp hair cortisol is a promising non-invasive biomarker for psychological distress in patients with sarcoidosis.

Digital clubbing is considered typical in IPF and has been associated with poor prognosis of disease. Clubbing is also seen in other fibrotic ILDs, but little is known about the prevalence and clinical meaning of clubbing, and the best method to assess clubbing in these ILDs. In **chapter 5** we aimed to evaluate agreement between different clubbing assessment methods in patients with fibrotic ILDs. Additionally, we assessed the prevalence of clubbing in these ILDs, and the relationship between clubbing, disease severity and QoL. We included 153 consecutive outpatients with fibrotic ILDs (68 IPF patients) of two tertiary referral centers. Clubbing was assessed with the phalangeal depth ratio, the digital index, the Schamroth sign test, and by the treating physicians and investigator. Additionally, patients completed PROMs on QoL, capability, frailty and symptoms. We found no to weak agreement on the presence of clubbing between the different clubbing measuring methods. Strikingly, the assessment of clubbing by the physician and investigator showed a much better agreement. Prevalence of clubbing ranged from 7-42% in the total group and 7-52% in IPF, depending on assessment method used. Clubbing did not correlate with disease severity (FVC and transfer capacity for carbon monoxide corrected for hemoglobin (TLCOc): $p>0.2$) or with QoL.

Part 2: Improving quality of life in interstitial lung diseases

Chapter 6 summarizes the most recent insights into improving QoL in patients with IPF and discusses challenges in the management of this devastating disease. In a relentless disease such as IPF, striving to optimize QoL should complement the endeavor to prolong life. Unfortunately, there is a paucity of interventions and research focusing on symptom improvement and optimizing (heath-related) QoL. As symptoms, perceptions and reactions interact, and may change over time, a synchronized comprehensive management strategy is vital to match patients' needs throughout the disease course. We, therefore, proposed a new model for continuous care in IPF – 'the ABCDE of IPF care': *Assessing* patients' needs; *Backing* patients by giving information and support; delivering *Comfort care* by focusing on treating symptoms and taking into account *Comorbidities*; striving to prolong life by *Disease modification*; helping and preparing patients and their caregivers for the *End-of-life*. To optimize QoL for patients with IPF, we need to provide patient-centered care that is comprehensive and not mainly focused on disease modification therapies.

Chapters 7 describes the latest insights into chronic cough in IPF. Chronic cough is a frequent, distressing and disabling symptom in IPF, with a major impact on QoL. It has also shown to be an independent predictor of disease progression in IPF. The pathogenesis of cough is most likely "multifactorial" and influenced by mechanical, biochemical and neurosensory changes. Increased cough reflex sensitivity, due to increased levels of

neurotrophins or alteration of nerve fibers by mechanical distortion, might play a role in the pathogenesis of IPF-related cough. Also, pressure changes might cause recurrent stretch injury leading to sheer stress and activation of pro-fibrotic mechanisms. This hypothesis could explain why cough is an independent predictor of disease progression in IPF and corresponds with the finding that mechanical ventilation is a risk factor for acute exacerbations in pulmonary fibrosis. Comorbidities also have an important role, in particular gastro-esophageal reflux disease. While insight into the pathogenesis of cough in IPF is increasing, more research to find effective therapies is still needed. Currently, treatment of IPF-related cough is a major challenge for both the patient and treating physician, as the cough is often refractory. Clinical trials of cough treatment in IPF have only recently started, with either compounds developed for "general" chronic cough or new compounds in development for IPF that also evaluate a potential effect on cough. It is crucial that both objective and subjective validated cough measurements are included in these trials. Hopefully, these new studies will ultimately lead to adequate treatment of cough, thereby improving QoL in patients with IPF.

The anti-fibrotic drug pirfenidone may contribute to adequate treatment of cough in IPF, as several observations suggested that it might decrease cough. In **chapter 8** we, therefore, aimed to objectively measure the effect of pirfenidone on cough in patients with IPF suffering from substantial cough. Additionally, we assessed the effect of pirfenidone on subjective cough and QoL measures. In this multicenter, prospective, observational study, patients with IPF and a cough visual analogue scale (VAS) score ≥40 mm, about to start on pirfenidone, were recruited from four European centers (Italy, France, United Kingdom and the Netherlands). The primary endpoint was change in 24-h objective cough counts at 12 weeks compared to baseline, measured with the validated ambulatory Leicester Cough Monitor. Secondary endpoints included changes in subjective cough-related QoL measured with the Leicester Cough Questionnaire (LCQ), cough severity with the VAS, and QoL measures. Of the 46 patients screened for the study, 43 were included. Pirfenidone significantly decreased objective 24-h cough by 34%. Importantly, this was also sensed by the patients, as the subjective PROMs on cough also significantly improved. Cough frequencies did not correlate with disease severity, measured with the FVC and TLCOc. Our study is the first to show a significant improvement of a pharmacologic treatment both on objective as well as subjective measures of cough in patients with IPF. The magnitude of these changes was clinically meaningful to patients.

In recent years, unmet needs of pulmonary fibrosis patients have increasingly been acknowledged, however, needs of partners often remain unnoticed. Also, little is known about the best way to educate pulmonary fibrosis patients and their partners. In **chapter 9** we investigated pulmonary fibrosis patients' and partners' perspectives and preferences in care. Additionally, we evaluated whether interactive interviewing could be a novel education method in this population, and if cultural differences in care needs existed between the Netherlands and Germany. Patients and partners were

interviewed during pulmonary fibrosis information meetings at two tertiary ILD centers. In the Netherlands, patients and partners answered questions anonymously via interactive voting boxes and results were projected directly. In Germany, questionnaires were handed out to all participants. In total, 278 patients and partners participated in the Netherlands and 51 in Germany. Our study confirms the major impact pulmonary fibrosis has on patients' and their partners' emotional wellbeing, and improves the current knowledge of their care needs. Participants expressed a need for better education, psychological and practical support, and care for partners. Treatment was preferred in expertise centers with access to ILD specialist nurses. The new method of interactively educating and interviewing could be a good and efficient way to acquire new insights into pulmonary fibrosis care and to educate patient and partners. Participants found the interactive voting system pleasant (70%) and informative (94%). No major cultural differences existed between the Netherlands and Germany.

Few studies currently exist that try to improve QoL of patients with IPF and their partners. In **chapter 10** we, therefore, studied the effect of a short multidisciplinary Patient and Partner Empowerment Program for IPF (PPEPP) on QoL. PPEPP consists of three afternoon meetings, divided over three consecutive weeks, and focuses on coping with IPF. The program is led by a psychologist experienced in group therapy, and a pulmonologist, specialized ILD nurse, oxygen supplier, social worker and physiotherapists also contribute to the sessions. Consecutive IPF outpatients and their partners were included in three blocks: two intervention groups and one control group. Participants completed QoL-related PROMs at baseline, after 3 weeks, and after 3 months. In total, thirteen couples were included in the two intervention groups and seven in the control group. PROM scores on anxiety, depression and ILD-specific QoL significantly improved after 3 weeks of PPEPP in the intervention group only. After 3 months, PROM scores did not significantly change in the intervention group, while in the control group QoL measures inexplicably declined. All participants considered PPEPP useful and would recommend it to others, and 25 participants (96%) found that PPEPP fulfilled their expectations. To our knowledge, PPEPP is the first support program demonstrating a positive short-term effect on the wellbeing of IPF patients and their partners.

Chapter 11 contains a general discussion on the findings described in this thesis.

Samenvatting

SAMENVATTING

Interstitiële longziekten (ILDs) is een verzamelnaam voor een heterogene groep aandoeningen die over het algemeen beide longen diffuus aantasten. Eigenlijk is de naam niet helemaal juist, want het interstitium is de ruimte tussen de alveoli en de bloedvaten, maar ILDs beperken zich niet alleen tot deze ruimte. Ook de alveoli, luchtwegen, pleura en bloedvaten kunnen zijn aangetast. Er zijn meer dan 200 verschillende ILDs. De meest voorkomende zijn idiopathisch pulmonale fibrose (IPF) en sarcoïdose.

Bij IPF is er sprake van progressieve verlittekening (fibrose) van de long. De oorzaak van IPF is onbekend en zonder behandeling kent de ziekte een gemiddelde overleving van 3-5 jaar. De enige curatieve optie is longtransplantatie. Helaas is longtransplantatie alleen maar geschikt voor een kleine groep patiënten. Gelukkig zijn er sinds kort twee anti-fibrotische medicijnen verkrijgbaar die de achteruitgang van de longfunctie vertragen en de levensverwachting verbeteren; pirfenidone en nintedanib. IPF patiënten hebben veel belastende klachten zoals dyspneu, vermoeidheid en hoesten. Deze klachten nemen toe naarmate de ziekte vordert en hebben een grote impact op kwaliteit van leven (KvL).

Sarcoïdose is een granulomateuze multisysteem ziekte met een onbekende oorzaak. De ziekte kan in elk orgaan voorkomen, maar wordt het meest gezien in de longen, huid, ogen, lever en perifere lymfeklieren. Sarcoïdosis kan zich op meerdere manieren manifesteren, variërend van asymptomatisch tot levensbedreigende pulmonale fibrose of cardiale ziekte. Klachten kunnen variëren en zijn afhankelijk van het orgaan dat betrokken is. De meest voorkomende klachten zijn hoesten, dyspneu, pijn en vermoeidheid. Vermoeidheid heeft van deze klachten de grootste impact op de KvL van patiënten.

Hoewel het bekend is dat KvL verminderd is in ILDs, richt de huidige behandeling zich vaak voornamelijk op het verbeteren van fysiologische uitkomstmaten, zoals longfunctie parameters en de zes minuten looptest. Deze fysiologische uitkomstmaten geven vaak niet goed weer wat voor impact ILDs hebben op de KvL van een patiënt. Patiënt-gerapporteerde uitkomstmaten (PROMs), meestal vragenlijsten, kunnen worden gebruikt om KvL en klachten te meten. Helaas is er gebrek aan goed ontwikkelde en gevalideerde ILD-specifieke PROMs en andere uitkomstmaten voor deze belangrijke aspecten van de ziekte. Tevens zijn er nauwelijks interventies die zich richten op het verbeteren van KvL in ILDs, of deze zijn weinig effectief.

Het doel van dit proefschrift was het meten en verbeteren van KvL in ILDs, door het genereren van betere klinische uitkomstmaten voor KvL (deel 1) en het ontwikkelen van interventies die zich richten op de verbetering van KvL (deel 2).

Deel 1: Uitkomstmaten in interstitiële longziekten

Hoofdstuk 2 beschrijft recente ontwikkelingen op het gebied van PROMs in IPF. PROMs kunnen voor meerdere doeleinden worden gebruikt. Ze kunnen dienen als uitkomstmaat voor de dagelijkse zorg en helpen bij beslissingen over de behandeling. PROMs kunnen ook worden gebruikt als uitkomstmaat in klinisch onderzoek, bijvoorbeeld om te kijken naar de werking van nieuwe medicatie. Tevens kunnen zij dienen als hulpmiddel bij het verzamelen van gegevens voor beleidsmakers in de gezondheidszorg, zodat zij de toegang tot zorg en kwaliteit van zorg kunnen verbeteren. Door PROMs kunnen nieuwe kenmerken van IPF aan het licht komen, dit kan bijvoorbeeld helpen bij het verklaren van verschillende reacties op behandeling. Helaas ontbreken er nog steeds goed gevalideerde IPF-specifieke PROMs. De eerdere IPF onderzoeken hebben daarnaast laten zien dat generieke PROMs slecht correleren met de gevestigde uitkomstmaten van behandeling, zoals de geforceerde vitale capaciteit (FVC). Gelukkig zijn er veelbelovende IPF-specifieke PROMs ontwikkeld die momenteel worden gevalideerd in grote cohorten. Naar verwachting zullen er in de komende jaren nieuwe gevalideerde PROMs beschikbaar komen. Zij zullen hopelijk nuttige data gaan leveren aan onderzoekers, zorgverleners, patiënten en beleidsmakers, waarmee de kwaliteit van en toegang tot IPF zorg geoptimaliseerd kan worden.

In **hoofdstuk 3** is een sarcoïdose PROM vertaald en gevalideerd, omdat er nog geen sarcoïdose-specifieke vragenlijst bestond in het Nederlands. Deze sarcoïdose-specifieke vragenlijst, de King's Sarcoidosis Questionnaire (KSQ) is ontwikkeld in 2012 in Engeland. De KSQ is een korte PROM die de gezondheidstoestand van sarcoïdose patiënten meet door middel van vijf modules; Algemene gezondheidstoestand, Long, Medicatie, Huid en Ogen. We vertaalden de KSQ volgens internationale richtlijnen en valideerden deze in een Nederlandse populatie. De KSQ werd getest op relevantie en toepasbaarheid in 10 gestructureerde patiënten interviews. Vervolgens vulden 98 poliklinische patiënten (85 long, 22 huid en 24 oog betrokkenheid) meerdere PROMs tweemaal in, met een tussenpoos van twee weken. Psychometrische validatie liet een goede construct validiteit zien tussen de KSQ modules en bijhorende vragenlijsten, behalve voor de Medicatie module. Interne consistentie was goed voor alle KSQ modules (Cronbach's α 0.70-0.90) en de intraclass correlatie coëfficiënten en Bland-Altman plots toonden een goede herhaalbaarheid van de KSQ. De Nederlandse KSQ bleek een valide en betrouwbare PROM voor het meten van de KvL van Nederlandse patiënten met sarcoïdose en vergemakkelijkt internationale samenwerking in klinische onderzoeken naar sarcoïdose.

De KvL van sarcoïdose patiënten wordt vaak beperkt door klachten als vermoeidheid en stress. Er is echter weinig bekend over de etiologie van deze klachten. Factoren die mogelijk een rol spelen, zijn spanningen, systemische inflammatie, hypocortisolisme en hypogonadisme. Deze factoren kunnen cortisol en testosteron waarden beïnvloeden. Voor het monitoren van acute stress worden vaak serum en speeksel cortisol concentraties gebruikt. Chronische concentraties van cortisol en andere steroïden kunnen worden

gemeten met een nieuwe methode, waarbij gebruikt wordt gemaakt van hoofdhaar analyse. In **hoofdstuk 4** onderzochten wij of er een verschil was in hoofdhaar cortisol, cortison en testosteron waarden tussen vermoeide en niet-vermoeide sarcoïdose patiënten, en tussen sarcoïdose patiënten en een controlegroep uit de algemene bevolking. Tevens analyseerden wij of deze steroïd hormonen konden dienen als objectieve biomarker voor stress in sarcoïdosis. Hoofdhaar steroïd concentraties werden gemeten met vloeistof chromatografie-tandem massa spectrometrie in glucocorticoïd naïeve sarcoïdose patiënten. Haar steroïd concentraties van 293 deelnemers van de Lifelines cohort studie dienden als controlegroep. In totaal werden er 32 sarcoïdose patiënten geïncludeerd, waarvan 23 vermoeide (Fatigue Assessment Scale score ≥22). Opvallend genoeg waren hoofdhaar cortisol en cortison waarden significant hoger in sarcoïdose patiënten dan in de controlegroep. Er werden geen significante verschillen gevonden in haar testosteron waarden tussen mannelijke sarcoïdose patiënten en controles, en in haar steroïd waarden van vermoeide en niet-vermoeide sarcoïdose patiënten. Toename in haar cortisol waarden van sarcoïdose patiënten correleerde significant met toename in angst, depressie en verminderde mentale gezondheid, maar was niet geassocieerd met vermoeidheid. Onze studie is de eerste studie die hoofdhaar steroïden onderzoekt in sarcoïdose, en laat zien dat hoofdhaar cortisol een potentieel veelbelovende objectieve biomarker is voor stress in patiënten met sarcoïdose.

Clubbing van de vingers wordt beschouwd als kenmerkend voor IPF en is geassocieerd met een slechte prognose. Hoewel clubbing ook wordt gezien in andere fibrotische ILDs, is er maar weinig bekend over de prevalentie en klinische betekenis van clubbing, en de beste methode om clubbing te meten. In **hoofdstuk 5** onderzochten wij de overeenstemming tussen verschillende meetmethodes voor clubbing bij patiënten met fibrotische ILDs. Daarnaast onderzochten wij de prevalentie van clubbing in deze ziektebeelden en de relatie tussen clubbing, de ernst van de ziekte en KvL. Er werden in totaal 153 poliklinische patiënten met fibrotische ILDs (68 IPF patiënten) geïncludeerd in twee tertiaire verwijzingscentra. Clubbing werd gemeten met de phalangeal depth ratio, de digital index, de Schamroth sign test en vastgesteld door de behandelende arts en onderzoeker. Deelnemers vulden daarnaast verscheidende PROMs in. We vonden geen tot een zwakke overeenstemming betreffende de aanwezigheid van clubbing tussen de verschillende meetmethodes. Opvallend genoeg kwam de beoordeling van clubbing door de arts en onderzoeker veel beter overeen. Prevalentie van clubbing varieerde van 7-42% in de totale groep patiënten en 7-52% in IPF, afhankelijk van welke meetmethode was gebruikt. Clubbing correleerde niet met de ernst van ziekte (FVC en transfer capaciteit voor carbon monoxide gecorrigeerd voor hemoglobine (TLCOc): $p>0.02$) of met KvL.

Deel 2: Verbeteren van kwaliteit van leven in interstitiële longziekten

Hoofdstuk 6 vat de meest recente inzichten in het verbeteren van KvL van patiënten met IPF samen en behandelt uitdagingen in de zorg voor patiënten met deze ziekte. In een ongenadige ziekte als IPF moeten we trachten te streven naar een verbetering van KvL in aanvulling op levensverlenging. Helaas is er een tekort aan interventies en onderzoek dat zich richt op het verbeteren van klachten en optimaliseren van KvL. Symptomen, percepties en reacties hebben een onderlinge wisselwerking en kunnen veranderen gedurende de ziekteperiode. Een flexibel en veelomvattend behandelplan is cruciaal, zodat er kan worden voorzien in de wisselende behoeften van patiënten gedurende het ziekteverloop. Vandaar dat wij een nieuw model voor continue zorg in IPF voorstellen 'de ABCDE van IPF zorg': *Assessing (vaststellen) van* de behoeften van de patiënten; *Backing (bijstaan) van* patiënten door ze te informeren en te ondersteunen; het geven van *Comfort care (klachten verlichting)* door het gericht behandelen van symptomen, rekening houdend met *Comorbidities (bijkomende ziekten);* streven naar levensverlenging door *Disease modification (fibrose remming);* en het helpen en voorbereiden van patiënten en hun naasten op het *End-of-life (fase rondom het overlijden).* Om KvL van IPF patiënten te optimaliseren is er een patiëntgerichte zorg nodig die breder is dan het remmen van de longfibrose met medicijnen.

Hoofdstuk 7 beschrijft de laatste inzichten op het gebied van chronische hoest in IPF. Chronische hoest is een frequente, zeer belastende klacht in IPF en heeft een enorme impact op KvL. Het is tevens een onafhankelijke voorspeller van ziekte progressie. De pathogenese van hoest is waarschijnlijk "multifactorieel" waarbij mechanische, biochemische en neurosensorische veranderingen een rol spelen. Zo speelt toename van de hoest reflex sensitiviteit, door toename van neurotrofine concentraties of door de aantasting van zenuwvezels door mechanische vervormingen, mogelijk een rol in de pathogenese van IPF-gerelateerde hoest. Daarnaast kunnen drukveranderingen zorgen voor herhaaldelijke rekschade en leiden tot activatie van pro-fibrotische mechanismen. Deze hypothese zou kunnen verklaren waarom hoest een onafhankelijke voorspeller is van ziekte progressie in IPF en sluit aan bij de bevinding dat mechanische beademing een risico factor kan zijn voor een acute exacerbatie van longfibrose. Comorbiditeiten, in het bijzonder gastro-oesofageale reflux, spelen ook een belangrijke rol. Hoewel er veel vooruitgang is geboekt in onderzoek naar de pathogenese van hoest in IPF, is onderzoek naar effectieve behandelingen nog steeds beperkt. Behandeling van IPF-gerelateerde hoest is op dit moment een enorme uitdaging voor zowel de patiënt als de behandelende arts, omdat de hoest vaak therapie resistent is. Klinisch onderzoek naar hoest medicatie in IPF is pas recent gestart en richt zich op nieuwe middelen voor chronische hoest in het algemeen. Bovendien wordt bij nieuwe middelen, die getest worden voor IPF, steeds vaker gekeken naar een potentieel effect op hoest. Het is belangrijk dat zowel objectieve als subjectieve gevalideerde hoest metingen worden gebruikt in deze studies. Hopelijk zullen nieuwe studies uiteindelijk leiden tot succesvolle behandeling van hoest in IPF en hiermee de KvL van IPF patiënten verbeteren.

Het anti-fibrotische middel pirfenidone zou kunnen bijdragen aan de behandeling van hoest in IPF. Verscheidene observaties suggereerden dat het middel mogelijk hoestklachten vermindert. In **hoofdstuk 8** hebben we daarom het effect van pirfenidone op hoest objectief gemeten in patiënten met IPF met hoestklachten. Tevens werd het effect van pirfenidone op subjectieve hoest en KvL uitkomstmaten onderzocht. In deze internationale, multicenter, prospectieve, observationele studie werden patiënten geincludeerd met IPF die op het punt stonden om te starten met pirfenidone en een hoest visueel analoge schaal (VAS) score hadden van ≥40 mm. De primaire uitkomstmaat was de verandering in 24-uur objectieve hoest frequentie na 12 weken pirfenidone ten opzichte van baseline zonder behandeling, gemeten met de gevalideerde ambulante Leicester hoest monitor. Secundaire uitkomstmaten waren verandering in subjectieve hoest-gerelateerde KvL, gemeten met de Leicester Cough Questionnaire (LCQ), de ernst van hoest gemeten met de VAS en KvL gemeten met de King's Brief Interstitial Lung Disease vragenlijst. Van de 46 gescreende patiënten werden er 43 geïncludeerd. Pirfenidone verminderde objectieve 24-uur hoest frequentie significant met 34%. Belangrijker is dat dit ook door de patiënten werd ervaren, want de subjectieve uitkomstmaten verbeterden ook significant. Hoest frequenties correleerde niet met de ernst van de ziekte, gemeten met FVC en TLCOc. Onze studie is de eerste die een significante verbetering van een farmacologische behandeling op zowel objectieve als subjectieve hoest uitkomsten laat zien in IPF patiënten. Deze verandering was klinisch relevant voor patiënten.

In de afgelopen jaren zijn de zorg behoeften van patiënten met longfibrose steeds meer erkend. Echter de naasten van patiënten werden hier vaak niet bij betrokken. Ook is er weinig bekend over de beste manier om patiënten en hun naasten te informeren over longfibrose. In **hoofdstuk 9** onderzochten wij de opvattingen en voorkeuren van longfibrose patiënten en hun naasten over de zorg. Daarnaast evalueerden wij of interactief interviewen een nieuwe onderwijsmethode kan zijn voor deze populatie. Een deel van dit onderzoek werd ook gedaan in Duitsland, zodat we konden bekijken of er culturele verschillen in zorg behoeften waren. Patiënten en naasten werden geïnterviewd tijdens longfibrose informatie bijeenkomsten in twee tertiaire ILD centra. In Nederland beantwoorden patiënten en naasten vragen anoniem via interactieve stemboxen en werden de resultaten direct geprojecteerd. In Duitsland werden vragenlijsten uitgedeeld aan alle deelnemers. In totaal deden 278 patiënten en naasten mee in Nederland en 51 in Duitsland. Onze studie bevestigt de enorme impact die longfibrose heeft op het emotionele welzijn van patiënten en hun naasten en verbetert de huidige kennis van hun zorgbehoeften. Deelnemers hadden behoefte aan beter onderwijs, psychologische en praktische support en zorg voor naasten. Patiënten werden bij voorkeur behandeld in expertise centra met toegang tot gespecialiseerde ILD verpleegkundigen. De nieuwe methode van interactief lesgeven en interviewen kan een goede en efficiënte manier zijn om longfibrose zorg te optimaliseren en om patiënten en naasten te informeren. Deelnemers vonden het interactieve stemsysteem prettig (70%) en informatief (94%). Er bestonden geen grote culturele verschillen tussen Nederland en Duitsland.

Er zijn op dit moment weinig studies die proberen de KvL van patiënten met IPF en hun naasten te verbeteren. In **hoofdstuk 10**, onderzochten wij daarom het effect van een kort multidisciplinair Patiënt en Partner Empowerment Programma voor IPF (PPEPP) op KvL. PPEPP bestaat uit drie middag bijeenkomsten, verdeeld over drie opeenvolgende weken, en richt zich op het omgaan met IPF. Het programma wordt geleid door een psycholoog met ervaring in groepstherapie. Een longarts, gespecialiseerd ILD verpleegkundige, zuurstofleverancier, maatschappelijk werker en fysiotherapeuten dragen tevens bij aan de sessies. Poliklinische IPF patiënten en hun partners werden achtereenvolgend geïncludeerd in drie blokken: twee interventiegroepen en één controlegroep. Deelnemers vulden KvL-gerelateerde PROMs in op baseline, na 3 weken en na 3 maanden. In totaal werden er dertien koppels in de twee interventiegroepen en zeven in de controlegroep geïncludeerd. Angst, depressie en ILD-specifieke KvL PROM scores verbeterden alleen in de interventie groep significant na 3 weken PPEPP. Na 3 maanden veranderden PROM scores niet significant in de interventie groep, terwijl de KvL uitkomsten in de controle groep verslechterden. Alle deelnemers vonden PPEPP nuttig en zouden het aan anderen aanbevelen. Vijfentwintig deelnemers (96%) vonden dat PPEPP aan hun verwachtingen voldeed. Voor zover ons bekend is PPEPP het eerste support programma dat een positief effect laat zien op het welzijn van IPF patiënten en hun partners.

Hoofdstuk 11 bevat een algemene discussie over de bevindingen beschreven in dit proefschrift.

About the author

ABOUT THE AUTHOR

Mirjam van Manen was born on April 21th 1991 in Reeuwijk, the Netherlands. In 2009, she graduated from secondary school 'de Goudse Waarden' in Gouda. In the same year she followed an English course in Cambridge and started to work as volunteer and later on as employee at the Pediatric Oncology department of the Erasmus Medical Center-Sophia Children's Hospital in Rotterdam. She started medical school in 2010 at the Erasmus University in Rotterdam, and received her B.Sc. in 2013. After obtaining her B.Sc., Mirjam continued with her medical school and did her research master in 2014 at the department of Respiratory Medicine of the Erasmus Medical Center. During this 5-months research master she validated the Dutch King's Sarcoidosis Questionnaire, and was asked to continue her research as a PhD student. Under supervision of Prof. dr. H.C. Hoogsteden and Dr. M.S. Wijsenbeek she started her PhD project in 2014, which resulted in this thesis. As for October 2017, Mirjam will start her internships.

PhD Portfolio

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Mirjam J.G. van Manen	**PhD period**: September 2014 – Mei 2017
Erasmus MC Department: Respiratory Medicine	**Promotor**: Prof. dr. H.C. Hoogsteden
Research School: Molecular Medicine	**Supervisor**: Dr. M.S. Wijsenbeek

1. PhD training		
Courses, seminars and workshops	**Year**	**Workload (ECTS)**
Systematic Literature Search (course 1+2)	2015	1.0
BROK course	2015	1.5
Introduction in GraphPad Prism	2015	0.3
Course on R	2016	1.4
ILD course – Davos	2016	1.0
Workshop presenting skills	2016	1.0
Good clinical practice	2016	0.1
Biomedical English Writing and Communication	2016	2.0
Scientific exchange to cough expert center – Hull, UK	2016	2.0
Workshop on Photoshop and Illustrator CS6	2016	0.3
Workshop on InDesign CS6	2016	0.3
Research Integrity	2016	0.3
Basic course SPSS	2016	1.0
Basic course Excel	2016	0.2
Presentations and (inter)national conferences		
WASOG conference – Kusadasi, Turkey (*poster presentation)*	2014	1.0
Sarcoïdosis belangen vereniging patient meeting – Colijnsplaat *(presentation)*	2015	0.3
ATS conference – Denver, U.S.A. *(2 poster presentations)*	2015	1.0
Glucocorticoid meeting – Rotterdam, the Netherlands *(2 presentations)*	2015	0.2
ERS conference – Amsterdam, the Netherlands *(poster discussion)*	2015	1.0
Lung fibrosis patient day – Rotterdam, the Netherlands *(presentation)*	2015	0.3
Sarcoïdose belangen vereniging patient meeting – Nijkerk *(presentation)*	2015	0.3
PFF summit – Washington, U.S.A. *(2 poster presentations)*	2015	1.0
PFF focus group – Washington, U.S.A.	2015	0.1
Managing difficult symptoms in pulmonary fibrosis – Hull, UK *(presentation)*	2016	0.3
Lung days – Ermelo, the Netherlands *(3 oral presentations)*	2016	3.0
ATS conference – San Francisco, U.S.A. *(2 poster discussions)*	2016	1.0
Cough conference – London, UK	2016	1.0
ERS conference – London, UK *(poster presentation)*	2016	1.0
Lung fibrosis patient day – Rotterdam, the Netherlands *(presentation)*	2016	0.2

Presentations and (inter)national conferences	Year	Workload (ECTS)
DGP conference – Stuttgart, Germany *(poster discussion)*	2017	1.0
Lung days – Ermelo, the Netherlands *(oral presentation)*	2017	1.0
Text, reviews and committee		
Interview Sarcoscoop	2014	0.1
Article ild care website – King's Sarcoidosis Questionnaire	2014	0.1
Interview Lung days public price – IPF online	2016	0.1
Promotion movie Lung days public price – IPF online	2016	0.3
Article ild care today – IPF online	2016	0.3
Interview PICASSO newsletter – IPF online	2016	0.1
Interview lung fibrosis patient association – PPEPP study	2016	0.1
Review article for Health and Quality of Life	2016	0.4
Review article for Sarcoidosis Vasculitis and Diffuse Lung Disease	2016	0.3
Review article for European Respiratory Journal	2017	0.2
Junior member of ERS Taskforce on Cough guidelines	2017	0.1
2. Teaching		
Lecture lung specialists (in training) – 'Cough in idiopathic pulmonary fibrosis'	2016	0.4
Lecture lung function analysts – 'Clinical lesson on cough in idiopathic pulmonary fibrosis'	2016	0.2
Lecture research nurses – 'Update cough study in idiopathic pulmonary fibrosis'	2016	0.1
Supervising master's thesis R. Vrijenhoeff, Medicine, Erasmus University, Rotterdam	2016	5.0
Supervising master students J. Berendsen, W. Botterman and T. Janssen, course Medical Device Prototyping, University of Technology, Delft	2016	1.0
3. Awards		
Jan Gerrit Mulder abstract Scholarschip – WASOG conference, Kusadasi	2014	
Sarcoïdose belangen vereniging Nederland (SBN) persoonlijke onderzoeksondersteuning 2015 for the 'KSQ study'	2015	
Trust fonds scholarschip – PFF summit, Washington	2015	
Longfonds Public price 2016 for 'IPF online'	2016	
NRS young investigator travel grant – ATS conference, San Francisco	2016	
Förderung des wissenschaftlichen Nachwuches preis 2017 award for the 'cough study'	2017	
Total ECTS		34.9

List of publications

LIST OF PUBLICATIONS

- **Mirjam J.G. van Manen**, Monique Wapenaar, Bert Strookappe, Marjolein Drent, Marjon Elfferich, Jolanda De Vries, Harry R. Gosker, Surinder S. Birring, Amit S. Patel, Leon van den Toorn, Bernt van den Blink, Karin Boomars, Elske Hoitsma, Marlies S. Wijsenbeek. Validation of the King's Sarcoidosis Questionnaire (KSQ) in a Dutch sarcoidosis population. Sarcoidosis Vasc Diffuse Lung Dis. 2016 Mar;33(1):75-82.

- Marlies Wijsenbeek, **Mirjam van Manen**, Francesco Bonella. New insights on patient-reported outcome measures in idiopathic pulmonary fibrosis: only PROMises? Curr Opin Pulm Med. 2016 Sep;22(5):434-441.

- **Mirjam J.G. van Manen**, Surinder S. Birring, Carlo Vancheri, Vincent Cottin, Elisabetta A. Renzoni, Anne-Marie Russell, Marlies S. Wijsenbeek. Cough in idiopathic pulmonary fibrosis. Eur Respir Rev. 2016 Sep;25(141):278-286.

- **Mirjam J.G. van Manen**, Michael Kreuter, Bernt van den Blink, Ute Oltmanns, Karin Palmowski, Eva Brunnemer, Simone Hummler, Nelleke C. Tak, Leon van den Toorn, Jelle Miedema, Henk C. Hoogsteden, Marlies S. Wijsenbeek. What patients with pulmonary fibrosis and their partners think: a live, educative survey in the Netherlands and Germany. ERJ Open Res. 2017 Feb;3(1).

- **Mirjam J.G. van Manen**, J.J. Miranda Geelhoed, Nelleke C. Tak, Marlies S. Wijsenbeek. Optimizing quality of life in patients with idiopathic pulmonary fibrosis. Ther Adv Respir Dis. 2017 Mar;11(3):157-169.

- **Mirjam J.G. van Manen**, Adriaan van 't Spijker, Nelleke C. Tak, Carla T. Baars, Sandra M. Jongenotter, Liesbeth R. van Roon, Jitske Kraan, Henk C. Hoogsteden, Marlies S. Wijsenbeek. Patient and partner empowerment programme for idiopathic pulmonary fibrosis. Eur Respir J. 2017 Apr;49(4).

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Clinical Outcomes in Interstitial Lung Diseases

Measuring and improving quality of life

Interstitial lung diseases (ILDs) contain a wide variety of disorders, usually affecting both lungs diffusely. The most common ILDs are idiopathic pulmonary fibrosis and sarcoidosis. ILDs have a major impact on quality of life. Although it is well-known that quality of life is impaired in ILDs, treatment is often mainly focused on improving physiological outcome measures, such as pulmonary function parameters. These physiological outcome measures frequently do not reflect the impact ILDs have on a patient's quality of life. Patient-reported outcome measures (PROMs) can be used for measuring quality of life and symptom burden. Unfortunately, there is lack of well-developed and validated ILD-specific PROMs and other measures to assess quality of life and symptoms. Also, interventions on improving quality of life in ILDs are scarce. The aim of this thesis was to measure and improve quality of life in ILDs by generating better clinical outcome measures for quality of life and developing interventions focused on improving quality of life.