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Ciclo XXVIII

Ambulatory oxygen in Fibrotic Lung Diseases

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Introduction

Fibrotic Lung Diseases (FLDs) are chronic and progressive conditions resulting in substantial morbidity and mortality. The cardinal symptom of all fibrotic Interstitial Lung Diseases (ILDs) is shortness of breath. Although initially present only on strenuous activities, this unfortunately progresses until even routine activities of daily living become severely limited. This has a devastating impact on Quality of Life (QoL). Measures aimed at improving respiratory symptoms, social interactions and mobility are key to maintaining acceptable QoL standards for as long as possible. Patients with ILD can experience marked desaturation on exercise (1; 2). Exercise limitation in ILD is thought to be caused by multiple factors, including oxygen diffusion limitation, ventilation/perfusion mismatch and low mixed venous oxygen tension, although the pulmonary vasculature is the main limiting factor (3). In keeping with this, desaturation on exercise is significantly associated with pulmonary hypertension, and may contribute to pulmonary hypertension at rest (4). As pulmonary fibrosis advances, exertional breathlessness is triggered by ever decreasing activity levels. Eventually basic tasks, such as washing and dressing, become a challenge. An improved understanding of the effects of ambulatory oxygen in patients with ILD should lead to significant benefits in terms of exercise performance, reduced symptoms of breathlessness and improved mobility in daily life. Currently, there is no standardised approach to the assessment and prescription of ambulatory oxygen in ILD patients. In many centres, the need for ambulatory oxygen in ILD is not routinely assessed. Although several centres including

the centres participating to this study, routinely prescribe ambulatory oxygen to ILD patients with desaturation on exercise, there are no guidelines to direct ambulatory oxygen prescription, and no studies to indicate its benefits and drawbacks in patients with ILD.

There are very few studies investigating the physiological effects of supplemental oxygen on exercise capacity in ILD. Bye et al observed improvement in maximal oxygen uptake, maximal exercise workload and exercise duration in 16 patients with ILD breathing supplemental oxygen during incremental exercise (5).

We have recently completed a retrospective assessment showing that supplementary ambulatory oxygen improves the performance of a Six Minute Walk Test (6MWT) in atients with ILD (6). Frank and co-authors reported that further up titration of ambulatory oxygen in order to maintain saturation value above 90% or reach a 6L/min flow rate during 6MWT seemed to improve exercise capacity in IPF, as measured by a 6MWT, even in patients already using oxygen at home (7). Although the results of these retrospective reviews are highly encouraging, a prospective standardised study is needed to assess the impact of ambulatory oxygen on ILD patients' day to day Quality of Life (QoL).

There are no prospective studies assessing whether ambulatory oxygen provides benefit to patients with ILD and no guidelines for use of oxygen in diffuse lung diseases. In particular, NICE guidelines for oxygen use only address COPD: (http://guidance.nice.org.uk/CG101), a disease which markedly differs from IPF or other ILDs, while the BTS document on oxygen use, only briefly touches on ambulatory oxygen (http://www.library.nhs.uk/GuidelinesFinder/ViewResource.aspx?resID=111561), and gives no specific guidance on its use in any of the Interstitial Lung Diseases (ILD). Specifically, there are no studies investigating the effects of ambulatory oxygen on day-today life in patients with Fibrotic Lung Disease (FLD), or assessing whether oxygen-induced

improvements in 6MWT performance predict response to supplemental oxygen during activities of daily living, and an overall improvement in health status. We have therefore planned a prospective study to assess whether ambulatory oxygen increases the health status of patients with Fibrotic Lung Disease (FLD) who experience oxygen desaturation on a 6MWT. The proposed project is the first of its kind in ILD, and addresses an under-researched area in urgent need of study. The study has the potential to lead to significant advances in the treatment and the understanding of exercise limitation in patients with ILD, and will represent an essential step towards the development of guidelines on oxygen use in ILD.

Currently, the prescription of ambulatory oxygen in ILD varies widely across the UK, with many respiratory centres only prescribing supplemental oxygen when the patient is hypoxic at rest. A 6MWT in ILD patients does not form part of the routine work up of ILD patients outside of specialised centres. This study aims to assess whether individuals with Fibrotic Lung Disease (FLD) whose SaO2 falls ≤ 88% on a 6MWT benefit from the use of ambulatory oxygen in their daily lives, by assessing changes in health status. The risks associated with the use of ambulatory oxygen are limited and highly manageable. As patients selected for the study will not be hypoxic at rest, and therefore will not be on long term oxygen, the risk of inappropriately low oxygen concentrations will not apply. The main reason for performing this study is to assess whether using ambulatory oxygen in ILD patients who desaturate on exercise, is associated with significant subjective benefits. One of the potential risks is that the lack of supplemental ambulatory oxygen during the two trial weeks off ambulatory oxygen could be associated with worse symptoms of breathlessness and increased fatigue. However, it is precisely because this is not yet known that the study

is justified. There is a theoretical risk of inappropriately high oxygen flows causing hypercapnia. However, this is mainly an issue in patients with COPD, where type II

respiratory failure is relatively frequent. Conversely, in Fibrotic Lung Diseases (FLD), hypercapnia usually only occurs during the final stages of Fibrotic Lung Disease (FLD), when patients are hypoxic at rest and require continuous supplemental oxygen, a subgroup which will be excluded in this study. Ambulatory oxygen will be provided through nasal cannula.

Study objectives

The main aim of this project is to establish whether ambulatory oxygen in patients with fibrotic ILD whose oxygen saturation falls ≤ 88% on a 6MWT, leads to a significant improvement in their health status. The core of the project will be randomised, controlled trial ambulatory oxygen used at home at an optimal flow rate determined by titration at screening visit and administered for a two-week period, compared to two weeks off oxygen. Secondary outcomes will include dyspnoea scores (including the University of California San Diego Shortness of Breath Questionnaire hereafter referred to as the Shortness of Breath Questionnaire), global patient assessment, monitored and patient-recorded activity parameters, and Quality of Life (QOL) scores assessed by the King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and the St George's Respiratory Questionnaires, as well as the Hospital Anxiety and Depression Scale. We also aim to assess whether the improvement in 6MWT performance induced by portable oxygen can predict benefit of ambulatory oxygen in day to day living. In addition, semi-structured interviews at the end of the four-week period in a subgroup of 20 patients will be conducted to evaluate patients' and carers' experiences regarding the use of ambulatory oxygen and trial participation.

Trial Design

The planned study is a randomised, controlled crossover trial of ambulatory oxygen against no ambulatory oxygen over a four week period (two weeks on ambulatory oxygen and two weeks on room air), to evaluate the effects of ambulatory oxygen on health status in patients with ILD. A short crossover study in this context has many advantages, since ambulatory oxygen has immediate effect, with no wash-out period needed after use. At the start of the trial, the effects of ambulatory oxygen on 6 Minute Walk Test (6MWT) performances will be evaluated on oxygen and on air-filled canisters, with the patient blind to the contents of the canister, to assess whether oxygen-induced improvements in 6MWT parameters can predict its effectiveness in day to day life. The 6MWT is a well-established and highly reproducible test validated in ILD patients (8; 9), with significant prognostic implications (10).

Patients with a diagnosis of IPF, or with another fibrotic ILD (including fibrotic non-specific interstitial pneumonitis, fibrotic organising pneumonia and fibrotic hypersensitivity pneumonitis) according to established guidelines, (12; 13), whose oxygen saturation (SaO2) at rest on room air is $\geq 94\%$ and falls $\leq 88\%$ on a baseline 6MWT and meet the inclusion and exclusion criteria (table 1) will attend Visit 1 and as part of routine clinical care, all patients ill undergo: past and current medical history, current concomitant medications, demographics, routine blood tests including BNP, echocardiogram, physical assessment and oxygen saturation on room air (RA).

Following the initial screening visit (Visit 1) subjects consented for the study will enter a two week run in period. There should be no changes to treatment or lifestyle in this period. Subjects who fail to meet the eligibility criteria at the end of the run-in period will be withdrawn from the study. Subjects who meet eligibility criteria with stable respiratory symptoms (no changes in medications and no chest infections during the four weeks before

the baseline visit including the run in period) will be assigned in random order to two weeks on ambulatory oxygen or no treatment for two weeks during the baseline visit (visit 2).

Table 1.

Inclusion criteria:
1. IPF or any other Fibrotic Lung Disease (FLD)
2. patients aged 18 – 99 yrs
3. Desaturation ≤ 88% on a 6MWT on room air
4. Stable respiratory symptoms (no changes in medications and no chest infections) in the 4 weeks preceding the randomisation including the run in period
Exclusion criteria:
1. Patients meeting criteria for long term oxygen therapy, SaO2 at rest on room air < 94%
2. Patients expected to change treatment during the course of the study
3. Significant locomotor or communication difficulties
4. Patients with sarcoidosis or connective tissue disease affecting the musculoskeletal system
5. Current smokers
6. Pregnancy
7. History of symptomatic ischaemic cardiac disease (exertion-induced chest pain)
8. Anaemia, Hb < 9g/dl

At visit 2 patient will be asked to complete the K-BILD (14) questionnaire in addition to other questionnaires (the Shortness of Breath Questionnaire (SOBQ (15)), St George's Respiratory Questionnaire (SGRQ) (16), Hospital Anxiety and Depression Scale (HDAS) (17,18)), and to perform two 6MWTs, one on oxygen and one on air-filled canisters at the flow rate identified during the screening visit, in random order, with a rest of at least 30 minutes between tests. The patient will be blind to the content of the canisters.

Measured parameters will include 6-minute walk distance, oxygen saturation and heart rate measured continuously (WristOx2™ model 3150), Borg dyspnoea and fatigue score before and at the end of the test, time to recovery of heart rate, oxygen saturation, Borg dyspnoea and fatigue. These parameters will be related to any changes in the primary and secondary outcome variables in the current trial, to identify any baseline predictors of responsiveness.

According to the randomization the patient will start using ambulatory oxygen or room air during daily life activities for two weeks and then switch the treatment at the crossover (visit 3). During the second week of each of the two week periods of the study treatment, patients will be asked to wear an activity monitor during waking hours, the Sensewear armband (Bodymedia - Pittsburgh, Pennsylvania), which measures energy expenditure, daily number of steps, and time spent at different levels of physical activity.

Sensewear-derived measurements are sensitive and repeatable in chronic lung disease patients (22). Patients will also be asked to complete a diary of daily activities as measure of physical activity, by using the modified diary method of Follick et al (23, 24). Participants will be asked to complete this diary at least 3 times daily, recording the activity undertaken for the majority of each two hour block, in addition to specifying whether oxygen cylinders were used. In addition, total hours of outings each day will be recorded. Ambulatory oxygen

as provided by light weight portable oxygen cylinders, will be set up to provide an optimal oxygen flow rates established on study entry.

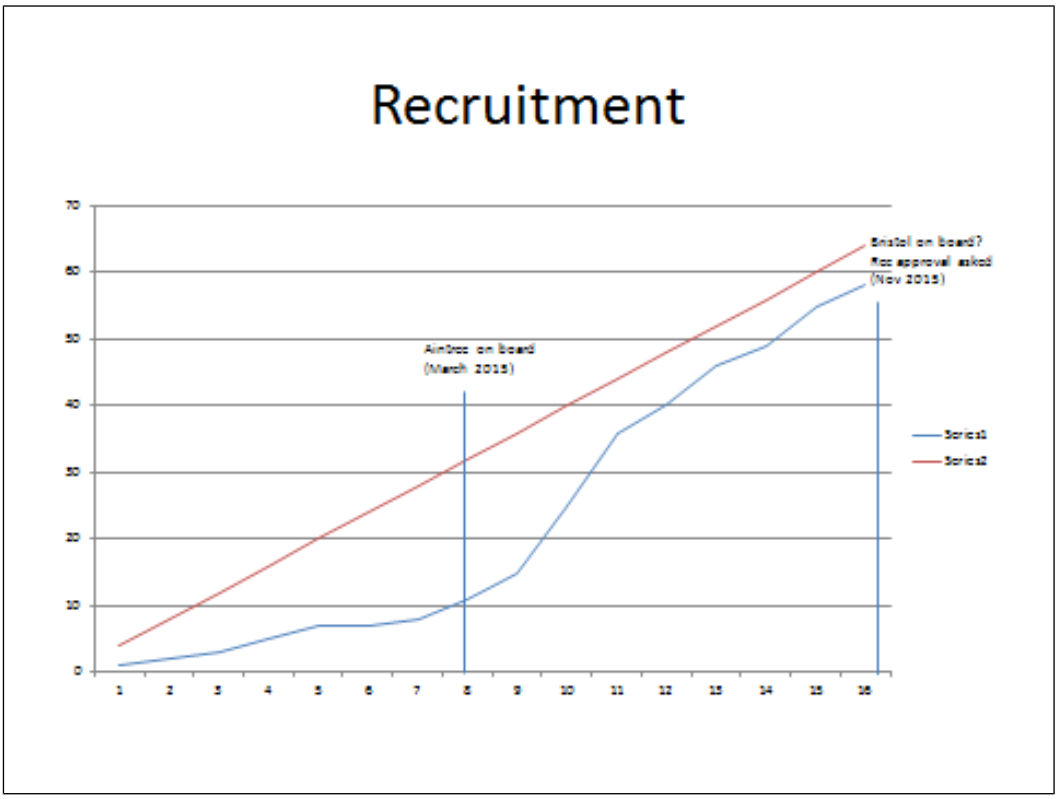
The flow rate to be used for the individual patient will be the one identified in the baseline 6MWT on Ambulatory oxygen, as the flow necessary to maintain optimal saturation during the walk test. We do not envisage that the flow rate will change during the two weeks of the trial. Oxygen use will be expressed as number of full, half full and unused cylinders as self reported by the patient after the two weeks on oxygen, which will be crossed checked by assessing accountability record provided by the relevant oxygen company. Patients will also be asked to fill in a daily oxygen use diary card to write down the time of use of oxygen canisters, and the activity being performed. This will be crossed check with the continuous oxygen saturation data recorded by the portable oxymeter, which they will be asked to wear for two days a week, so as to correlate the two.

Visit 4 is the end of the trial and the patient has the opportunity to discuss his/her experience of using oxygen. In the end the patient will judge whether he wants to keep oxygen or not. The questionnaires including K-BILD questionnaire (14), Shortness of Breath Questionnaire (SOBQ) (15), St George's Respiratory Questionnaire (SGRQ) (16), Hospital Anxiety and Depression Scale (HDAS) (18), should be filled in at Visit 2, 3 and 4.

Update regarding the study timeline up to November 2015

The recruitment started in August 2014 at a slow pace, but after the amendment of the protocol and having the second recruiting centre active in March 2015, there has been a speed up. We are hoping to open another recruiting centre in Bristol at the beginning od 2016. (Figure 1)

Figure 1



The target population is 80 randomized pts in total by January 2017.

160 pts have been screened from August 2014 at the Royal Brompton Hospital (Table 2) and 9 at Aintree since March 2015 (mean 10.56pts/week). 50pts have been consented at the Royal Brompton Hospital and 7 at Aintree. (mean 3.5pts/month). 43 pts have been randomized at the Royal Brompton and 6 at Aitree. 32 pts have completed the study at the Royal Brompton and 6 at Aitree.

According to the protocol pt is ready to be randomized if the respiratory symptoms (no changes in medications and no chest infections) have been remained stable in the 4 weeks preceding the randomization including the run in period. We have lost 5pts among the 57 before the randomization: 4 were not stable during run in period and 1 changed his mind and wanted to start oxygen. The baseline characteristics of the patients are listed in Table 3.

Table 2.

Screening outcome	Number of patients
Ineligible (no desaturation on 6MWT, LTOT, locomotor difficulties, changes in medication)	79
Eligible but declined	33
Eligible to be randomized	57

Table 3.

Variables	Descriptive Statistic
Number pt	52
Age: mean ± SD, range	65.0 ± 10.4 ; (33, 85)
Gender: Male – n (%)	32 (66.7%)
Ethnicity: Caucasian – n (%)	38 (79.2%)
Smoker: Current	0
Ex	25 (54.4%)
No	21 (45.6%)
Diagnosis: IPF	14/46 (30.4%)
Other Fibrotic ILD	32/46 (69.6%)
FVC: mean ± SD; range	67.1 ± 18.3; (41, 127.9)
Tlco: mean ± SD; range	36.9 ± 10.0; (19.9, 64.7)
Kco: mean ± SD; range	75.2 ± 19.0; (35.3, 119.1)
MWTD: median (range)	400 (90, 561)
BMI: mean ± SD	28.2 ± 5.9