Journal of
Pulmonary & Respiratory Medicine
ISSN: 2161-105X

Varney et al., J Pulm Respir Med 2019, 9:3

Research Article Open Access

Longitudinal Follow-Up Data on Cotrimoxazole Treatment in Idiopathic Pulmonary Fibrosis and Fibrotic Non-Specific Interstitial Pneumonia

Veronica Varney[1]*, Helen Parnell[1], Ginny Quirke[1], Siva Ratnatheepan[1], David Salisbury[1], Ford Brian[2] and Alaa Witwit[3]

[1]*Department of Respiratory Medicine, St. Helier Hospital, Wrythe Lane, Carshalton, UK*
[2]*Department of Immunology, St. Helier Hospital, Wrythe Lane, Carshalton, UK*
[3]*Department of Radiology, St. Helier Hospital, Wrythe Lane, Carshalton, UK*

Abstract

Introduction: Studies suggest that cotrimoxazole may have use in patients with idiopathic pulmonary fibrosis (IPF). We present longitudinal data from our current on-going study, looking at safety and stability of lung function, oxygen saturations and walking tests out to 6 years.

Methods: Randomization was (double-blind) to cotrimoxazole or placebo for 12 weeks in patients who desaturate <90% on a shuttle walking test (SWT). At 12 weeks all commence active treatment with out-of-study follow-up and continued measurement of FVC (forced vital capacity), oxygen saturations and SWT. Data is presented on the first 53 patients.

Results: Tolerance to study drugs was good. Lab based Lung function at 1 year showed significant improvement from individual baseline entry values for total lung capacity (+600 mls, p=0.0025), residual volume (+723 mls, p=0.0004) and functional residual capacity (+528 mls, p=0.005). Absolute FVC (+0.5%), vital capacity (+1.5%) and transfer factor TLCO (-2.0%) showed no significant change, remaining stable at 1 year.

Arterial PO_2, SWT and oxygen saturations improved at 12 weeks along with MRC dyspnoea scores. The SGHQ-IPF symptom scores improved at 1 year. Mixed effects analyses have shown that relative FVC levels are associated with a decline by 0.005litres (0.002-0.009) per month on average, Oxygen saturations on air decrease by 0.06% (0.03-0.09) per month and SWT by 2.3metres (1.10-3.48) per month.

Conclusion: Cotrimoxazole was well tolerated. Total lung capacity improved by a mean of + 10.7% at 1 year along with residual volume +25.6%. Symptom scores significantly improved but there was no reduction in radiographic changes. This data has fulfilled 2 of the 3 required criteria by the ATS/ERS statement (2000) for a favourable response. Cotrimoxazole may be a useful alternative in patients intolerant of the anti-fibrotic drugs.

Keywords: IPF, cotrimoxazole, total lung capacity, forced vital capacity, SGRQ-IPF, HRCT scores, Shuttle walking tests. Matrix metalloprotease-7.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial lung disease of unknown cause. The incidence of IPF has continued to rise in the UK and now accounts for 1% of all death certificates with 5000 new cases diagnosed each year [1].

The median age at diagnosis is 70yrs presenting with breathlessness and cough initially on exertion but later leading to a decline in lung function and quality of life [2]. The prognosis is difficult to predict at diagnosis, as some patients can deteriorate rapidly. Mean survival from diagnosis in the UK is 3yrs with 20% surviving for >5yrs [3].

IPF is classified among the interstitial lung diseases and presents a difficult management problem since the cause of the disease is poorly understood. Initially immunosuppressing treatment (prednisolone and azathioprine) was commonly used, but discontinued after 2011 when a study of N-acetyl cysteine demonstrated increased mortality in the standard treatment arm compared with no treatment [4]. This fitted the findings of a prior Cochrane meta-analysis showing no convincing evidence of disease regression or improved survival with immunosuppressive treatments [5].

The new anti-fibrotic drugs of pirfenidone and nintedanib are now approved for treatment in the UK by NICE [6, 7]. These drugs do not reverse the lung damage but appear to slow down the fibrotic progression in treated patients, and studies are now underway to combine both drugs in an effort to halt the fibrotic process further.

In 2008 we published the results of a pilot study of 20 patients looking at the use of cotrimoxazole in advanced fibrotic lung disease which included predominantly IPF and fibrotic NSIP with some mixed subtypes [8]. This study showed benefit, and had followed the chance observation in a 50 year old man of improvement with cotrimoxazole given for a presumed pneumocystis infection. The patient had been awaiting a lung transplant with biopsy proven advanced fibrotic lung disease, (fibrotic NSIP) but cotrimoxazole permitted his oxygen to be weaned off with a return to work as a carpet layer. No lung transplant occurred in the remaining 16yrs on cotrimoxazole, although he did developed late pulmonary hypertension with a return to continuous oxygen use in the last 3-4 years of his life.

***Corresponding author:** Veronica Varney, Department of Immunology, St. Helier Hospital, Wrythe Lane, Carshalton, Surrey SM5 1AA, UK, Tel: 00-44-20 8296-2401; E-mail: veronica.varney@nhs.net

Received October 19, 2019; **Accepted** December 17, 2019; **Published** December 24, 2019

Citation: Varney V, Parnell H, Quirke G, Ratnatheepan S, Salisbury D, et al. (2019) Longitudinal Follow-Up Data on Cotrimoxazole Treatment in Idiopathic Pulmonary Fibrosis and Fibrotic Non-Specific Interstitial Pneumonia. J Pulm Respir Med 9: 493.

Following our pilot data, the TIPAC-study of 181 patients also showed that cotrimoxazole added to standard care (predominately prednisolone with azathioprine) reduced mortality, and improved quality of life over 1 year without improved lung function [9]. To date there are other ongoing studies of cotrimoxazole including EME-TIPAC and the USA study (CleanUp IPF study) which is due to report after July 2020. The USA study examines time to acute exacerbation, hospital admission or death in IPF patients openly randomised to cotrimoxazole or doxycycline. When concluded, these studies will indicate if cotrimoxazole could be a further treatment option for patients with IPF, especially for those who maybe intolerant of anti-fibrotic drugs or not fit the treatment criteria. Data on larger numbers of patients will establish the degree of benefit that cotrimoxazole can offer.

Our current ongoing study (double blind randomised placebo controlled) is a full power expansion of our pilot (planned 120 patients). It commenced in 2012 with delays mainly from replacement active/placebo drug supplies coupled with a short shelf-life on arrival.

This publication looks at our data from the first 53 enrolled patients. We have carefully recorded hospital admissions, mortality and any adverse effects from cotrimoxazole during this follow up period that now extends out to >6 years for those patients enrolled at the beginning of the study. The study responses to treatment over the first year (without decoding) will be compared with American Thoracic Society/European Thoracic Society (ATS/ERS) 2000 statement of a favourable response to treatment. The out of study follow up data will show the stability or otherwise of our main endpoints (FVC, SWT, oxygen saturations) over the longer term [10].

Method

This is a single site double-blind randomised placebo-controlled (DBRPC) study of cotrimoxazole or placebo over 12 weeks in patients with idiopathic pulmonary fibrosis (IPF) or fibrotic NSIP (non-specific interstitial pneumonia).

This study is approved by the National Research Ethics Committee for London-South East (REC reference 2006-004927-12). The ISTCRN registration number is 87032740.

The study conforms to the declaration of Helsinki and good clinical practice and all participants gave written informed consent. The data presented has been collected between October 2012 and April 2019 and is presented without decoding of the double blind part of the study.

Main Study End Points

Change from baseline in the following parameters and comparison with the ATS/ERS 2000 definition of a response to treatment [10],

The primary end point

1. Forced vital capacity (FVC).

Secondary end points

1. Shuttle walk test (SWT)
2. Lab based lung function changes
3. Arterial pO2
4. Quality of life scores

The intervention

Randomisation was by computer generated random numbers (without stratification) to active or placebo treatment (cotrimoxazole 960mg BD) with folic acid 5mg taken 3 times a week for 12 weeks. At 12 weeks all patients received active treatment and follow up without decoding. The follow up period (as per the protocol) is 1 year, but "out of study follow up" has continued indefinitely at 3-4 monthly intervals in view of the nature of the disease and the need for blood tests and this has allowed longer term outcome data to be gathered on the treatment.

Patient inclusion criteria

Eligible patients with a clinical and radiological diagnosis of UIP/IPF or fibrotic NSIP were confirmed at the radiology multi-disciplinary meeting from their HRCT chest scans. This used the ATS/ERS criteria of 2011 which was an upgraded statement from the 2000 consensus [11]. HRCT criteria are slowly changing for UIP with a further updated ATS/ERS statement in 2018 [12].

Enrolled patients had restrictive lung function and fitted the ATS/ERS entry criteria [10,11]. The patients were a mixture of incident and prevalent cases. Only 1 patient in this study had a surgical lung biopsy.

Inclusion criteria

1. Male or female, age 40-86yrs
2. UIP or fibrotic NSIP
3. MRC dyspnoea score ≥ 3 ('I walk slower than people of my own age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level').
4. Oxygen desaturation <90% during the shuttle walk test without the use of oxygen at entry.
5. Corrected Vitamin B12 deficiency (if present)
6. A stable dose of prednisolone if already commenced on that treatment prior to enrolment.

Exclusion criteria

1. Secondary causes of lung fibrosis.
2. Significant COPD or asthma, right heart failure, pulmonary hypertension, long-term oxygen therapy.
3. Significantly impaired liver or kidney function (creatinine >175μmol/l)
4. Allergy to sulphonamides or suspected G6PD deficiency
5. Inability to perform the shuttle walk test
6. Excluded if taking azathioprine, cyclophosphamide, methotrexate, D-Penicilliamine. Patients with a connective tissue disorder associated ILD were not selected for study entry in order to minimise adverse drug interactions from their other treatments.

Measurements

Enrolled patients in the first year of the study: had 2-6 weekly attendance for shuttle walk test (SWT), spirometry, oxygen saturations, MRC-5 point dyspnoea and Borg score, blood tests, physical examination and assessment of compliance/ side effect and treatment changes.

Enrolled patient after 1 year of Study: All patients continued cotrimoxazole 960mg BD (+folic acid) with 3-4 months attendances for SWT, spirometry, examination, oxygen saturations, blood tests and

safety assessments. Additional tests could be performed as necessary on clinical grounds.

Shuttle walk test (SWT): A validated and standardised, externally paced field walking test that reproducibly measures symptom-limited maximum exertion [13]. Studies of SWT in IPF show this to be a validated test with distance walked reflecting the patient's maximum oxygen uptake (VO2 max) and arterial oxygen levels, and as for COPD, an increase of 3 shuttle lengths (30m) is significant [13].

A shuttle length is 10 meters and 12 levels exist. At each minute (or level) the number of shuttles required is increased by 1. Failure to achieve the number of shuttles at each level ends the test as per the protocol. During the SWT, oxygen saturations were recorded via a Pulsox watch (Minolta range-Devilbiss Sunrise Medical Ltd) to give a computer printout of the oxygen desaturation during the test. Changes (in meters) from baseline entry are calculated for each individual in the study to show their individual (±) change at each time point in order to more accurately represent mean change for the group.

Laboratory based lung function tests using the comprehensive laboratory system:

(N-spire-comprehensive pulmonary lab) were measured at start, 3, 6 and 12 months during the first year. This data is presented as % predicted (absolute) values with standard deviation, including percentage change from baseline or volume change mls. Helium dilution is used for lung volumes, RV (residual volume) and FRC (functional residual capacity) measurement.

Forced Vital capacity (FVC): Both absolute (% predicted) and relative (e.g. from 4L to 3.6L is a relative decline of 10%) has been calculated from baseline start values. Absolute FVC measurements (% predicted) are believed to reveal greater lung function deterioration than relative FVC change [14].

Arterial oxygen (PO2) and resting saturations (%) on air: Mean arterial oxygen levels (kPa) and resting oximeter readings on air were recorded for each subject with change from their baseline value calculated at 3, 6 and 12 month.

Two Quality of life questionnaires scores were assessed at start and 1 year: The Kings Brief interstitial lung disease questionnaire (K-BILD) [15]. Is a brief validated, self-completed health status measure for ILD.

St Georges respiratory questionnaire for IPF (SGRQ-IPF) with sub-sections including activities, symptoms, impacts and total scores [16]. Lower scores represent improvements in any parameter. The spread sheet supplied calculates the scores for each parameter on data entry.

Mean HRCT chest scores: These were scored at entry and 1yr according to the method of Hansell & Wells [17], with scores for ground glass change, septal lines, honeycomb and emphysema assessed at 4 levels (aortic arch, carina, inferior pulmonary veins and lung bases). The scoring for each abnormality was (zero= no abnormality, score 1=<5%, score 2= 5- 25%, score 3= 25-50%, score 4= 50-75% and score 5= >75%). This gives a maximum score of 20 for each parameter at the 4 levels assessed in each lung, with a total possible score of 160 for both lungs. Scoring was "Blind for the chest radiologists" who had no other information about the patient. Since we use the same scoring system for "non-study outpatients" also for assessment of disease progression, mixtures of study and non-study patients were scored in batches. No other information apart from name, date of birth and hospital numbers were known to the radiologists.

Matrix Metalloproteases-7 (MMP-7) assay:MMP-7 is increased in fibrotic lung disease and even in subclinical interstitial lung disease, and is a marker of extracellular matrix turnover and deposition. Data suggests rising levels predict progression and mortality. MMP-7 does not appear to be elevated in hypersensitivity pneumonitis, sarcoidosis or COPD associated-ILD [18, 19].

Serum MMP-7 levels were measured at start and after 12 months of treatment in 20 study patients and once only in 20 healthy controls for comparison using the R&D systems ELISA kit for human total MMP-7 in ng/ml (catalogue No. DMP700). The samples were stored awaiting analysis at -20°c. Analysis was performed as one experiment.

Adverse events were recorded formally as a SAE reports (Serious Adverse Event) in every patient under follow up including after the official 1 year study period was completed.

Enrolment numbers, Compliance, exacerbation, side effects and death have been recorded for every patient throughout the entire study period including out of study follow-up.

Calculation of the data and Statistical Analysis: Year 1 data: For lung function results, arterial oxygen and saturations the mean positive or negative change for each individual from their baseline (start values) has been calculated for each time point. This gives a more accurate representation of the "group means" at the different time points. No decoding of the 3 month time point has occurred. Column statistics were used to determine means, standard deviation and 95% CI (confidence intervals) using the statistical package Prism graph pad 3.03 and Sigma Stats 3.1 version statistical package.

Paired t tests and p valves were used to assess significance at different time points for the objective tests (quality of life, HRCT scores, arterial gases). A p-value of < 0.05 were considered significant, but was adjusted through the Bonferroni correction (predetermined by the number of comparisons performed) to avoid false positives with the level of significance indicated on the tables ($0.05 \div$ no. of comparison). All p values are two tailed.

Mixed effects analysis of longitudinal data for relative FVC, SWT and oxygen saturations on air out to 72 months:

Mixed models (random intercepts and slopes) have been fitted to the longitudinal outcomes [20]. This method correctly accounts for the variability in the data (between patients as well as within patients) and for the effect of time. Missing data are assumed to be at random for the purpose of the estimation. Since patient enrolment was continuous and deaths had occurred, the number of study patients at each time point from which the data is calculated varies. The mixed effect model (random intercepts and random slopes) has been fitted to the relative FVC data, SWT distance and percent-oxygen saturations on air. The model accommodates individual profile variability to derive an average curve (fixed effects) across potential groups in the cohort of patients. This is then analysed for gender and age by univariant and multivariable analysis to generate predicted change with time as a slope including p value and 95% confidence intervals.

Results

The mean age of the study patients was 75yr with 80% male. 68% were new incident cases of cough and dyspnoea, while 32% were prevalent cases now re-presenting with more symptoms and fitting the entry criteria for enrolment. 3 patients were already on prednisolone prior to referral at doses of ≤10mg/a day long-term. 85% of cases had a

HRCT chest scan consistent with UIP/IPF (Table 1).

Baseline FVC was 75% and TLCO 44.4% indicating moderate restrictive defects [21]. Baseline FEV 1 was 79% for the group with the FEV1/FVC ratio of 102%, suggesting no severe airway obstruction despite 14% showing some emphysematous change on the CT scan with 22 subjects being ex-smokers (Table 2).

Mean SWT improved by 42 metres at week 12 (P=0.002) despite up to 50% of cases likely to be taking placebo treatment only at that time point. At the 6 + 12 month time point the SWT distance was largely stable (+18m and + 6.2m respectively) as shown in table 2.

The post-SWT saturations were 82% (mean value) and remained stable in the first year with desaturation below 88% associated with higher mortality [22].

Mean arterial PO2 improved from 10.9 to 11.8 KPa (p=0.013) at week 12 (+0.87 KPa) and remained stable at 6 + 12 months (+0.24 KPa and +0.20 KPa respectively) as shown in table 2.

Oxygen saturations on air improved at week 12 (p=0.035) following which no further change occurred.

Relative FVC remained stable in the first year. There was a +2.5% mean improvement at 12 weeks (representing +59mls), +3.9% at 24 weeks (+79mls) followed by a -3.7% change (-73mls) from baseline value at 1 year that was not statistical significance suggesting no overall change (Table 3).

The data over the first 12 months shows overall stability for absolute FVC (+0.5%), vital capacity (+1.5%), transfer of carbon monoxide (-2% TLCO) + forced expiratory flow (FEF 25-75%) +0.5% from the baseline entry to 1 year.

Total lung capacity (TLC), residual volume (RV) and functional residual capacity (FRC) improved at all time points with significance at 1 year (table 3). At 1 year, TLC had improved by + 10.7% (+600mls), RV by +25.6% (723mls) and FRC by +14.6% (528 mls) with only 1 patient missing their week 24 lung function tests due to surgery. Inspiratory capacity (IC) showed a non-significant improvement at 3, 6 and 12 months of +106 mls, +45mls, +23mls respectively.

Data for the TLC, FRC and IC is shown in figure 1 including the relationship:-

TLC = FRC + IC. The improvement in TLC is predominately due to increases in FRC not IC, and therefore more likely to be occurring distal to the terminal bronchi and within the alveoli. When FRC, RV + ERV (Expiratory Reserve Volume) were examined due to the relationship FRC = RV+ERV. The increase in FRC was due to increases in RV with a reduction in ERV as shown in figure 1. This suggested that improvement was again distal to the terminal bronchi.

Indicators of disease progression at year 1 assessed by changes in FVC + TLCO

The percentage of subjects showing an absolute reduction in FVC of <5%, 5-10% and >10% at the 3, 6 and 12 months' time point from their baseline entry value is shown in figure 2. An FVC decline > 10% is considered evidence of progression in IPF studies. Our data showed 7% of the group (3 subjects) at both the 3 + 6 months time point showed a > 10% FVC decline from their entry value. This increased to 8% at 1year (still 3 subjects).

For transfer factors (absolute TLCO) reductions of >10% and >15% are shown for the 3, 6 and 12 months' time point from entry values (figure 2). TLCO reductions >15% are considered to indicate disease progression. Our data shows 2% (1 subject) had a >15% change at 6 months rising to 6% (3 subjects) at 1 year, with zero change in the first 3 months (Table 4).

The quality of life scores over the first 12 months: The MRCP-5

Demographic parameters	Number of cases
Number of patients to date	53
Mean age (range)	75 yrs (56-86)
M: F ratio	4:1
% of cases with UIP/IPF	85%
% of cases with fibrotic NSIP	15%
New Incident cases	68%
Incident cases: Duration of cough ± shortness of breath prior to diagnosis (months)	15
Prevalent cases duration of cough ± shortness of breath (months)	32
No of cases on prednisolone at entry (≤10 mg/day)	3
No. of cases on azathioprine or other immune suppression	0
No. on pirfenidone or nintenanib at entry	0
% of cases on oxygen at entry	0
No of cases with emphysema on CT scan	14
No. of Current smokers ex-smokers never smoked	0 22 31
Baseline FVC % predicted (range)	75% (95% CI 70.2, 80)
Baseline TLCO % predicted (range)	44.4% (95% CI 40.1, 48.7)
Baseline FEV-1 % predicted (range)	79% (69-119%)
Mean FEV-1/FVC ratio (range)	102% (65-131%)
Finger clubbing	56%
% diabetic (type-2)	17%
Number if known connective tissue disease	0

Table 1: Demographics of enrolled patients.

Group Means (95% confidence intervals)	Baseline (start) pre-treatment N=53	Week 12 Double blind active/placebo N=51	6 months Follow up on cotrimoxazole N=50	I year study follow up on cotrimoxazole N=48	Paired t test Baseline Vs Week 12*	Paired t test Baseline Vs 6 month*	Paired t test Baseline Vs 1year*
Mean Shuttle walk test (SWT) in metres	337 (CI; 294, 379)	379 (CI; 332, 425)	361 (CI; 310, 413)	353 (CI; 295, 411)	**P=0.002**	P=0.04	P=0.92
Saturations post SWT	82% (CI; 80, 83)	82% (CI; 79, 85)	82% (CI; 79, 85)	82% (CI; 79, 85)	P=0.73	P=1.0	P=0.82
Mean arterial PO_2 (KPa)	10.9 (CI; 10.3, 11.4)	11.8 (CI; 11.0, 12.6)	11.24 (CI; 10.4, 11.9)	11.13 (CI; 10.2, 12.0)	**P=0.013**	P=0.6	P=0.07
Mean change in PO_2	-	**+**0.87 KPa	**+**0.24 KPa	**+**0.20 KPa	-	-	-
Relative FVC (Litres) ± SD	2.30 ± 0.57 (CI; 2.1, 2.46)	2.31 ± 0.58 (CI; 2.1, 2.4)	2.35 ± 0.55 (CI; 2.1, 2.5)	2.19 ± 0.68 (CI; 1.9, 2.4)	P=0.64	P=0.21	P=0.22
% change in FVC from baseline as percent and volume (mls) (95% CI)	-	**+**2.5% (**+**59 mls)	**+**3.9% (**+**79 mls)	**-**3.7% (**-**73 mls)	-	-	-
Mean oxygen saturation on air	94.7%	95.0%	94.5%	94.2%	p=0.35	p=0.22	p=0.11
*Significance at p<0.016							

Table 2: 1 year data on shuttle walk test (SWT), arterial oxygen levels, and relative FVC and oxygen saturations for the group.

Parameters Absolute (% predicted) with SD (% change from baseline)	Baseline (Start) N=53	Week 12 Active or placebo N=51	Week 24 active treatment N=50 ■	1 year N=48	Baseline Vs week 12 Paired t-test*	Baseline Vs week 24 Paired t-test*	Baseline vs. 1 yr Paired t-test*
Mean **FVC %** predicted ± SD	75.1 ± 16.8	76.9 ± 18.2 (+1.85%)	77.6 ± 17.9(+2.5%)	75.7 ± 19.2 (+0.5%)	P=0.208	P=0.18	P=0.066
Mean **FEF *25-75*** % predicted ± SD	84.6 ± 38.0	86.4 ±36.5 (+6.7%)	95.3 ± 46.4 (+7.2%)	86.5 ± 41.0 (+0.5%)	P=0.082	P=0.218	P=0.97
Mean **Total Lung Capacity %** predicted ±SD	67.6 ± 12.5	72.8 ± 17.4 (+5.09%)	75.0 ± 22.6 (+8.8%)	78.5 ± 22.1 (+10.7%)	P=0.017	P=0.042	**P=0.0025**
Mean **Residual Volume %** predicted ± SD	68.2 ±26.2	80.17 ± 37.1 (+10.5%)	83.1 ± 43.7 (+14.5%)	97 ± 42.3 (+25.6%)	P=0.032	P=0.041	**P=0.0004**
Mean **Vital Capacity %** predicted ± SD	72.8 ± 17.3	72.6 ± 18.0 (+0.5%)	74.0 ± 18.6 (+0.7%)	72.4 ± 18.8 (+1.5%)	P=0.945	P=0.901	P=0.716
Mean Absolute **Functional Residual Capacity %** predicted ± SD	68.6 ± 19.0	75.9 ± 26.4 (+6.8%)	79.5± 36.3 (+9.9%)	84.0± 29.9 (+14.6%)	P=0.04	P=0.05	**P=0.005**
Mean **Expiratory Reserve Volume** % predicted ± SD	71.7 ± 40.7	66.14 ± 42.3 (-77 mls)	63.64 ± 35.1 (-97 mls)	65.4 ± 33.3 (-89 mls)	P=0.19	P=0.09	P=0.19
Mean **Inspiratory Capacity** % predicted ± SD	76.6 ± 23.9	81.2 ± 24.9 (+ 106 mls)	80.9 ± 23.8 (+46 mls)	80.5± 27.9 (+23 mls)	P=0.017	P=0.21	P=0.41
Mean **TLCO %** predicted ±	44.4 ± 14.7	44.8 ± 14.38 (+1%)	43.8 ± 15.2 (+0.64%)	41.7 ± 18.9 (-2.0%)	P=0.315	P=0.576	P=0.310
FVC: Forced Vital Capacity, **FEF**: Forced Expiratory Flow, Capacity, TLCO: Transfer Factors. ■-Missing data for 1 patient due to surgery. *Significance <0.016							

Table 3: Laboratory based lung function results for the first year (% predicted).

point dyspnoea score improved significantly at all time points (p=0.0005) with most patients scoring 2 (I get short of breath when hurrying on the level or up a slight hill') compared with their level 3 score at enrolment [23]. The SGHQ-IPF showed a significant improvement for symptom at 12 months (p=0.034), with no significant changes seen for the Borg score or K-BILD, both of which remained stable [15, 24] (Table 4).

HRCT scores at start and 1 year: Mean total scores increased from 24.6 at entry to 30.3 at 12 months but this was not significant. For ground glass change and emphysema there was no significant change in scores. For septal lines there was a significant increase (p=0.0035) along with honeycomb change at 1 year (p=0.012). No data on expected rates of progression in IPF are available due to the variable progression rates. Data from our original pilot study of 20 cases did show reduced ground glass change with increased emphysema scores only at 1year (Table 4).

Serum Matrix Metalloprotease-7: This showed the fibrosis study patients to have mean MMP-7 levels = 11.54 ng/ml at study entry (95% CI 8.7, 14.3). This value is above the expected normal range of 1.07-4.40 ng/ml and remained stable at 12months without significant change =11.43ng/ml, (95% CI 8.7, 14.1) p=0.937).

The 20 healthy controls had a group mean MMP-7 value of 4.67ng/ml (95% CI 2.9, 6.3) that is just above the expected normal range. These findings suggest stability of the extracellular matrix turnover at 12 months for patients on cotrimoxazole despite the increase in septal lines and honeycomb change. There is currently limited long term data on MMP-7 changes in IPF, but a recent publication shows higher values

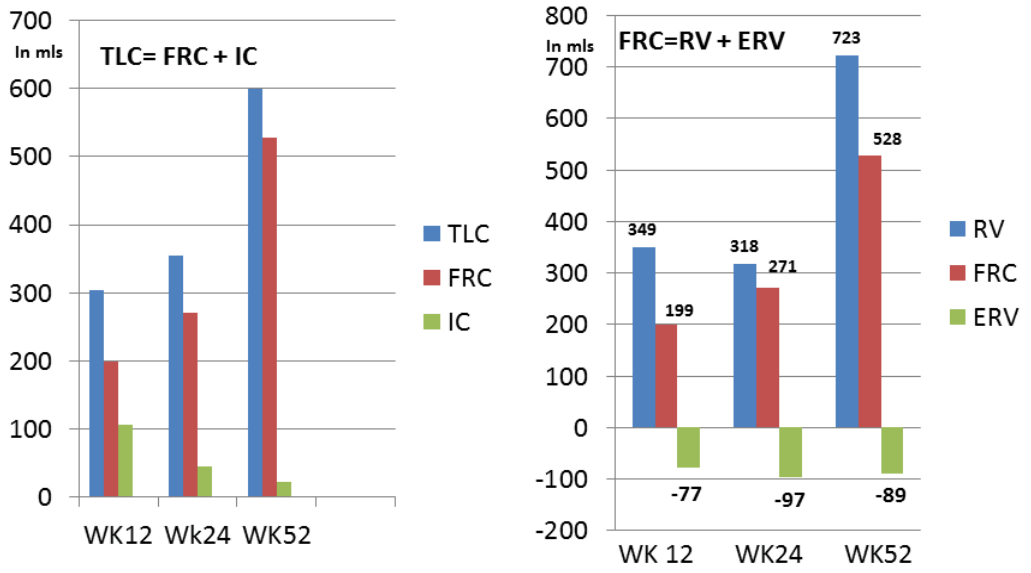

Figure 1: Changes in laboratory based total lung capacity, functional residual and inspiratory capacity and expiratory reserve volume (% predicted) in the first year of treatment.

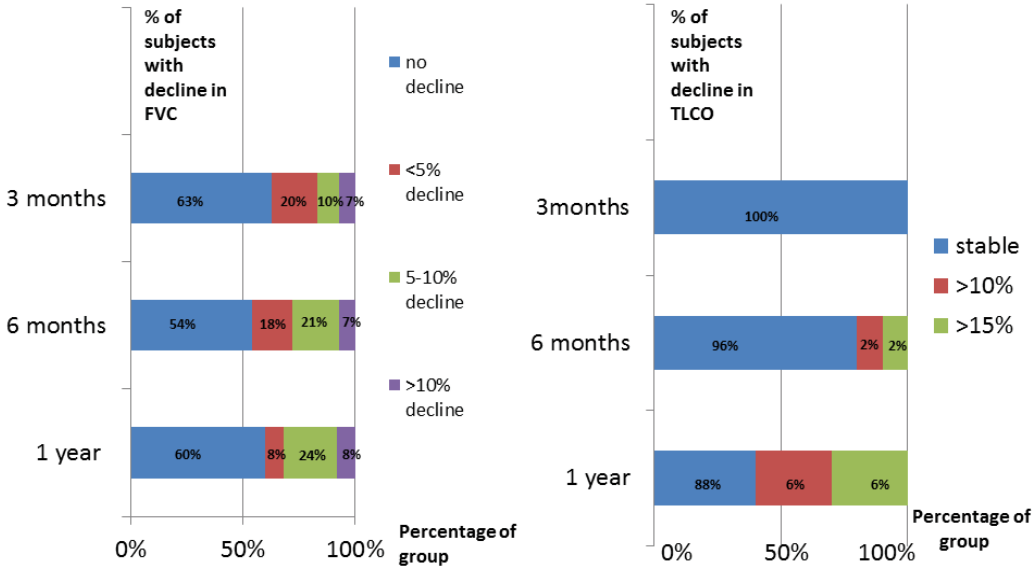

Figure 2: Changes in FVC (>10%) and TLCO (>15%) in the first year that indicate disease progression.

in progressive than stable disease. Other studies have suggested that elevations of these markers by 12 weeks are associated with increased mortality [18,19,25], (Figure 3) Longitudinal (relative) FVC data out to 72months "Mixed Effects Multivariable analysis" shows that time affected FVC decline after adjustment for age and sex. The FVC decline for the group was -0.005 litres (5mls) per month or -60mls per year (95% CI 0.024, 0.108) P=0.004. As shown in figure 3.

At study entry FVC was lower in females (mean 1.92 litres) than males (mean 2.47 litres) at the mean age of 75yrs as expected, but declined faster in men with increasing age. In men FVC declined by -0.028 litre or 28mls in a year (95% CI 0.008, 0.049) p=0.006 for every 1 year increase in age, but remained relatively constant in women 0.034 (95% -0.008, 0 .075) although this was not significant.

Longitudinal SWT distance and oxygen saturation data out to 72months:

(Figure 4) shows longitudinal data for SWT distance after adjustment for age and gender. The average SWT distance at enrolment was 370m at 75 years for men (95% CI 328.9, 411.4) with a decline was 2.3metres per month (95% CI 1.12, 3.49) p=0.001 or 27.6 metres per year showed by mixed effects analysis.

(Figure 5) The longitudinal oxygen saturations on air at age 75yrs

Parameters	Baseline (start) pre-treatment N=53	Week 12 Double blind N= 51	6 months on cotrimoxazole N=50	I year study on cotrimoxazole N=48	Paired t test Baseline Vs Week 12	Paired t test Baseline Vs 6 month	Paired t test Baseline Vs 1year
MRC dyspnoea mean score*	3.0	2.4	2.3	2.3	**0.0018***	**0.0005***	**0.0005***
Borg breathlessness score 0-10*	3.28 (95% CI 2.8, 3.7)	2.72 (95% CI 2.3, 3.1)	3.00 (95% CI 2.6, 3.3)	3.14 (95% CI 2.5, 3.8)	0.027	0.501	0.742
Parameters	**Baseline Score**			**1 year score**			**P value**
K-BILD Mean total	73			72			0.41
scores #	(95% CI 67, 78)			(95% CI 65, 78)			
Activities	17.5			17.3			0.77
Chest symptoms	16.0			15.8			0.32
Psychological	39.9			39.5			0.58
SGHQ-IPF-total #	57752			54682			
SGHQ-IPF-symptoms	264 (95% CI 225, 303)			235 (95% CI 195, 275)			**P=0.034 #**
SGHQ-IPF-activities	412 (95% CI 339, 485)			409 (95% CI 331, 487)			P=0.88
SGHQ-IPF-impacts	492 (95% CI 393, 590)			442 (95% CI 338, 547)			P=0.21
Mean total HRCT score■	24.6 (95% CI: 20.7, 28.4)			30.34(95% CI: 24.6, 36.0)			P=0.02
Mean scores for Ground glass	1.1 (95% CI: 0.3, 1.8)			0.5 (95% CI: -0.04.+1.1)			P=0.43
Septal lines	12.3 (95% CI: 9.7, 14.0)			15.6 (95% CI: 12.2, 18.7)			**P=0.0035 ■**
Honeycomb Score	7.9 (95% CI: 5.6, 9.5)			10.4 (95% CI: 7.2, 13.0)			**P=0.012 ■**
Emphysema	3.4 (95% CI: 1.8, 5.3)			4.2 (95% CI: 2.0, 6.7)			P=0.94
*MRC + Borg scores significance P<0.016 , # K-BILD + SGHQ-IPF significance below p ≤ 0.05, ■ HRCT scores p<0.01							

Table 4: Quality of life scores and high resolution CT scores.

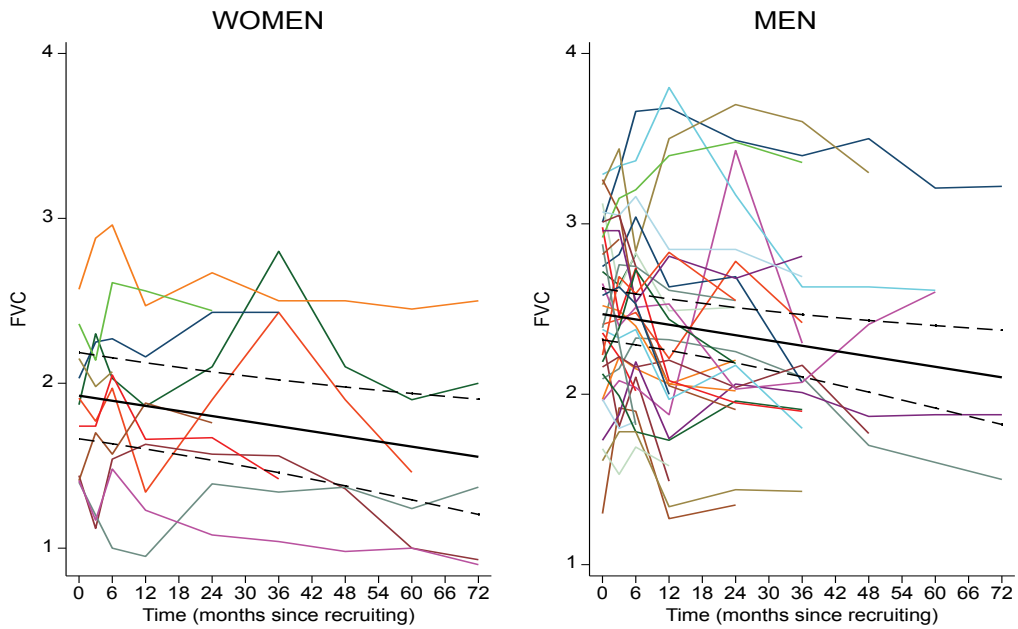

Figure 3: Relative FVC in liters by mixed effects analysis including gender for study subjects on cotrimoxazole out to 72 months.

were 94.8%. Mixed effects analysis showed this to decrease with time (irrespective of gender) by an average of 0.06% per month (95%CI 0.029,0.92) p=0.001. This is the equivalent of -0.72% per year.

(Table 5) Safety and compliance to cotrimoxazole was excellent in the first year with no gastrointestinal, renal, liver or blood count disturbance. Any potential vitamin B12 deficiency was treated at entry and monitored. The requirement for folic acid supplement was greatly emphasized to the patients so compliance with folic acid was high. There was no requirement to open the treatment codes held by the R&D pharmacist.

2 patients noticed a macular rash without itch after a short course of Amoxil from their GP's, having been on cotrimoxazole without problems prior to that. Both drugs were stopped temporarily and cotrimoxazole restarted. In one patient the rash reappeared and the patient was changed to trimethoprim without problems.

Our previous experience with cotrimoxazole for this disease

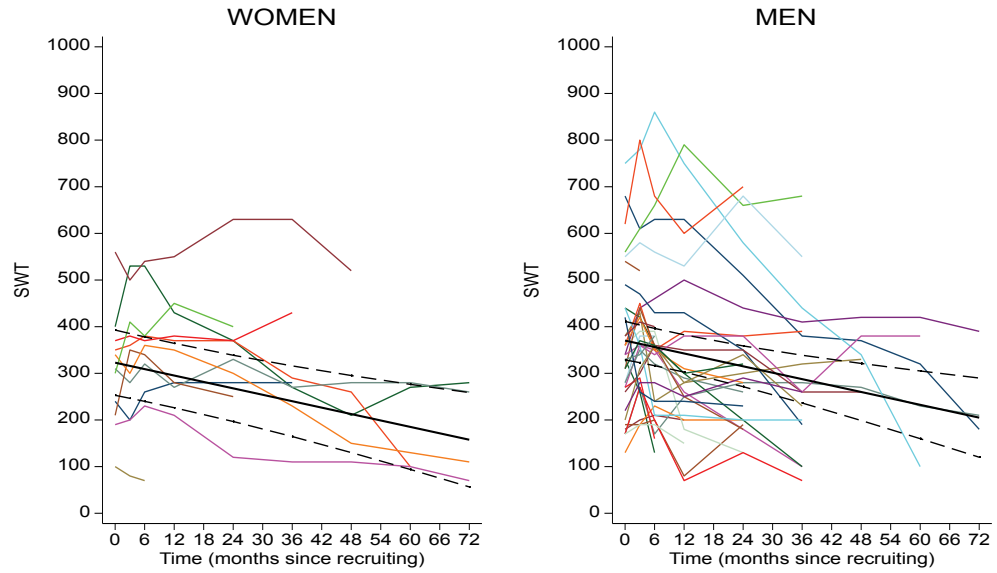

Figure 4: Shuttle walk distance change (in meters) by mixed effects analysis including gender for study subjects on cotrimoxazole out to 72 months.

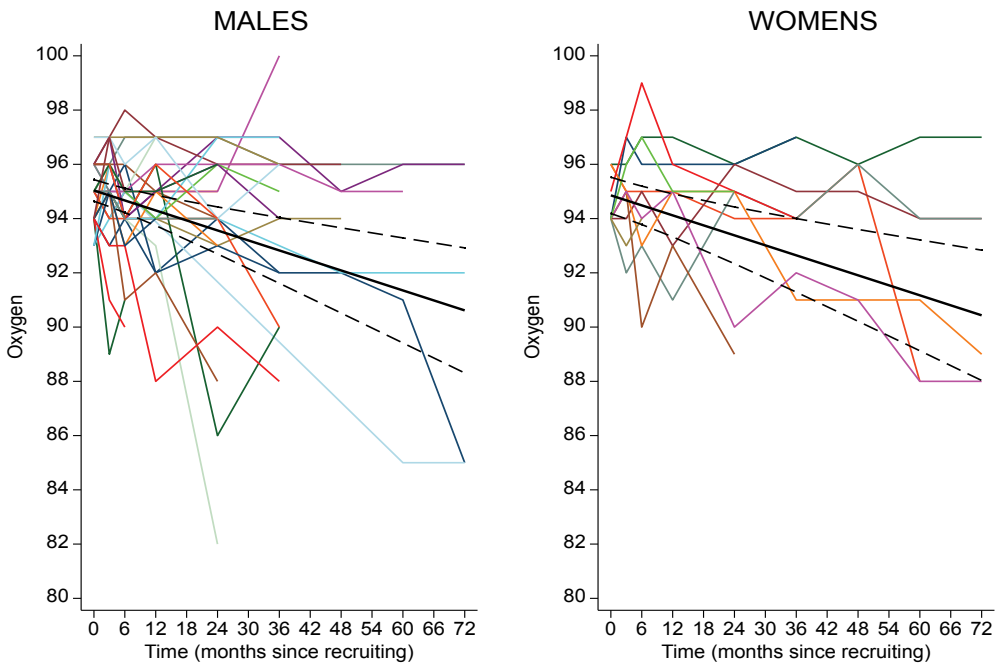

Figure 5: Oxygen saturations on air (as a percentage) by mixed effects analysis including gender for study subjects on cotrimoxazole out to 72 months.

showed that stopping the treatment could lead to deterioration over 4-12 weeks in previously stable patients. One patient (a qualified nurse) at year 5 did stop treatment due to a lifetime dislike of taking tablets; this was despite our warnings that she risked a potential decline. After admission with a chest infection to a different hospital she suddenly exacerbated and became oxygen dependant and limited (bed to chair) and died at the end of year 6 of the study from progressive IPF without returning to cotrimoxazole.

Two other patients who responded well in the first year started to show signs of progressive IPF at year 2 in the study. Relatives informed us that there were lapses in collecting cotrimoxazole regularly from the GP after the first years' hospital supply was switched to the GP. One of these patients collapsed and died suddenly 6 months later while visiting relatives with a suspected pulmonary embolus recorded by the admitting A&E department. The second patient became regular with medication but was no longer able to walk his dog long distances and gradually became oxygen dependent over a year with nintedanib

Parameters	Start (2019)	Week 12	Week 24	Year 1 (2018)	Year 2 (2017)	Year 3 (2016)	Year 4 (2015)	Year 5 (2016)	Year 6 (2013)	Year 6.5+ (2012)
Current Total number of active patients at each time point in the study	53	51	50	48	32	19	14	11	9	6
Number of patients commencing regular use of home oxygen	0	0	0	2	5	4	1	1	3	0
Adverse drug effects										
Rash	0	0	0	2	0	0	0	0	0	0
Haematological	0	0	0	0	0	0	0	0	0	0
Hepatic/renal	0	0	0	0	0	0	0	0	0	0
GI upset	0	0	0	0	0	0	0	0	0	0
Causes of death										
Total number who died at each time point	0	2	1	2	11	5	2	1	1	0
Acute IPF exacerbation/admission/death	0	1	0	0	0	0	0	0	0	0
IPF progression ± pulmonary hypertension and death	0	0	0	1	3	3	0	0	1	0
Pneumonia	0	0	0	0	3	1	1	0	0	0
Sudden death/cardiac/ PE/cancer	0	1	1	1	5	1	1	1	0	0

Table 5: Enrolment number, mortality, oxygen requirements and adverse drug effects.

added later to his cotrimoxazole. He developed signs of pulmonary hypertension and declined further after developing pneumonia.

A stable patient admitted with chest pain and a confirmed MI had his cotrimoxazole discontinued by the admitting hospital despite our requests not to do so. He developed a ward based chest infection and then became oxygen dependant and died suddenly at home 1 week following discharge. A further patient at year 5 was told by the chemist that there was a "shortage of cotrimoxazole 960mg tablets". Since he was well and on the golf course daily, he thought he could probably try without it after 5yrs! At 4 weeks off treatment he became very breathless and was hypoxic and needed 24hr oxygen delivered urgently. He was re-commenced quickly on very high dose cotrimoxazole and oxygen was weaned down to nocturnal use only after 1 month. He requires a buggy to complete his golf now and has confirmed pulmonary hypertension (Table 5).

Mortality, exacerbations and requirement for oxygen in the study subjects.

48 patients out of 53 completed the first year with 5 deaths (11%). 2 deaths occurred during the double-blind period (1-acute exacerbation and 1 MI in a recent ex-smoker). One further death occurred at 6 months (new AF with Left Ventricular Failure) with 2 at 11 months involving 2 of the 3 patients who were on long-term prednisolone. One died from progressive IPF with PTH (pulmonary hypertension) while the other had a sudden death. Similar to our pilot study data, there were no acute IPF exacerbations in patients outside the double-blind period who stayed on cotrimoxazole treatment. There were no drug related deaths.

There have been a total of 20 deaths after the first year (table 5). 4 cancers (2 were lung), 1 peritonitis (acute diverticular perforation), 4 progressive IPF, 3 IPF with PHT, 5 severe pneumonia, 1 pulmonary embolus, and 2 sudden unexpected deaths (one occurred within 12 hours of outpatient GI investigations at a different hospital) and the other following the complaint of chest pain.

From the 2012 enrolment (the study start) 9 patients still remain in the study out of 24 enrolled (October 2012-October 2013) giving a 38% survival to year 5-6, but interpretation of is limited until greater numbers of patients are followed long-term.

Discussion

The data shows that cotrimoxazole was well tolerated without any serious adverse events. Importantly there were no acute exacerbations outside the double-blind treatment period if compliance was maintained. There is good safety data on cotrimoxazole use in HIV and transplant medicine that indicates safety with long-term use [26,27]. Progression of IPF and the later development of pulmonary hypertension (PTH) was still seen and accounted for 7 deaths after the first year especially in patients who interrupted their treatments.

There was benefit to lung function in the first year at all time points for TLC, RV and FRC with significance at 1 year and overall stability of FVC (both relative -3.7% or -73mls) and absolute FVC (+0.5% or +5mls) along with TLCO in the first year.

This was in contrast to the TIPAC study where no change in lung function was found, but patients were taking prednisolone ± azathioprine that may have influenced the results [9].

The SWT also improved and was maintained at 1 year. Reductions in saturations on walking tests to <88% are listed by the American Thoracic Society as associated with increased mortality in IPF, and our patients showed mean saturation falls to 82% post SWT [22].

Arterial oxygen levels improved at 3 months and remained stable suggesting improved gas exchange consistent with the greater walking distance and its known relationship to VO2 Max. Subjective improvements were seen for the MRC-dyspnoea scores and SGHQ-IPF "symptom scores" at 12 months. Total HRCT scores at 1 year increased for septal lines and honeycomb, but do not represent a large change in total score and did not influence the improved objective and subjective parameters measured.

The stability of MMP-7 level at 12 months suggests no increase in extracellular matrix deposition and remodelling and probably supports the stability noted in the other parameters at 1 year [18,19].

The ATS/ERS (2000) criteria: - for a favourable response to treatment in interstitial lung disease is defined by documentation of two or more of the following improvements over 3-6 months [10].

1. **> 10% increase in FVC/TLC (at least 200 mls) or > 15% increase in DLCO, an improvement in oxygen saturations (> 4% increase).**

2. **Reduced pulmonary parenchymal abnormalities on chest X-ray or HRCT.**

3. **A decrease in symptoms (cough and dyspnoea).**

Our data shows a +354 ml (+8.8%) improvement in TLC at 6 months, a time point at which all patients were on active treatment for 3 or 6 months depending on their initial randomisation. It reaches significance with an increase of +600mls (+10.7%) at 1 year. Stability of FVC, TLCO and oxygen saturations only was seen at 6-12 months.

Our HRCT scans do not show a reduction in parenchymal abnormalities, although there is uncertainty as to how reversible these changes are in IPF as they represent fibrotic scars. Total HRCT scores at 1 year increased for septal lines and honeycomb, but do not represent a large change in total score and did not influence the improved objective and subjective parameters measured.

The improved objective measures (SWT distance and arterial oxygen) and subjective measures (MRC-dyspnoea scores and SGHQ-IPF symptoms) do support reduced symptoms, suggesting an overall favourable response to treatment according to the ATS/ERS statement of 2000 has been met [10].

Within the first year of treatment our data shows that 8 % of subjects had a FVC decline (>10%) with 6% showing a TLCO decline >15% [30].

Prior studies suggest that an FVC decline of >10% predicts disease progression along with a >15% decline in DLCO.

For Pirfenidone this is 10.7% at 1 year (>10% FVC) compared with untreated cases at 25%, and 11.3% for DLCO (>15% decline) [29]. For nintedanib, data at 9 months shows a >10% FVC decline in 14% of subjects [28].

It is generally accepted that the FVC decline in mild/moderate IPF is -200ml per year in untreated cases irrespective of age and race [28]. Studies with oral nintedanib show this decline to be reduced to an average of -113 ml per year for FVC in treated patients, with Pirfenidone studies showing an average FVC reduction of -122 ml at 1 year [28, 29]. Longitudinal data out to 72 months for patients for cotrimoxazole treatment showed the relative FVC decline was -60 mls per year for the group. This supports a reduction from the expected decline of -200ml/year in IPF, but is still double that expected in healthy individuals (-30ml/year) from longitudinal regression data in subjects > 46 years of age [31,32]. For the longitudinal data on SWT and oxygen saturations there is little comparable data as 6-minute walk is more commonly used. Studies of pirfenidone report a lower percentage of patients with 6 minute walk declines > 50metres at 1 year and nintedanib studies show a + 5 metre improvement relative to placebo at 6 months [33].

IPF is associated with increased oxidative stress and mitochondrial dysfunction giving increased reactive oxygen series (ROS) generation with activation of TGF-β (transforming growth factor beta) that predisposes to the development of pulmonary fibrosis as shown in animal models and man [34]. Currently Danger Associated Molecular Patterns (DAMP's) especially of mitochondrial origin are the focus of attention [35]. One such "DAMP" released upon mitochondria dysfunction and apoptosis are formyl peptides. These, like the mitochondria themselves, are originally of bacterial origin and can stimulate the formyl peptide receptor on neutrophils and monocytes causing non-bacterial inflammation and immune system activation [36]. The stimulation of M2 macrophages is believed to be particularly associated with the release of TGF-beta and increased fibrotic processes that can lead to IPF [37]. New studies are looking at Pentraxin-2 infusions which have anti-DAMP receptor blocking activity and bind upstream of the fibrotic pathway with monthly infusions under study as a further way forward for this disease [38].

Studies of dapsone, a sulphonamide structurally similar to cotrimoxazole, have shown the reduced generation of oxygen free radicals (ROS) by neutrophils in a dose dependent manner due to dapsone's ability to block the formyl peptide receptor (FPR) on neutrophils responsible for both intra and extracellular release of ROS [39]. Since formyl peptides are released upon mitochondrial injury and activate neutrophil formyl peptide receptors this is of particularly interest [40]. Blocking the FPR can reduce endothelial damage, lipid peroxidation and apoptosis, all of which are known to be occurring in IPF [41,42]. The previous dapsone studies did not examine these effects in monocytes, but we have recently shown that both healthy controls and IPF patients on oral cotrimoxazole show significant blocking of both monocytes and neutrophil formyl peptide receptors [43]. This data suggests that like Dapsone, cotrimoxazole can reduce the release of ROS and potentially reduce monocyte and neutrophil activation reducing disease progression and acute exacerbations in IPF as a possible mechanism of action.

Conclusion

Cotrimoxazole was well tolerated with no acute exacerbations outside the double blind limb in those compliant with cotrimoxazole. Total lung capacity increased significantly at 1 year along with residual volume and functional residual capacity suggesting effects distal to the terminal bronchi. Symptom scores and walking tests improved. There was no reduction in radiographic changes at 1 year. This data impart fulfils 2 of the required criteria by the ATS/ERS statement (2000) of a favourable response to treatment. Longitudinal data out to 72months showed the decline in relative FVC to be -60ml/year. Cotrimoxazole may be a useful drug in IPF and particularly for those intolerant to anti-fibrotic drugs.

Acknowledgements

The study patients for their good humour and regular attendance Pharmacy for randomisation and drug issue. Irina Chisster (statistician) for help with analysis of data.

Funding

Peel Trust Fund for funding of oral co-trimoxazole and placebo tablets, Scadding-Morriston Davies grant for the study, Surrey Rotary Club donation to study costs District 1140, Our respiratory dept charity account with donations from patients, lecture fees etc.

Declaration of conflicting interest statement

There is no conflict of interest and the funding received was made without any influence over the study design or analysis.

Datasets

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Navaratnam V, Fleming KM, West J, Smith CJP, Jenkins RG, et al. (2011) The rising incidence of idiopathic pulmonary fibrosis in the UK. Thorax 66: 462-647.

2. Snell N, Strachen D, Hubbard R, Gibson J, Mather T, et al. (2016) Epidemiology of idiopathic pulmonary fibrosis in the UK: Findings from the British Lung Foundation's Respiratory Health of the Nation Project. Thorax 71: 236.

3. Strongman H, Kausar I, Maher TM (2018) Incidence, prevalence and survival of patients with Idiopathic pulmonary fibrosis in the UK. Advances in Therapy 35: 724-736.

4. Demedts M, Behr J, Buhl R, Costabel U, Dekhuijzen R, et al. (2005) High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 353: 2229-2242.

5. Richeldi L, Davies HR, Ferrara G, Franco F (2003) Corticosteroids for idiopathic pulmonary fibrosis. Cochrane Database Systematic Rev 3: CD002880.

6. Noble PW, Albera C, Bradford WZ, Costabel U, Du Bois RM, et al. (2016) Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. Eur Respir J 47: 243-253.

7. Troy LK, Corte TJ (2016) Therapy for idiopathic pulmonary fibrosis: Lessons from pooled data analysis. Eur Respir J 47: 27-30.

8. Varney VA, Parnell HM, Salisbury DT, Ratnatheepan S, Tayar RB (2008) A double blind randomised placebo controlled pilot study of oral cotrimoxazole in advanced fibrotic lung disease. Pulm Pharmacol Ther 21: 178-87.

9. Shulgina L, Cahn AP, Chilvers ER, Parfrey H, Clark AB, et al. (2013) Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: A randomised controlled trial. Thorax 68: 155-162.

10. American Thoracic Society (2000) Idiopathic pulmonary fibrosis: Diagnosis and treatment. International consensus statement. American Thoracic Society and the European Respiratory Society. Am J Respir Crit Care Med 161: 646-64.

11. An official ATS/ERS/JRS/ALAT Statement (2011) Idiopathic pulmonary fibrosis: Evidence-based Guidelines for diagnosis and management. Am J respire Crit Care Med 183: 788-824.

12. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, et al. (2018) An official ATS/ERS/JRS/ALAT clinical practice guideline: Diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 198: 44-68.

13. Moloney ED, Clayton N, Mukherjee DK, Gallagher CG, Egan JS (2000) The shuttle walk exercise test in idiopathic pulmonary fibrosis. Respir Med 97: 682-687.

14. Richeldi L, Ryerson CJ, Lee JS, Wolters PJ, Koth LL, et al. (2012) Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis. Thorax 67: 407-411.

15. Patel AS, Siegert RJ, Brignall K, Gordon P, Steer S, et al. (2012) The development and validation of the King's Brief Interstitial lung disease (K-BILD) health status questionnaire. Thorax 67: 804-810.

16. Yorke J, Jones PW, Swigris J (2010) Development and validity testing of an IPF-specific version of the St George's Respiratory Questionnaire. Thorax 65: 921-926.

17. Hansell DM, Wells AU (1996) CT Evaluation of fibrosing alveolitis-applictions and insights. J Thoracic Imaging 11: 231-249.

18. Pardo A, Selman M (1996) Matrix metalloproteinases and lung injury. Brazillan J Med Biol Res 9: 1109-1115.

19. Maher TM, Oballa E, Simpson JK, Habgood A, Fahy WA, et al. (2017) An epithelial biomarker signature for idiopathic pulmonary fibrosis: an analysis from the multicentre PROFILE cohort study. Lancet Respir Med 5: 946-955.

20. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, et al. (2009) Multiple imputation for missing data in epidemiological and clinical research; potential and pitfalls. BMJ 338: 2393.

21. Cortes-Telles A, Fokert L, O'Donnell DE, Moran-Mendoza O (2014) Idiopathic pulmonary fibrosis: New insights to functional characteristics at diagnosis. Can Respir J 21: 55-60.

22. An Official ATS/ERS/ALAT Statement (2011) Idiopathic pulmonary fibrosis : Evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 183: 788-824.

23. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, et al. (1999) Usefulness of the medical research council (MRC) dyspnoea scale as a measure of a disability in patients with chronic obstructive pulmonary disease. Thorax 54: 581-586.

24. Borg GAV (1982) A category scale with ratio properties for intermodal and interindividual comparisons. In: Geissler H-G, Petzold P (Eds). Psychophysical Judgement and the Process of Perception. Berlin: VEB Deutscher Verlag der Wissenschaften 5: 25-34.

25. Tzouvelekis A, Herazo-Maya JD, Slade M, Chu JH, Deiuliis G (2016) Validation of the prognostic value of MMP-7in idiopathic pulmonary fibrosis. Respirology 22: 486-493.

26. Ruskin J, LaRiviere M (1991) Low-dose co-trimoxazole for prevention of pneumocystis carinii pneumonia in human immunodeficiency virus disease. The Lancet 337: 468-471.

27. Manyando C, Njunju EM, D' Alessandra U, Van geertruyden JP (2013) Safety and efficacy of co-trimoxazole for treatment and prevention of plasmodium falciparum malaria: A systematic review. PLOS-ONE 8: 1-12.

28. Brunnemer E, Waischer J, Tenenbaum S, Hausmanns J, Schulze K, et al. (2018) Real-world experience with nintedanib in patient with idiopathic Pulmonary fibrosis. Respiration 95: 301-309.

29. Zurkova M, Kolek V, Lostakova V, Sterclova M, Bartos V, et al. (2019) Effect of pirfenidone on lung function decline and survival: 5-yr experience from a real-life IPF cohort from Czech EMPIRE Registry. Respir Res 20: 1-11.

30. Martinez FJ, Flaherty K (2006) Pulmonary function testing in idiopathic interstitial pneumonias. Proc Am Thorac Soc 3: 315-321.

31. Sherrill DL, Lebowitz RJ, Knudson RJ, Burrows B (1992) Continuous longitudinal regression equations for pulmonary function measures. Eur Respir J 5: 452-462.

32. Flether C, Peto R (1977) The natural history of chronic airflow obstruction. Br Med J 1: 1645-1648.

33. Nathan S, Bradley S, Costabel U, Albera C, Behr J, et al. (2018) Effects of pirfenidone on exercise capacity and dyspnoea in patients with IPF and more advanced lung function impairment. Chest 154: 432-433.

34. Koli k, Myllarniemi M, Keski-Oja J, Kinnula VL (2008) Transforming growth factor-β activation in the lung: Focus on fibrosis and reactive oxygen species. Antioxidants & Redox signalling 10: 333-341.

35. Schmidt EP, Tuder RM (2010) Role of apoptosis in amplifying inflammatory responses in lung disease. J Cell Death 3: 41-53.

36. Napolitano F, Rossi FW, Pesapane A, Varricchio S, Llardi G, et al. (2018) N-formyl peptide receptors induce radical oxygen production in fibroblasts derived from systemic sclerosis by interacting with a cleaved form of urokinase receptor. Frontiers in Immunology 9: 574.

37. Zhu L, Fu X, Chen X, Han X, Dong P (2017) M2 macrophages induce EMT through the TGF-β/Smad2 signaling pathway. Cell Biol Int 41: 960-968.

38. Raghu G, Van den Blink B, Hamblin MJ, Brown AW, Golden J, et al. (2018) The effect of recombinant human Pentraxin-2 versus placebo on forced vital capacity in patients with IPF: A randomised clinical trial. JAMA 319: 2299-2307.

39. Suda T, Suzuki Y, Inoue T, Nilde O, Yoshimaru T, et al. (2005) Dapsone suppresses human neutrophil superoxide production and elastasw release in a calcium-dependant manner. Brit J Dermatol 152: 887-895.

40. Debol SM, Herron MJ, Nelson RD (1997) Anti-inflammatory action of dapsone: Inhibition of neutrophils adherence is associated with inhibition of chemoattractant-induced signal transduction. J Leukocyte Biology 62: 827-836.

41. Cloonan S, Choi AMK (2016) Mitochondria in lung disease. J of Clinical Investigation 126: 809-820.

42. Wozel G, Blasum C (2014) Dapsone in dermatology and beyond. Arch Dermatol Res 306: 103-124.

43. Varney VA, Smith B, Quirke G, Parnell H, Ratnatheepan S, et al. (2017) The effects of oral cotrimoxazole upon neutrophil and monocyte activation in patients with pulmonary fibrosis and healthy controls: Does this relate to its action in idiopathic pulmonary fibrosis? Thorax 72: 109.