CLINICAL EVALUATION OF FIBROTIC IDIOPATHIC INTERSTITIAL PNEUMONIA

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Declaration

I declare that this thesis has been composed by Dr Ludmila Shulgina and includes work performed by myself between February 2008 and March 2011 at the School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, UK. The study in Chapter 4 was the result of a joint work with Dr Andrew Wilson (a Chief Investigator of the study) and physicians in Respiratory departments of 28 NHS Trusts who acted as study Principal Investigators and enrolled patients for this interventional trial. All of the other chapters contain studies, which have been designed, conducted, and written by myself. Statistical analysis was performed by Dr Allan Clark for the studies in Chapter 4 and 6. This thesis has not been submitted for any other degree, diploma or professional qualification.

This thesis is 65,828 words in length (excluding references and appendices).

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a fatal condition with limited treatment options. The diagnosis is usually made radiologically but a careful history to exclude identifiable causes of interstitial lung disease is required. Although the median survival is poor, there is considerable variability in disease progression. This thesis investigates the diagnostic accuracy of IPF, a novel treatment option for IPF and biomarkers predictive of disease progression.

An audit project determined a confident diagnosis of IPF in only 9% of patients due to lack of aetiological factors assessment. In a double-blind, multi-centre study, 181 patients with fibrotic idiopathic interstitial pneumonia was randomised to receive co-trimoxazole or placebo for 12 months in addition to usual care. Measurements were made of forced vital capacity (FVC), and quality adjusted life years (QALYs). All-cause mortality, costs, and adverse events were recorded. Co-trimoxazole had no effect on measures of lung function. However in those adhering to treatment, co-trimoxazole showed a significant reduction in all-cause mortality associated with reduction in respiratory tract infections and improvements in QALYs gained. Treatment with co-trimoxazole was cost-effective at UK thresholds.

The role of clinical-physiological parameters, exhaled alveolar nitric oxide concentration (CaNO) and plasma vascular endothelial growth factor (VGEF) in predicting disease behaviour were assessed in two studies. Prednisolone therapy was predictive of death at 12 months and 10% decline in FVC at 6 months, St George's Respiratory Questionnaire score was predictive of death at 12 months. A prospective pilot study of 27 patients with IPF showed that CaNO has a strong predictive value for subsequent significant decline in diffusing capacity of carbon monoxide and that VGEF level is a strong predictive factor of subsequent significant FVC decline.

Structured proforma could aid diagnostic process in IPF while biomarkers could be used in prediction models. Survival of IPF is improved by prophylactic treatment with antibiotics.

Abbreviations

AE	Adverse event
ATS	American Thoracic Society
BAL	Broncho-alveolar lavage
BTS	British Thoracic Society
CaNO	Alveolar concentration of nitric oxide
CFA	Cryptogenic fibrosing alveolitis
COPD	Chronic obstructive airways disease
CPET	Cardiopulmonary Exercise Testing
CXR	Chest radiograph
DLCO	Diffusing capacity of carbon monoxide
DPLD	Diffuse parenchymal lung diseases
eNO	Exhaled Nitric Oxide
EQ-5D	EuroQol Questionnaire
ERS	European Respiratory Society
FeNO	Fraction of exhaled NO
FF	Fibroblastic foci
FVC	Forced vital capacity
HRCT	High Resolution Computed Tomography
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IIP	Idiopathic Interstitial Pneumonias
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
ITT analysis	Intention to treat analysis
JawNO	Total flux of nitric oxide
MID	Minimum important difference
MDT	Multi-disciplinary team meeting
MRC	Medical Research Council
NAC	N-acetylcysteine
NSIP	Nonspecific interstitial pneumonia
PFT	Pulmonary function tests
PP analysis	Per protocol analysis
RTI	Respiratory tract infection
QALYs	Quality Adjust Life Years
SAE	Serious adverse event
SGRQ	Saint George Respiratory Questionnaire
SLB	Surgical lung biopsy
TBB	Transbronchial lung biopsy
VATs	Video-assisted thoracoscopic biopsy
VC	Vital capacity
VEGF	Vascular endothelial growth factor
UIP	Usual interstitial pneumonia
6MWT	6 minute walk test

Clinical evaluation of fibrotic Idiopathic Interstitial Pneumonia

Chapter 1
Introduction

1.1. Interstitial Lung Disease

Idiopathic Pulmonary Fibrosis (IPF) is the commonest of the Interstitial Lung Diseases (ILD), which comprise over 200 conditions. Interstitial Lung Disease describes a heterogeneous group of disorders involving the pulmonary parenchyma, that are characterised by inflammation and/or fibrosis of varying extent and severity. Interstitial lung disease and Diffuse Parenchymal Lung Disease (DPLD) are inter-changeable terms.

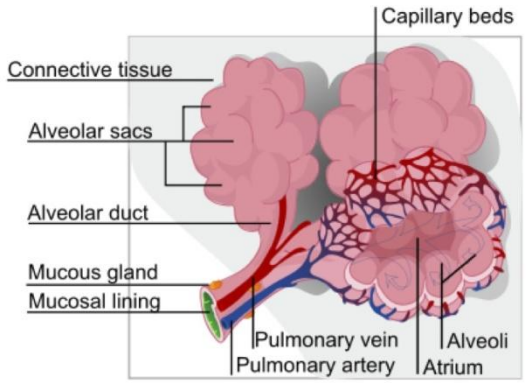


Figure 1.1 A diagram demonstrating the components of the pulmonary parenchyma

The pulmonary parenchyma consists of the alveolar epithelium, the alveolar-capillary interface and air-spaces at the level of the alveolar sacs, ducts and respiratory bronchioles (Figure 1.1) [1]. The alveolar epithelium consists of two cell types: type I and type II. The majority of the alveolar surface that comes in contact with inspired air is covered by flat type 1 alveolar epithelial cells, which act principally as a physical barrier to regulate ion and fluid balance via tight junctions. Whereas the cuboidal type II epithelial cells cover 5% of the alveolar surface area and have three essential functions: surfactant synthesis, alveolar epithelial repair, and ion and fluid transport. Surfactant consists predominantly of lipids (90%) and proteins, in particular surfactant protein A (SP-A), SP-B, SP-C and SP-D. The hydrophilic proteins SP-A and SP-D play a role in innate immunity, whilst the hydrophobic surfactant proteins B and C maintain the biophysical properties of the lung. Furthermore, SP-A and SP-C mutations have been reported with ILD[2]. Following injury, type II alveolar epithelial cells undergo hyperplasia and differentiation into type I cells as part of the normal repair process.

The alveolar epithelial cells are supported and separated from the capillary network by a basement membrane. Capillary endothelial cells are joined

by tight or semi-tight junctions that allow molecules to traverse the capillary wall and contribute to its high permeability. Other components of the alveolar wall include the extracellular matrix constituents collagen, elastin and proteoglycans, as well as nerve endings, mast cells, fibroblasts and small numbers of lymphocytes. Alveolar macrophages can engulf ingested particles by migrating into the interstitium. Thus the interstitium not only provides structure to the lung, but is important for regulating allergen exposure, fluid and gas exchange. It is not surprising that diseases that target the interstitium can affect all these components, in particular the epithelial cells and fibroblasts.

1.2 Classification of ILDs

1.2.1 First classification by Leibow and Carrington in 1969 and Katzenstein classification in 1998 with new entities

Hamman and Rich first described the histopathologic features in 4 patients with IIP in 1944 [3]. As a result of an increased use of surgical lung biopsies, Leibow and Carrington published a classification of IIPs in 1969 consisting of the following five patterns: usual interstitial pneumonia (UIP), bronchiolitis obliterans with interstitial pneumonia, desquamative interstitial pneumonia (DIP), lymphoid interstitial pneumonia (LIP), and giant cell interstitial pneumonia. It was not until the classification of Kazenstein and Myers in 1998 that the importance of quantifying the presence of fibrosis and inflammation as well as its distribution, intensity and nature [4] was highlighted. This classification not only described a new entity - nonspecific interstitial pneumonia (NSIP) but also emphasized the importance of separating the histological entities to help predict prognosis for individual patients. Furthermore, Kazenstein and Myers identified specific histological characteristics, including temporal heterogeneity of the fibrosis, accumulation of intra-alveolar macrophages, and grade of cellularity and fibrosis, to aid with the diagnosis making process. They concluded that the term idiopathic pulmonary fibrosis (IPF) should be reserved only for cases of UIP histology [4].

In order to provide a unifying approach and set an international standard for the diagnosis of IPF the American Thoracic Society (ATS) and European Respiratory Society (ERS) published a joint International Consensus Statement Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. Some of its key conclusions are as follows:

1. Usual interstitial pneumonia (UIP) is the histopathological pattern that identifies patients with IPF, whilst the patterns of desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated interstitial lung disease (RBILD), nonspecific interstitial pneumonia (NSIP), lymphoid interstitial pneumonia (LIP), acute interstitial pneumonia (AIP), and idiopathic bronchiolitis obliterans organising pneumonia (BOOP) are considered separate entities.

2. Surgical lung biopsy is recommended in most patients, particularly those with atypical features of IPF [5].

3. The IPF consensus also for the first time suggested major and minor criteria for the diagnosis of IPF in an immunocompetent adult in the absence of lung biopsy.

Generally ILDs are classified according to whether a known associated factor can be identified such as occupational, environmental, or drug exposures, and collagen vascular diseases. In the absence of an identifiable cause, the ILDs are grouped as idiopathic interstitial pneumonias (IIP) (Figure 1.2) [6]. Clinical and radiological features of IIP are not always diagnostic, hence a surgical lung biopsy is often required for a histolopathological diagnosis.

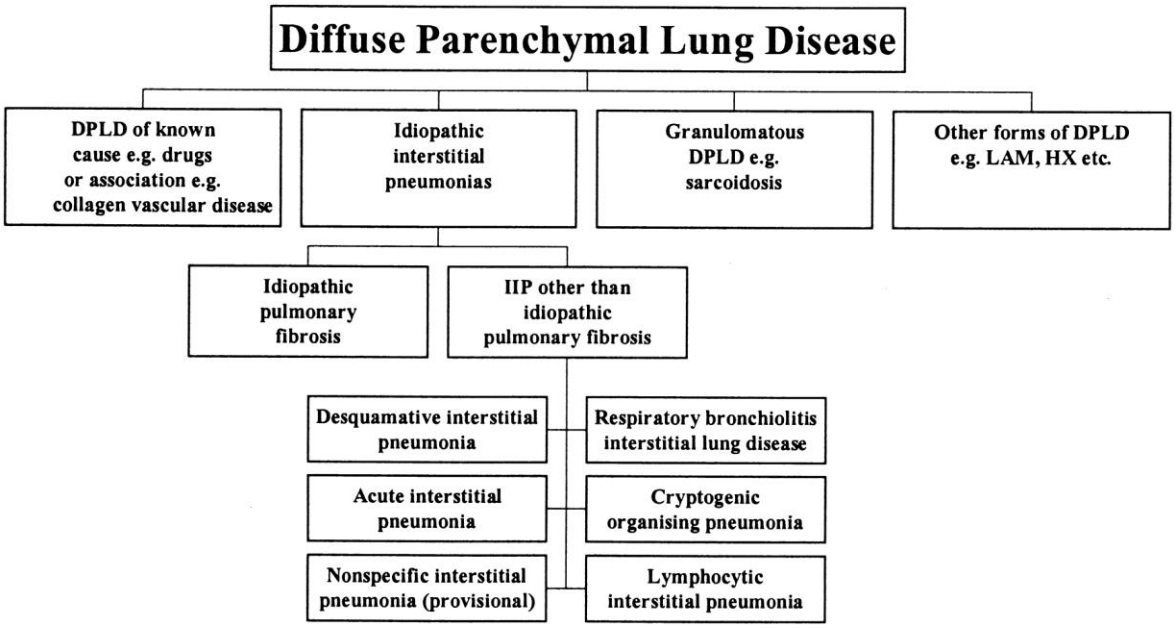


Figure 1.2 Diffuse parenchymal lung diseases (DPLDs) or ILDs consist of disorders of known causes (collagen vascular disease, environmental or drug related) as well as disorders of unknown cause. The latter include idiopathic interstitial pneumonias (IIP), granulomatous lung disorders (e.g. sarcoidosis), and other forms of interstitial lung disease including lymphangioleiomyomatosis (LAM), pulmonary Langerhans' cell histiocytosis/histiocytosis X (HX), and eosinophilic pneumonia. (Reproduced from American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias (2)).

Based upon the Kazenstein and Myers classification system, the American Thoracic Society and European Respiratory Society established a uniform set of definitions and criteria for the diagnosis of IIP(2). This classified IIP into seven clinical-radiologic-pathologic entities. The consensus recommended the use of the term "pattern" when describing the histopathology in order to distinguish it from the clinical-radiologic-pathologic diagnosis (Table 1.1, [6]).

Histopathological pattern	Clinical-radiologic-pathologic pattern
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis
Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Organising pneumonia	Cryptogenic organising pneumonia
Diffuse alveolar damage	Acute Interstitial Pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Lymphoid interstitial pneumonia	Lymphoid interstitial pneumonia

Table 1.1 Histopathologic and clinical classification of the idiopathic interstitial pneumonias[6]

1.2.2 Advantages and limitations of the histological classification system

Clinical and radiological features cannot always distinguish between the various IIP and histopathology may be required for establishing a clinical-pathologic diagnosis. This allows the patient and clinician to make a more informed decision about prognosis and therapy. This limits unnecessary risks and side effects of treatment in the presence of diagnostic uncertainty [6]. It may also identify specific, often occupational, exposures as the cause of the underlying ILD that may be compensatable [6]. Nevertheless this approach has a number of limitations. The most important being the low level of inter-observer agreement in some histologic scores [7]. Secondly, the presence of histopathologic heterogeneity with discordant UIP (i.e. UIP and NSIP present in specimens from different lobes) may potentially lead to an erroneous diagnosis when only a single lobe biopsy is performed [8]. Thirdly, sampling error may result in a specimen of "end stage fibrosis" being obtained which would not enable accurate diagnosis. Finally, the histopathologic pattern should not be interpreted without appropriate clinical and radiological information. This is particularly important for UIP as it can be associated with connective tissue disease, occupational exposures, familial fibrosis, chronic hypersensitivity pneumonitis as well as IPF (Figure 1.3).

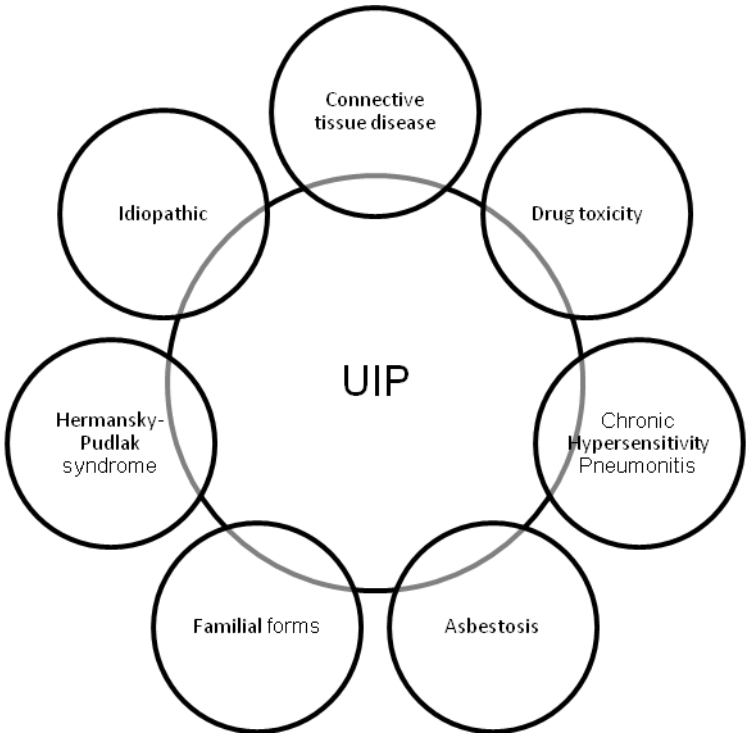


Figure 1.3 Interstitial Lung Diseases are associated with UIP histopathology.

IPF is the commonest of the IIPs, accounting for 47 to 62% of cases [6, 9], whereas NSIP occurs in 14 to 36% of cases [10-12].

1.3 What is IPF?

1.3.1 Definition

Historically different terms have been used for IPF, including cryptogenic fibrosing alveolitis or CFA. This term encompassed a group of conditions clinically typical of IPF but also present in other IIPs and hypersensitivity pneumonitis. At this time, the clinical relevance of distinguishing between different IIPs had not been established [13, 14]. It was not until the ATS/ERS consensus classification of IIP, which considered the importance of histolopathological classification for predicting clinical outcome, that led to worldwide adoption of the term IPF. Based upon this, IPF is a chronic, progressive and fatal fibrosing interstitial pneumonia, characterised by the radiological and/or histopathological pattern of UIP [5].

1.3.2 Histopathological features of IPF

Microscopically IPF has the histopathological pattern of UIP. UIP is characterised by spatial heterogeneity i.e. an abrupt transition between areas of remodelled lung parenchyma, consisting of interstitial inflammation, fibrosis and honeycomb change, with normal lung tissue (Figure 1.4a). This transition occurs through patchy areas of lung injury with lymphocytes and plasma cells infiltrating the alveolar septa, hyperplasia of type II alveolar epithelial cells and fibroblast proliferation [6]. The remodelled lung is present predominantly in a subpleural and perilobular distribution. Although inflammation is not a major feature of UIP, chronic inflammatory cells, lymphoid aggregates with germinal centres, and occasionally acute inflammation may be prominent in and around honeycomb areas [15].

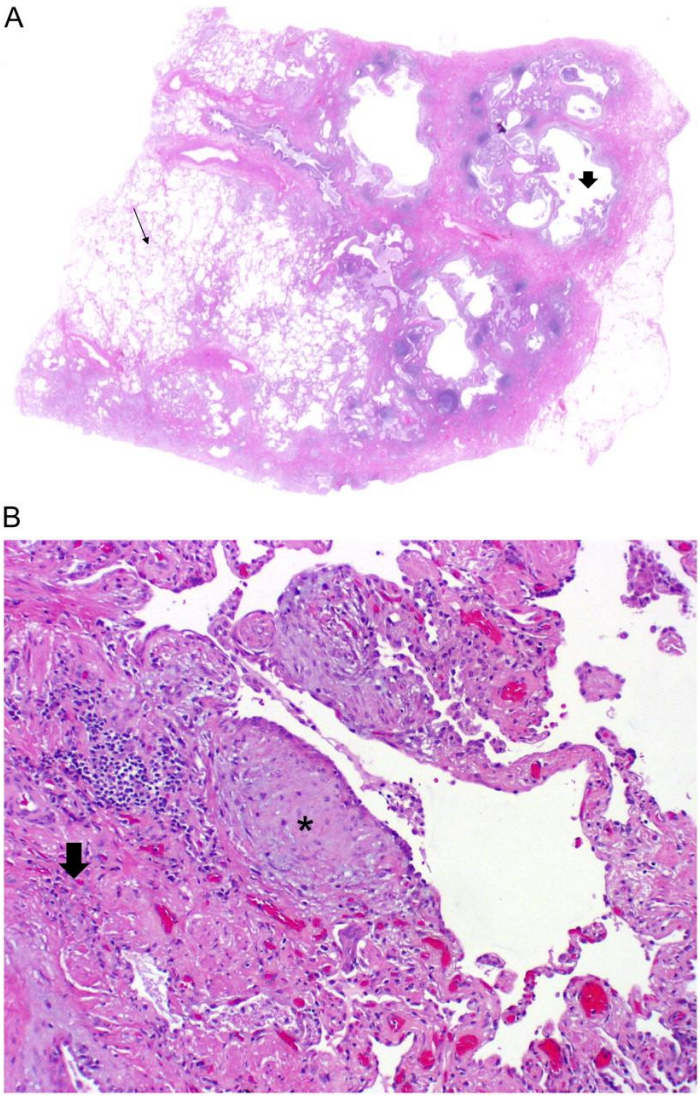


Figure 1.4 Microscopic appearance of UIP. Surgical lung biopsy specimens demonstrating UIP pattern. (A) Scanning power microscopy showing a patchy process with honeycomb spaces (thick arrow), some preserved lung tissue regions (thin arrow), and fibrosis extending into the lung from the subpleural regions. (B) Adjacent to the regions of more chronic fibrosis (thick arrow) is a fibroblast focus (asterisk), recognized by its convex shape and composition of oedematous fibroblastic tissue, suggestive of recent lung injury[16].

The areas of fibrosis are at various stages of maturity, from fibroblastic foci to dense collagen, which is referred to as temporal heterogeneity. Fibroblastic foci (Figure 1.4) represent a collection of proliferating spindle-shaped fibroblasts and myofibroblasts within mixoid stroma. They synthesise and secrete collagen and extracellular matrix constituents. Although fibroblastic foci are not pathognomonic of UIP their presence is supportive of this diagnosis. In addition, the number of fibroblastic foci has been shown to be predictive of a poorer outcome in IPF[17], but this has been disputed by others[18].

The areas of pleural fibrosis may contain proliferating smooth muscle cells and microscopic honeycombing. These cysts are lined by ciliated columnar

epithelium and typically are filled with mucus and inflammatory debris[15]. Exactly how these honeycomb cysts form is unclear. One possibility is that they arise from centrilobular airways that are trapped in the fibrous remodelling, becoming pulled to the periphery of the lobule. In support of this concept, a visible central airway is often absent in lobules with microscopic honeycombing. With more advanced disease, gross honeycomb cysts form giving the macroscopic appearance of “honeycomb lung” as seen with end-stage UIP (Figure 1.5)

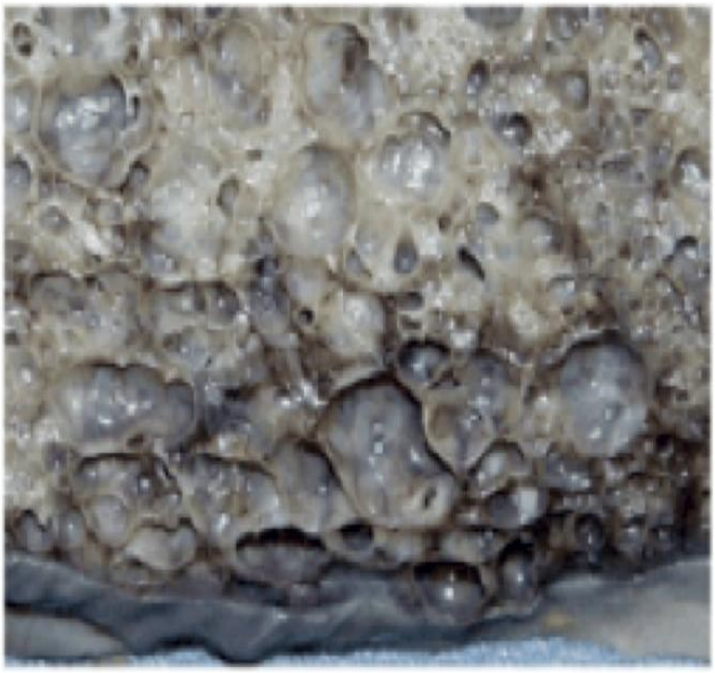


Figure 1.5 Macroscopic appearance of IPF lung. End-stage UIP is characterised by honeycomb cysts, containing mucus and inflammatory cell debris.

The main histopathologic criteria for UIP are summarised in Table 1.2 [19]. Along with key histologic criteria helping to confirm the diagnosis of UIP ATS/ERS consensus specifies pertinent negative findings the presence of which would suggest against the diagnosis of UIP as in Table 1.2 [6].

Histopathological diagnostic criteria for UIP	Pertinent negative findings
Patchwork pattern of parenchymal involvement (nonuniformity, spatial heterogeneity) Architectural distortion (honeycomb change and/or scars) Temporal heterogeneity (fibroblast foci and collagen deposition)	Lack of active lesions of other interstitial diseases (i.e. sarcoidosis or Langerhans' cell histiocytosis) Lack of marked interstitial chronic inflammation Granulomas: inconspicuous or absent Lack of substantial inorganic dust deposits, i.e. asbestos bodies (except for carbon black pigment) Lack of marked eosinophilia

Table 1.2 Histopathological diagnostic criteria for UIP and pertinent negative findings

In the presence of an acute exacerbation or an accelerated phase of IPF, there may also be histological features of diffuse alveolar damage (DAD), organising pneumonia and capillaritis [6]. Areas of DAD are characterised by areas of interstitial fibroblast proliferation that are larger and more confluent than the small and discrete fibroblastic foci of UIP hyaline membranes are present; squamous metaplasia in bronchial epithelium lining honeycomb areas and small arterial thrombi; organising pneumonia is recognised by prominent clusters of fibroblast plugs within airspaces of otherwise typical UIP [15]. DAD may obscure the histological findings of UIP.

1.3.3 Clinical significance of histological classification/diagnosis

Following publication of the ATS/ERS consensus statement for IIP, a number of studies have assessed how the histopathological diagnosis effects survival, disease progression and response to therapy. Flaherty et al. undertook a prospective study of 168 patients who had a diagnostic surgical lung biopsy (SLB) and determined that the most important predictor of survival was the absence of UIP[20]. This study also demonstrated that amongst patients with NSIP there were more responders to treatment compared to those with UIP. This was one of the earliest studies to confirm the importance of UIP histopathological diagnosis for predicting mortality.

Two studies have addressed if specific histopathological features of UIP are predictive of poor outcome. In a study by King et al. four experienced pathologists independently graded single lung biopsies from 87 patients with UIP for the extent and severity of specific histopathologic features, including the stages of fibrosis (ongoing and established). Their

multivariate age-, sex-, and smoking adjusted survival analysis identified that only the granulation /connective tissue score (comprising the alveolar space granulation tissue and fibrotic/reparative changes in immature extracellular matrix) was a significant predictor of survival in patients with IPF, with a one unit increase in it being associated with a 1.74-fold greater risk of death [17]. This study was the first to demonstrate that immature fibrosis was associated with a better outcome and supported the hypothesis of epithelial injury and persistent fibroblastic proliferation as key to the pathogenesis of IPF. These findings were supported by the study of 53 patients with IPF and a histological diagnosis of UIP by Nicholson et al. (83 separate biopsies). Mortality was independently linked to an increasing fibroblastic foci (FF) score (p=0.006) and a decreasing DLCO% predicted (p=0.01) and was not influenced by age and sex; increasing FF scores were independently associated with greater declines in FVC and DLCO at both 6 and 12 months[10].

Flaherty et al. and Monaghan et al. determined if multiple biopsy specimens from the same patient with IIP would show the same histological pattern and assessed if histological variability (or discordance) would affect the prognosis. The study by Flaherty et al [8] confirmed the presence of histologic heterogeneity as it demonstrated the coexistence of histologic patterns of UIP and NSIP in the same patient with 28 out of 109 patients having discordant UIP (UIP in at least one lobe and NSIP in at least one lobe) [8]. Histological diagnosis and heterogeneity affected survival and patients with NSIP had a better survival: risk of mortality was 24.3 greater (95% CI: 3.3 to 177; p<0.0001) for patients concordant for UIP and 16.8 times greater (95% CI: 2.8 to 98.9, p<0.0001) for patients with discordant UIP compared with NSIP patients. This study had the following major implications: patients who have a combination of UIP and NSIP patterns should be classified as having UIP as it is associated with a poor prognosis and that more than one lobe should be biopsied, with sampling from areas of relatively preserved lung. These results were supported by the findings of Monaghan et al which showed that among 64 patients with UIP and NSIP histology patterns, 75% of concordant NSIP group were alive 5 years after biopsy while only 17% in the concordant and 37% in the discordant UIP group were alive [21].

1.3.4 Importance of distinguishing from NSIP

NSIP is the second commonest pattern of the IIP. Until the late 1990s, NSIP was considered a similar disease to UIP and was frequently misdiagnosed as UIP. Subsequently, NSIP has been recognised as a distinct clinical entity with characteristic clinical, radiologic, and pathologic features that differ from other IIPs [22]. Though radiologically and histologically it might be difficult to distinguish from UIP, there are features that would favour a diagnosis of NSIP: radiological features would include bilateral symmetrical predominantly lower lung reticular opacities with traction bronchiectasis and lower lobe volume loss that is usually diffuse or subpleural in the absence of honeycomb change [22]; histological features would differ from UIP by a uniform and diffuse type of change [15, 22]. The population of NSIP is not homogeneous as it can be divided histopathologically into fibrotic NSIP (the majority of cases) and cellular NSIP. Patients with fibrotic NSIP have a worse prognosis than those with cellular NSIP [22]. Overall the 5-year mortality rate for NSIP is 18% [22]. Differentiating UIP from NSIP remains an important issue as it helps to predict prognosis and to target appropriate treatment as recommended by the BTS ILD guidelines, which recommends that all suitable patients with IPF should be considered for a clinical trial if available. On the other hand, the presence of severe functional impairment in patients with fibrotic NSIP renders a prognosis similar to that for UIP [23].

1.4 The epidemiology of IPF

1.4.1 Incidence and prevalence of IPF

The recently reported incidence and prevalence rates for IPF are calculated from data obtained from general practice databases, disease registries, clinic attendances and healthcare claims databases as well as death certificates in both the UK and USA. The annual incidence is reported to be 7.44/100000 in the UK and 6.8/100000 in the USA with an 11% increase between 1991 and 2003[24, 25]. Gribbin et al.[26] observed a higher incidence in men (5.69 (95% CI 5.24 to 6.18) than women (3.44 (95% CI 3.10 to 3.82)) and in older people. In addition, between 1991 and 2003 the incidence of IPF significantly increased, even after taking into account confounding factors such as age and male sex. After controlling for these variables, Gribbin et al. estimated the annual increase in the

incidence of IPF to be 11%. This could not be explained by aging of the UK population or accrual of milder cases as the prognosis was unchanged over this time interval. Hence, it is anticipated that 5000 new cases of IPF will be diagnosed in the UK annually[24]. Similarly in the US Raghu analysed the healthcare claims processing system database to calculate the incidence and prevalence of IPF to be 6.8 and 14.0 per 100 000 person-years respectively [25].

1.4.2 Risk factors for IPF

Epidemiological studies have identified several risk factors that affect incidence as well as the mortality associated with IPF. These include gender, advancing age, race and ethnicity, area of living, season, exposures to cigarette smoke, occupational exposures, height, comorbidities.

Race and ethnicity

The data on race and ethnicity and survival are conflicting. In a retrospective analysis of 2635 patients with IPF, listed for lung transplantation between 1994 and 2003 in 94 transplant centres in the USA, Lederer et al identified that black and Hispanic patients had a higher mortality rate than non-Hispanic whites, which was independent of age, gender, comorbidities, insurance status, transplantation and socio-economic status. This may be attributable to poorer lung function at the time of listing for a transplant, reflecting the barriers faced by minority patients to obtain high-quality health care and consequent later referral for transplantation [27]. In contrast, Olson et al. in their US Multiple Cause-of-Death mortality database study showed that overall age-adjusted mortality rates increased between 1992 and 2003, but that the increase in mortality was lower in Hispanics compared to white, non-Hispanics 1992 and 2003 [28]. However their recent study has shown that Hispanics were more likely to die of IPF than non-Hispanic whites[29]. This suggests that there are genetic differences between racial groups.

Geographical Location

The incidence of IPF varies significantly between areas in the UK, with the highest rates reported in Scotland and the North, whilst the lowest rates are in the South East [30]. In addition, a study of IPF in the USA observed that mortality rates differed with the lowest values (34.3-35.5 per

1,000,000) in New Jersey, New York and Nevada, and the highest levels (69.3-69.5 per 1,000,000) in Vermont and New Mexico [28]. This implies that local environmental factors may play a role in pathogenesis of IPF.

Smoking and occupational exposures

A number of epidemiological and observational studies have identified that certain environmental and occupational exposures are associated with an increased risk of IPF. A meta-analysis of 23 case-control studies demonstrated that cigarette smoking and exposures to agriculture and farming, livestock, wood and metal dust, stone and silica significantly increased the risk of IPF[31]. The highest population-attributable risk percentages were for smoking (Odds ratio (OR)=2.5), and agricultural and farming exposures (OR=2.8), suggesting that 49 and 21% of IPF could be prevented by eliminating these exposures, respectively [31].

There has been much debate about smoking and IPF as some studies suggested a protective smoking effect [17, 20, 32]. It was Antoniou et al. who emphasized the importance of adjustment for baseline disease severity in mortality studies, particularly in situations where a “healthy smoker” effect is possible, i.e. patients with milder disease and fewer symptoms are less likely to give up smoking, hence smoking cessation may be a surrogate marker of more advanced disease. The group used the composite physiologic index (CPI) to adjust for the confounding functional effects of concurrent emphysema (higher FVC and lower DLCO) to evaluate 240 patients with IPF (63 non-smokers, 166 former smokers, 20 current smokers). They observed that overall mortality was higher in former than current smokers, however severity adjusted survival assessed with the use of CPI did not differ significantly between the two groups. non-smokers had better survival than the combined group of current and former smokers (HR=0.63; 95% CI = 0.45, 0.90; p,0.01) and this changed little with adjustment for the extent of disease on CT (HR = 0.68; 95% CI = 0.47, 1.00; $p<0.05$) and DLCO levels (HR = 0.59; 95% CI = 0.40, 0.87; $p<0.01$) but increased with adjustment for CPI level (HR = 0.49; 95% CI = 0.33, 0.73; $p<0.0005$) [33].

Comorbidities

Two studies have identified an association between IPF and diabetes mellitus (DM). A case-control study from Japan of 52 untreated IPF patients and 184 controls noted that the prevalence of DM was higher in

the IPF group (32.7%) compared to the controls (11.4%), with an adjusted odds ratio of 4.04 (95% CI 1.8-9.15) [34]. A similar association between type II diabetes mellitus and IPF (11.3% in IPF vs 2.9% in chronic respiratory disease control group) was observed in a study from Mexico[35]. It remains to be determined why DM increases the risk of IPF.

A number of studies have suggested that abnormal acid gastroesophageal reflux (GER), is a risk factor for IPF due to its possible association with microaspiration[16]. Abnormal reflux is a common condition in patients with IPF but is often asymptomatic[36]. The use of GER medications is associated with decreased radiologic fibrosis and is an independent predictor of longer survival time in patients with IPF[37].

As shown in patients on transplant list who underwent left heart catheterization there is evidence of a higher prevalence of coronary artery disease in IPF patients (66%) compared to matched COPD group (46%) and this association is independent of usual coronary artery disease risk factors; IPF patients with significant CAD had a worse outcome[38]. It was also demonstrated that HRCT is a useful screening tool for the detection of significant CAD in patients with IPF and should be used routinely[39].

1.5 Clinical presentation

1.5.1 Symptoms/history

IPF typically presents in patients over 50 years of age with gradual onset exertional dyspnoea and a dry cough for more than 3 months, although symptoms may have been present for a few years. It is more common in males. Constitutional symptoms are unusual. With advanced disease, patients may experience weight loss due to respiratory failure and an increased work of breathing. As the disease progresses, features of right heart failure may become apparent with peripheral oedema, abdominal discomfort and increase in abdominal girth due to hepatomegaly and ascites.

1.5.2 Clinical examination

Digital clubbing is present in 25-50% of patients with IPF [6]. Velcro-type, fine end-inspiratory crackles initially confined to the basal areas are found on auscultation of the chest in 80% of cases [5]. As the disease progresses, cyanosis and signs of right heart failure, including accentuated pulmonary second heart sound, right ventricular heave and

peripheral oedema, become apparent. Extrapulmonary involvement does not usually occur.

1.5.3 Exclusion of other causes

It is important to establish a history of occupational, environmental, drug and smoking exposures as discussed in section 1.4.2. Symptoms and signs of connective tissue disease, such as arthralgia or synovitis, myalgia and weakness, fever, fatigue, photosensitivity, Raynaud's phenomenon, sicca and reflux symptoms, should be excluded. Sometime these features are subtle and can occur after the onset of the interstitial lung disease. It is important to consider the possibility of a connective tissue disease (CTD) even in patients with radiological evidence of UIP as they have a better prognosis and require different treatment to patients with IPF. Park et al. in a study of 269 cases of IPF-UIP and 93 CTD-UIP showed that those patients in the CTD-UIP group survived longer (mean 125.5 ± 16.0 months) than those in IPF-UIP group (mean 66.9 ± 6.5 months), p=0.001. Both the 3-year survival rate (81.6 vs 57.4%) and 5-year survival rate (81.6 vs 44.8%) were better in the CTD-UIP group compared to the IPF-UIP group, respectively (p=0.001) [40].

Up to 20% of patients with IPF have a family history of pulmonary fibrosis[41]. Familial pulmonary fibrosis affects at least two members of primary biological family (parent, child, sibling) and presents in a similar manner to IPF, except it has an earlier age of onset[42]. A number of studies support an autosomal dominant inheritance with variable penetrance[43]. At present, no genetic testing is available in the UK to identify familial forms of PF and clinical screening is crucial[43]. The study by Steele et al. suggests that nearly 8% of self-reported unaffected family members have a preclinical form of PF as assessed by HRCT or histopathological findings[43], which justifies the need for surveillance of family members of affected individuals.

1.6 Radiological Evaluation

1.6.1 Role of CXR

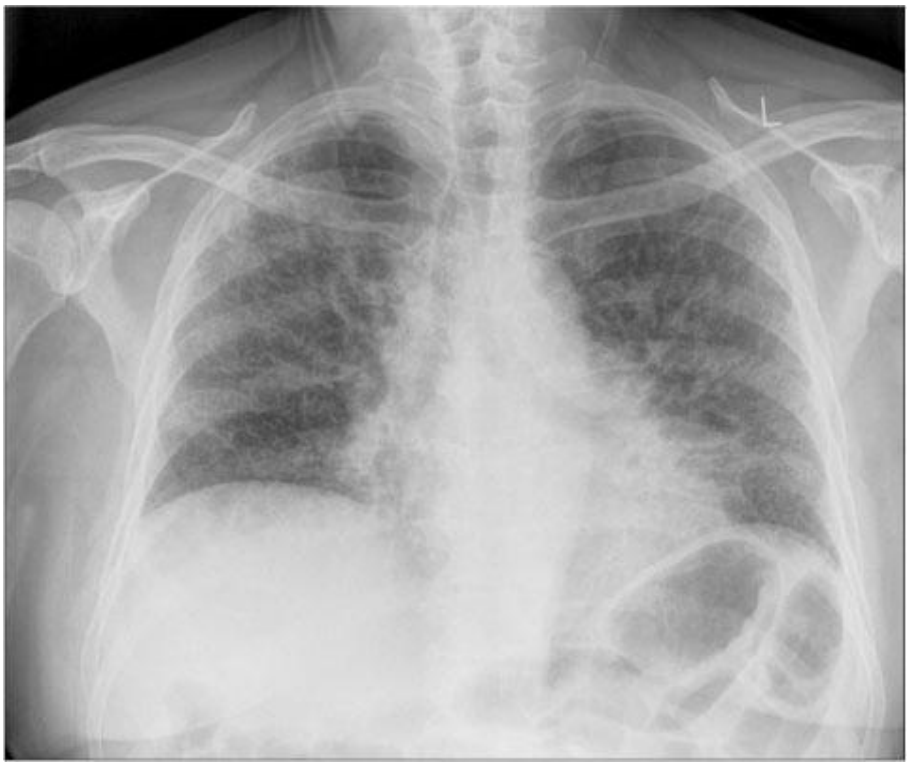


Figure 1.6 Chest radiograph in IPF

Typical chest radiograph (CXR) abnormalities in IPF include peripheral reticulation with a basal predominance, honeycombing and lower lobe volume loss. These changes may be the first clue to a possible interstitial lung disease. On review of previous CXRs it may become apparent that subtle changes have been present for a few years. Nevertheless a normal CXR in a symptomatic patient with a characteristic history and restrictive pulmonary function tests should not exclude the diagnosis. This demonstrates the insensitivity of CXR for diagnosing limited or early stage IPF. In this setting High Resolution Computed Tomography (HRCT) should be performed, as it is more sensitive for identifying and characterising parenchymal abnormalities. CXR remains a useful tool for monitoring disease progression and complications such as pneumothorax and lung cancer.

1.6.2 Role of HRCT

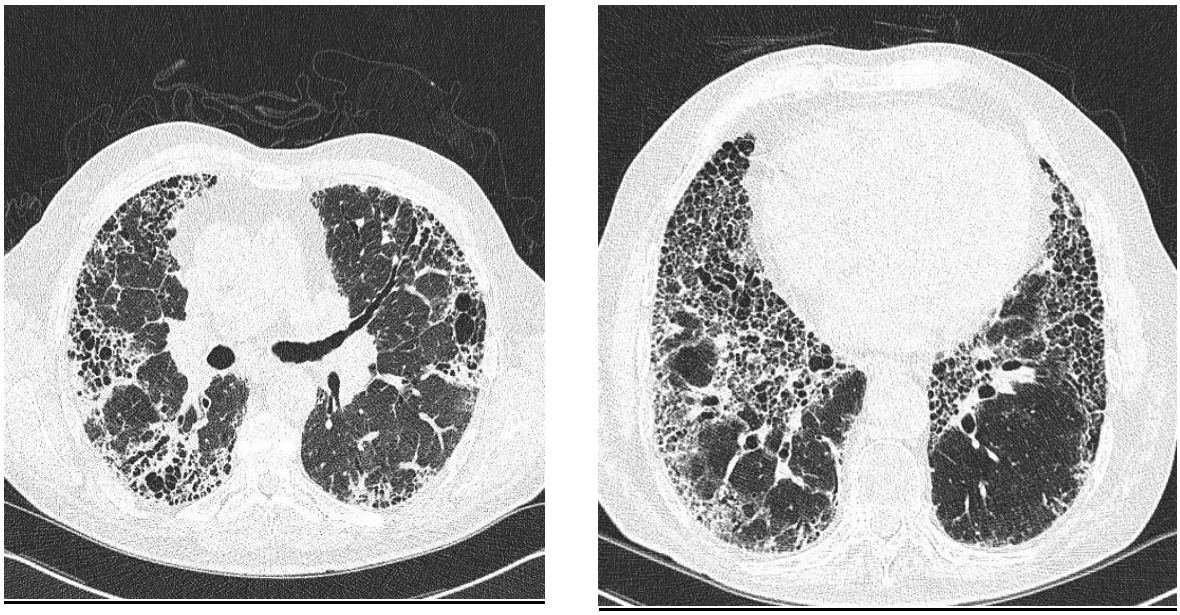


Figure 1.7 HRCT scan in IPF

HRCT has revolutionised the management of patients with ILD and is indicated for all patients with a suspected IIP [6]. It is an essential diagnostic tool for assessing the pattern and extent of the interstitial lung disease, progression as determined by serial scans, and associated emphysema and potential complications, including acute exacerbations, pneumothorax, lung cancer. and PE when complemented by a pulmonary angiogram.

The primary role of HRCT is to identify typical, often diagnostic patterns of ILD and to differentiate patients with typical findings of IPF from those with the less specific findings associated with other idiopathic IIP [6].

1.6.3 HRCT features supporting IPF

Thin-section CT images typical and not typical for UIP pattern are described in Table 1.3.

HRCT features typical for UIP[6]	**HRCT features not typical for UIP**[44]
reticular opacities	extensive ground glass opacification
traction bronchiectasis	consolidation
architectural distortion	micronodules
honeycombing	air trapping
lobar volume loss	nonhoneycomb cysts
basal and peripheral distribution (often patchy)	predominantly peribronchovascular distribution
ground glass opacities if present are less extensive than reticular abnormality	

Table 1.3 Typical and atypical HRCT features for UIP pattern

CT-pathologic correlation has been described with reticulation correlating with fibrosis and radiological honeycombing with histopathological honeycombing. When ground glass attenuation is associated with reticulation and traction bronchiectasis or bronchioloectasis, it usually indicates histologic fibrosis. However, the issue arises with isolated ground glass attenuation as this may indicate interstitial inflammation, airspace filling by macrophages or fluid, and/or fibrosis[6].

1.6.4 Sensitivity and specificity of HRCT

Since HRCT has became a diagnostic tool for IIP, a number of studies have addressed whether particular HRCT features would enable a confident diagnosis of IPF and obviate the need for a lung biopsy, whether some HRCT features aid prognostic information obtained by the biopsy and could serve as predictors of mortality, and how the experience of the radiologists influences interpretation of the HRCT findings.

Studies have shown that a positive predictive value of a CT diagnosis of IPF is 70-100% and that in more than 50% of cases with possible IPF the biopsy is not required due to a presence of typical HRCT features when they are interpreted by expert radiologists [45, 46].

The first study to prospectively determine pretest probability of the clinical diagnosis of ILD including IPF was a tertiary university centre study by Raghu et al. published in 1999 of patients with a new onset ILD referred by community physician for further evaluation when clinical and radiological (HRCT) diagnosis was made within a month prior to surgical lung biopsy. In 29 patients with an eventual histological diagnosis of IPF (out of total 59) the sensitivity and specificity of the radiological diagnosis was 78.5 and 90% respectively (the sensitivity and specificity of clinical diagnosis were 62 and 97% respectively), this showing that SLB is not required in all patients but that in a quarter of patients the diagnosis would be missed is based on assessment of HRCT features without SLB [46].

These findings are being supported by a later study of Hunninghake et al. [45] who in a prospective blinded study in 8 centres when the clinical and radiological findings of 91 patients with IIP were assessed by physicians and radiologists with subsequent provision of the diagnosis (rating its certainty as diagnosis certain, uncertain or unlikely) before the surgical lung biopsy, showed that sensitivity specificity, accuracy and positive predictive value for confident HRCT diagnosis of IPF were 87, 95, 90 and 96% respectively; positive predictive value of a confident clinical diagnosis

of IPF by the referring centres was 80%; as in previous study there was a substantial group of patients (50%) in who a confident CT diagnosis was not made and it would be a group of patients with uncertain or unlikely diagnosis of IPF who required lung biopsy as the probability of agreement as reflected by kappa score among pulmonologists and radiologists for that group was only fair (0.32 and 0.31 respectively). Of interest both Raghu et al and Hunninghake et al demonstrated that there were no patients with IPF who had normal HRCT [45, 46].

1.6.5 HRCT features that predict diagnosis and prognosis

The next important question to answer would be whether certain HRCT features predict diagnosis, add prognostic information and correlate with mortality.

Flaherty et al. classified HRCT scans of 96 patients (73 of which showed histological UIP and 23 histological NSIP) as definite UIP, probable UIP (honeycombing being the feature differentiating the two), indeterminate (equal probability of UIP and NSIP), probable NSIP, or definite NSIP. 27 patients were felt to have definite or probable HRCT diagnosis of UIP with all of them showing histological picture of UIP (in contrast to 18 of 44 patients with HRCT suggestive of probable or definite NSIP showing histological diagnosis of NSIP). As in previously mentioned studies radiologists demonstrated high specificity for the diagnosis of IPF (100%) but lower than previously reported sensitivity (37%). Patients with a histological diagnosis of UIP had worse survival than those with the histological diagnosis of NSIP (HR=7.24, 95% CI 1.74 to 30.2, log rank p=0.0015); more importantly there was no difference in survival when comparing patients with HRCT diagnoses of probable or definite UIP (HR=1.67, 95% CI 0.6 to 4.64, log rank p=0.32), or comparing patients with HRCT diagnoses of definite or probable NSIP (HR=1.31, 95% CI 0.38 to 4.54, log rank p=0.67) [47]. As evidenced by Figure 1.7 patients with UIP histology could have both definite/ probable HRCT diagnosis and indeterminate diagnosis and the first group of patients has the worst prognosis thus demonstrating that HRCT features do indeed add prognostic information to the histological diagnosis of UIP.

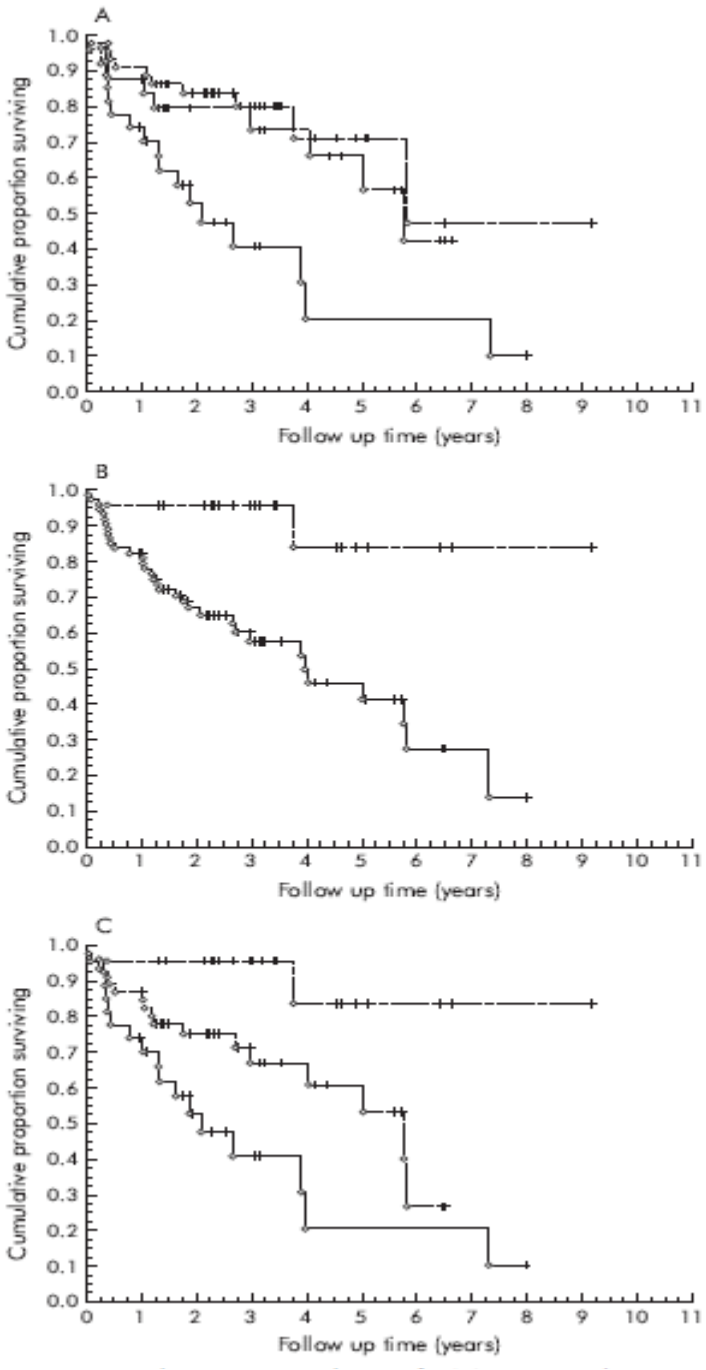


Figure 1.8 Kaplan-Meier survival curves for (A) patients with an HRCT diagnosis of NSIP (n=44, dotted line), indeterminate (n=25, dashed line), and UIP (n=27, solid line), p=0.01; (B) patients with a histopathological diagnosis of NSIP (n=23, dotted line) and UIP (n=73, solid line), p=0.0006; and (C) patients grouped by combining HRCT and histopathological features as follows: histopathological pattern showing NSIP and HRCT was interpreted as indeterminate or NSIP (n=23, dotted line), histopathological pattern showing UIP and HRCT was interpreted as indeterminate or NSIP (n=46, dashed line), and histopathological pattern showing UIP and HRCT was interpreted as UIP (n=27, solid line), p=0.001. + = last follow up visit; ø = death. [47]

A number of studies showed that out of all HRCT features typical for UIP only the extent of traction bronchiectasis and quantity of fibrosis are significant predictors of mortality. Having assessed the extent of interstitial opacity (CTfib) on a scale of 0-5 in 106 patients with histologically confirmed UIP Flaherty et al demonstrated that a mean CTfib score of ≥2 in any lobe (representing the presence of honeycomb change) or mean CTfib score of ≥2 for all lobes was highly predictive for the presence of UIP and that the RR for dying with a mean CTfib score of ≥2 for entire lung was 2.51 (95% CI 1.39-4.54; p=0.002) and 3.72 (95% CI 1.83-7.56; p=0.0003) for those with at least one lobe with a CTfib score of ≥2

(difference probably reflecting the disease heterogeneity) [20]. A positive predictive value of 92% suggested that these patients do not need to undergo a lung biopsy. A limited negative predictive value (47% for all lobes and 69% for at least one lobe) reflected the absence of honeycombing on HRCT of many patients with UIP. CTfib score <2 is not reliably predictive of absence of UIP therefore these patient should undergo a biopsy [20].

Lynch et al in a large cohort of patients (315) recruited into the study evaluating IFN-γ1b showed that DLCO was the only physiologic characteristic most highly correlated with HRCT findings and that a higher overall extent of fibrosis on HRCT was associated with a 2.7-fold increase risk of mortality in the multivariate analysis [44]. This finding agreed with the previous findings of Mogulkoc et al with percent predicted DLCO and the HRCT fibrosis score being the sole two predictors of mortality of 2 year survival in 115 patients with UIP [48].

1.6.6 Inter-observer differences

The majority of clinical trials performed in IPF originate from large academic centres and this should be taken into account as the expertise and experienced in IIP of tertiary centres radiologists and radiologists from community hospitals might differ which will lead to different radiological interpretation of the same scans. Agreement between expert radiologists is good as demonstrated by Hunninghake et al. in his study of 91 patients HRCT of which were independently assessed by 4 radiologists. The probability of agreement for presence or absence of IPF was 0.77 (kappa 0.54) while positive predictive value of UIP diagnosis was 85%, this improved to 96% for cases of confident UIP diagnosis [45]. An interobserver agreement for the combination of probable and definite UIP was similar (64%, kappa 0.52) in 2 other studies of 73 and 69 patients respectively [47, 49]. In a large study involving 315 patients where core radiologists were not blinded to the radiological and histological diagnosis of the patients their interpretation of HRCT confirmed the diagnosis in 90% of cases originally reviewed by radiologists of 58 sites, 19 of which were community based. This could partly be a result of the use of predefined criteria for HRCT interpretation by study-site radiologists [44].

1.6.7 Definite vs probable IPF vs atypical

Thus several studies demonstrated that even radiologists with significant expertise in IIP can find diagnostic difficulty between UIP and NSIP patterns on HRCT [46, 47, 49]. Not all patients with IPF exhibit all typical features of HRCT as a result of which to enable accurate diagnosis of IPF on radiological grounds and identify patients who do not require a lung biopsy a set of criteria for “definite” and “probable” diagnosis of IPF has been determined. A radiographic diagnosis of “definite IPF” required all three of the following criteria: (1) presence of reticular abnormality and/or traction bronchiectasis with basal and peripheral predominance; (2) presence of honeycombing with basal and peripheral predominance; (3) absence of atypical features, such as micronodules, peribronchovascular nodules, consolidation, isolated (nonhoneycomb) cysts, extensive ground glass attenuation, or extensive mediastinal lymphadenopathy [44]. The presence of the first and third criteria (honeycombing not present) only qualifies as “probable IPF”. The presence of atypical radiological features (as in (3)) and/or atypical clinical features (young age, inconclusive exposure history, lack of dyspnoea, absence of restrictive lung defect on pulmonary function tests) is an indication for a biopsy to clarify the diagnosis [6].

1.6.8 Novel imaging modalities

Though HRCT is an imaging standard in IIP it is only a structural technique, hence Groves and Screaton decided to use Positron Emission Tomography (PET) which offers an ability to noninvasively investigate cellular mechanisms in vivo in combination with CT; this combination allows direct comparison of 18F-fluorodeoxyglucose (18F-FDG) uptake with the structural appearance of the lung parenchyma. The maximal pulmonary 18F-FDG metabolism is measured as standardised uptake value (SUVmax). As anticipated raised pulmonary 18F-FDG was associated with ground glass opacity on HRCT of 18 patients with IPF (mean SUVmax 2.9 ± 1.1) and 18 patients with other ILD (mean SUVmax 2.7 ± 0.9); but the site of maximal metabolism was corresponding to the ground glass changes in 7 out of 36 patients only, while reticulation and honeycombing encountered for 26 of 36 patients. The authors hypothesized that the area of HRCT reticulation and honeycombing might not represent burnt-out inert disease but be an area of metabolically active fibrotic process and hence

even patients with extensive fibrotic change on HRCT may still be amenable to pharmacologic manipulation [50].
This method is not routinely used in IPF and other form of IIP but adds to understanding of pathological mechanisms.

1.7 Role of BAL and TBB

Broncho-alveolar lavage (BAL) is a method used as an additional investigational tool during bronchoscopy. It is used in the first place to detect bronchial and alveolar cells metaplasia or to identify infectious pathogens. It could also be used for assessment of differential cell counts which might point towards a particular diagnosis. Normal BAL values from non-smoking subjects show the following: alveolar macrophages 80-90%, lymphocytes 5-15%, neutrophils 1-3%, eosinophils <1%, mast cells <1%.
Though there are no pathognomonic BAL features for UIP a finding of raised neutrophils (>4%) and raised eosinophils (>2%) is characteristic of UIP and is distinct from differential cell count in sarcoidosis and hypersensitivity pneumonitis.
Problem with obtaining a good size specimen that would represent both abnormal and normal lung parenchyma in UIP as well as lack of architectural preservation due to mechanical crash makes TBB unhelpful in IPF. This has been confirmed by an 85% rate of nondiagnostic TBB in 59 patients with ILD (29 of them IPF) [46].
BAL alone is used for the purpose of exclusion of infection and other diagnoses as well as to assess prognosis in IPF. To answer the question if baseline BAL cell count would predict higher mortality among persons with IPF Kinder et al. performed a prospective study of 156 patients with biopsy proven IPF. 67% of the cohort had an elevated BAL neutrophil count of >3%; the survival analysis demonstrated a linear relationship between increased neutrophil percentage and the risk of mortality, each doubling of neutrophil percentage was associated with a nearly 30% increased risk of death or transplantation in adjusted analysis (HR 1.28; 95% CI 1.01 to 1.62, adjusted p=0.04) (this was not affected by smoking or treatment status). The median survival time for those with neutrophil count >11% was 1.9 years, for those with a count of 3-10% was 2.3 years and those with a count of <3% - 3.7 years [51]. Therefore an increased BAL neutrophil percentage is an independent predictor of early mortality in IPF and could help to identify patients who require treatment at an earlier stage.

As mentioned previously NSIP particularly its cellular form can exhibit higher levels of BAL lymphocytosis. It had therefore been explored if BAL cell count differences in UIP and NSIP could help to differentiate between the two conditions. Veeraraghavan et al. retrospectively evaluated BAL findings in 54 patients with histological diagnosis of UIP (35 patients) and NSIP (19 patients). It was the first study where the diagnosis was confirmed surgically and was defined based on ATS/ERS criteria of IIP. There were no significant or marginal differences found in BAL data between UIP and NSIP patients and BAL cell counts did not predict changes in lung function; none of the constituents of BAL cell count predicted survival [52].

A more recent large retrospective study of 87 UIP and 35 NSIP patients demonstrated that UIP was characterised by a higher neutrophil count of 7% vs 3% in NSIP and a lower lymphocyte count of 5% vs 29% in NSIP [53]. In summary the diagnostic usefulness of BAL in IPF is limited but is helpful in identifying a group of patients who have worse prognosis although admittedly there is no evidence that an earlier commencement of treatment improves survival.

1.8 Surgical Lung biopsy

1.8.1 Who to biopsy

HRCT features of definite IPF obviate the need for lung biopsy in around 50% of IPF cases. The remaining 50% include cases of clinically or radiologically probable (lack of honeycombing) or atypical IPF when a surgical lung biopsy (SLB) is required as this could demonstrate UIP even in the absence of typical HRCT picture or an alternative diagnosis. Historically only about 10-15% of these cases are being referred for a SLB due to the fact that physicians are often reluctant to refer patients to a potentially risky procedure on one hand and to a limited availability of effective treatment options no matter what the final diagnosis is on the other hand. Nevertheless development of thoracoscopic video-assisted thoracoscopic (VATs) biopsy and of new treatment options (for example antifibrotic drugs) emphasizes the importance of accurate diagnose to enable prediction of survival in an individual case and correct use of new drugs in correct circumstances.

If biopsy is considered it should be taken early in the course of the disease and include both areas of end stage lung as well as less fibrosed areas, which could be targeted with the guidance from a radiologist.

1.8.2 Safety of lung biopsy.

A retrospective study of Utz et al. of 60 SLB (14 VATs biopsies and 46 open lung biopsies (OLB) of patients with atypical for UIP history or examination demonstrated a high early 30 day mortality rate of nearly 17% (10 patients of 60). A lower DLCO was predictive of mortality at 30 days (34.7% vs 52.1%) which might make one consider that patients who died had a more severe disease. Also 4 of 10 patients who died had evidence of DAD on biopsy meaning they had an accelerated course of the disease. 7 of 10 cases had OLB rather than VATs [54].

Lettieri [55] and Hunninghake [45] demonstrated that the early mortality rate after surgical lung biopsy was low (1.1% and 1.5% respectively) among patients who were not receiving immunosuppression or mechanically ventilated; the last two factors were the only ones that differentiated survivors from nonsurvivors in Lettieri study. At the same time gender, pulmonary function indices, oxygen use and age did not affect survival [55] .

1.8.3 Multiple biopsies

Returning back to the studies of Flaherty et al. [8] and Monaghan et al. [21] discussed in section 1.3.3 it is important to remember another implication toward SLB: patients who have a combination of UIP and NSIP patterns should be classified as having UIP as it is associated with a poor prognosis; biopsy technique should be such that multiple lobe biopsies should be considered from areas of relatively preserved lung. Patients with biopsies taken from only one lobe could be mistakenly classifies as NSIP due to possible co-existence of UIP and NSIP patterns in the same patient. Therefore biopsies should be taken from more than one lobe.

1.8.4 Does biopsy accelerate disease?

Case reports have described acute exacerbation of IPF after surgical lung biopsy, the majority of this cases died within 30 days of the biopsy [56, 57]. Kondoh et al hypothesized intraoperative respiratory management is contributing to the exacerbation: hyperoxia, prolonged anaesthesia during the procedure, excessive mechanical stretch/injury, this could contribute to free radical oxidative damage to the non-biopsied lung where most of the injury usually occurs [57].

1.8.5 Role of MDT

ATS/ERS consensus statement on IIP emphasizes that achieving a correct diagnosis is a dynamic process, it requires close communication between clinician, radiologist, and pathologist and that the diagnosis might need to be revised once more clinical, radiological and histological information becomes available [6]. This additional information is to mutual benefit to all three diagnostic parties. For example, pathologist suggesting a diagnosis of NSIP on histological grounds alone might reconsider the diagnosis in favour of UIP if an information about a presence of significant honeycombing on HRCT is provided by radiologist or when suggesting a diagnosis of UIP in favour of connective tissue disease related ILD if an information about joints involvement and positive autoimmune screen is provided by clinician. In turn a clinician might reconsider a diagnosis of IPF in favour of Hypersensitivity Pneumonitis if provided with information by a radiologist about air trapping and upper zone involvement on HRCT or on noncaseating granulomas in pathological lung specimens.

The most practical way of arranging a joint case discussion is at multidisciplinary meetings involving clinicians, radiologist, pathologist and surgeon.

Role of multidisciplinary approach to the diagnosis of IIP including IPF was looked at by Flaherty et al. in his 2 studies, one in academic settings and one comparing community settings with academic setting. In a prospective study of 58 cases of IIP including 28 cases of final consensus diagnosis of IPF in academic settings, when the information to participant was given in a stepwise fashion (HRCT first, then clinical information, then pathology data) it was shown that the level of agreement between observers and diagnostic confidence was improving as more clinical, radiographic and pathological data was provided and that the greatest improvement for the clinicians interobserver variation occurred after the discussion of clinical and radiological features with radiologists, thus underlining the importance of reviewing the actual scans jointly rather than relying on a report. In parallel it is important to note that a diagnosis of IPF by each of two clinicians and by each of three radiologists following the review of clinical and radiographic data (before pathology data) coincided in all but 2 cases which confirms that patients with clinical and radiographic picture consistent with confident diagnosis of IPF do not require surgical lung biopsy [58].

A retrospective study of 39 cases of DPLD (13 cases of IPF when diagnosis could not be based on radiological criteria only) looked at a diagnostic agreement between academic and community based physicians. It showed that clinically significant disagreement exists regarding the diagnosis of IIP among two groups of clinicians, with community-based clinicians more likely to make the diagnosis of IPF (with some cases subsequently being reconsidered by the academic clinicians as having secondary/identifiable causes); final diagnostic agreement was higher between academic physicians (k=0.71 vs 0.44 for community based physicians) and most diagnostic agreement occurred for cases of IPF [59].
In summary dynamic multidisciplinary approach to the diagnosis of IPF improves interobserver agreement among both community and academic clinicians (to a greater extent between the latter) and that patients without the clinical and radiological data suggesting confident diagnosis of IPF should be referred to specialist centres for clarification of diagnosis.

1.9 Physiological Assessment and Assessment of Disease Progression

Physiological assessment of the disease severity and progression could be made based on data obtained during pulmonary function tests, exercise testing and when using mathematical scoring system which take into account a number of clinical, physiological and radiological parameters at the same time. Though diagnosis of IPF carries a poor prognosis there is a significant variability in disease progression between patients and in their survival. Therefore it is important to clarify baseline parameters that would help to identify patients with more advanced disease at the time of diagnosis that would enable more proactive therapeutic approach including consideration of referral for a lung transplant assessment. At the same time for patients with milder disease at baseline it is important to clarify parameters that would help to identify those with progressive disease over time.
Characteristic findings of pulmonary function tests (PFT) in IPF include restrictive pattern on spirometry as reflected by reduced Forced Vital Capacity (FVC), normal or increased Forced Expiratory Volume in first second (FEV1) and normal or increased FEV1 to FVC ratio. Spirometry values might be normal in early disease and the only abnormality apparent could be reduced gas transfer (DLCO) corrected for haemoglobin level as a result of ventilation and perfusion mismatch and a reduction in alveolar and capillary bed. Lung volumes including Total Lung Capacity (TLC) and

Residual Volume (RV) are reduced as the disease progresses. In case of coexisting emphysema lung volumes could be increased and DLCO could be more significantly reduced.

PFTs are easily accessible in the majority of Chest clinics, are standardised and when assisted by a trained staff according to international guidelines are relatively easy to perform and are reproducible.

Exercise tests used for the assessment of severity and progression of IPF include six minute walk (6MW) and Cardiopulmonary Exercise Testing (CPET). The 6MW test is a simple, safe and inexpensive assessment of self-paced exercise capacity [6]. Its within subject reproducibility is good and it has a good prognostic value [60]. CPET assesses maximal oxygen uptake which is an integrated measure of cardiovascular, respiratory and neuromuscular function.

1.9.1 Role of FVC and DLCO

Four large studies of well defined population of biopsy proven IPF and NSIP from tertiary centres demonstrated the role of these physiological parameters both at baseline and over time. King et al. in his prospective study of 238 patients with IPF showed that the severity of impairment of spirometry and DLCO at baseline are significant ($p<0.05$) predictors of survival [61]. The other three studies looked at change in PFT over time.

Latsi et al in a retrospective study of 61 patients with UIP and 41 patients with NSIP along with once again confirming that the former diagnosis carries worse prognosis (the median survival of 33 months versus 56 months respectively), showed that reduction in FVC, FEV1 and DLCO at 6 months is an independent determinant of survival and that the predictive power of these changes is equivalent to the histopathologic diagnosis in predicting survival. Changes in these parameters at 12 months were also substantially more predictive of outcome than the histopathologic diagnosis. Importantly the study also showed that in patients with DLCO < 35% predicted biopsy evaluation (IPF or NSIP) provided no prognostically useful information as the survival did not differ between the two groups [23].

Collard et al. in a prospective study of 81 patients with IPF demonstrated that changes in both FVC % predicted and DLCO % predicted at both 6 and 12 months are predictive of survival time and importantly this remains unchanged after adjustment for the variables baseline measurements,

suggesting that the rate of progression is independent of the initial degree of disability. Patients who did not demonstrate a 10% decline in their PFT had improved survival compared to those with this clinically relevant decline [62].

While a variety of thresholds for change in FVC had been previously suggested (ranging from 10 to 15%) Flaherty et al. in a retrospective study of 80 patients with IPF documented that a 10% decrease in FVC over 6 months period from the time of the surgical lung biopsy exhibited strong predictive ability in defining long term survival; this remained unchanged on multivariate analysis, while changes in TLC and DLCO did not contribute further information once these factors were included in the multivariate model [63].

1.9.2 Exercise Testing

6 MW test and CPET are both used in IPF as gas exchange deteriorates on exercise in this condition.

6 MW test provides information on distance walked at submaximal exertion and on a degree of desaturation during exercise and has been used in studies to assess the significance of values at the time of diagnosis including in a separate group of patients on a waiting list for a lung transplant, to assess the significance of changes over a period of 6 and 12 months after diagnosis; it is also used for assessment of effect of treatment. Exertional desaturation is a result of ventilation/perfusion mismatch, limitation in oxygen perfusion and low mixed venous pO2 [64].

A consensus statement on IPF [5] suggests that a 4% decrease in oxygen saturation (SaO2) during 6 MW is an adverse prognostic sign. Lama et al. supported this statement in their study of 83 patients with biopsy proven UIP by showing a 14-fold increase in mortality for such a degree of desaturation; they also showed that desaturation is common (44 out of 83 patients) and that patients desaturating below 88% have a fourfold increased risk of death (HR 4.2; 95% CI 1.4-12.56; p=0.01) after adjusting for age, sex, smoking, baseline DLCO, FVC and resting saturation. The 4 year survival rate of those who desaturated below 88% was 34.5% compared to 69.1% in patients who did not desaturate [64].

In a subsequent study Flaherty et al. looked at the prognostic value of a baseline and serial changes in 6 MW in relation to changes in FVC and DLCO in 197 patients with IPF. It was demonstrated that subtle desaturation defined by increased desaturation area during a baseline 6

MW increases the risk of subsequent mortality even if saturation remains greater than 88%; 15% decline in DLCO % at 6 months time is a sole predictor of increased risk of mortality in those patients who desaturate below 88% at baseline while in those who do no not desaturate declines in DLCO, FVC, walk distance and worsening desaturation at 6 months will need to be used [65].

In order to identify a baseline cut off for 6 MW distance in IPF patients listed for a lung transplant Lederer et al. in a retrospective cohort study of 454 patients used receiver operating characteristic (ROC) curves for 6 MW distance, 6 MW distance % predicted and FVC % predicted for prediction of mortality at 6 months (for those who did not undergo transplant). It was shown that patients with a walk distance of less than 207 m had more than fourfold greater mortality than those with a walk distance of more than 207 m, despite adjustment for demographics, antropomorphics, FVC % predicted, pulmonary hypertension and medical comorbidities (adjusted rate ration 4.7; 95% CI 2.5-8.9; $p<0.0001$); in these patients 6 MW distance was a significantly better predictor of 6 months mortality than FVC % predicted [66].

Until recently it was not clear what distance would constitute a minimum important difference (MID) when assessing changes over time. Two recent studies made attempts to clarify this. Swigris et al. assessed changes in 6 MW distance in 123 patients with IPF over 6 and 12 months by two statistical methods. Though the study confirmed previously existing data that there was no statistically significant difference in mean 6 MW distance between any time point (378.1 m at baseline vs 376.8 at 6 months vs 361.3 m at 12 months, $p=0.5$), the mean MID was 28 m (10.8-58.5 m) [67]). Similar MID of 24-45 m was found to be clinically important in a study of 822 patients of du Bois; it also showed that a 24-week decline of greater than 50 m was associated with a fourfold increase in risk of death at 1 year (hazard ratio, 4.27; 95% confidence interval, 2.57- 7.10; $P < 0.001$); 6MWD was weakly correlated with measures of physiologic function and health-related quality of life; however, values were consistently and significantly lower for patients with the poorest functional status, suggesting good construct validity[68].

Maximal oxygen uptake during CPET is an integrated measure of cardiovascular, respiratory and neuromuscular function which more accurately than measures of lung volume reflects derangements in haemodynamics and ventilation during exercise [69]. In a study by Fell et

al. of 117 patients with IPF and longitudinal CPET assessed retrospectively it was shown that baseline maximal oxygen uptake of less than 8.3 ml/kg/min had an increased risk of death (HR 3.24; 95% CI 1.1-9.56; p=0.03) after adjusting for age, gender, smoking status, baseline FVC and DLCO; it appeared it was a more robust measure of survival than desaturation below 88% on 6 MW and resting pO2. The study team was unable to define a unit change in maximal oxygen uptake that would predict survival [69].

1.10 Prognosis

1.10.1 Survival in IPF

While the course of IPF is typically described as one of relentless decline in respiratory function, the course of individual patients is highly variable [70]. As previously described by Bjoraker [11] and Hubbard [71] in the studies that were performed prior to new classification of IIP the median survival in IPF is limited to 2.8 years from the time of diagnosis; the median survival in most studies performed after the development if new classification is between 2 and 4 years from the time of diagnosis and 5 year survival is between 20 and 40% [10, 12, 17, 63]. Nevertheless both Collard [62] and Flaherty [63] demonstrated that along with patients with evidence of decline in PFT over 6-12 months there is a group of patients who have either improvement or no significant change in their parameters over this period of time. Collard showed that only 27% of patients had decline in their FVC % predicted at 6 months while 61% had no change in their FVC % predicted and 12 % had improvement; Flaherty demonstrated that 49% of patients remained within 10% of baseline at 6 months, though by 12 months this reduced to 21% only. There are known cases of biopsy proven UIP who survive up to 10 years and more. Survival in prevalent cases is higher due to selection bias as some incident cases died earlier due to more aggressive disease [71].

Mortality rate have been shown to be high and to increase in a number of studies recently both in the UK and USA. Hubbard et al. was the first one to demonstrate the importance of using incident rather than prevalent cases in assessing incidence due to prevalent cases demonstrating survival bias by excluding those who die from aggressive disease while incident cases would represent the full spectrum; median survival for incident cases was 2.9 years and for prevalent cases 9 years compared to expected values of 10 and 13 years respectively; the expected life span

was therefore estimated to be reduced by approximately 7 years [71]. In the study of Gribbin et al. in the UK the 3 and 5 year survival percentage for patients with IPF were 57 and 43% respectively as opposed to 88 and 81% in a comparison cohort of non-IPF population; median survival time was 3.9 years [30]. Olson et al. on the grounds of analysis of the US Multiple Cause-of-Death mortality database in 1992 and 2003 demonstrated an increase in mortality rate of 27.5% in men (from 48.1 deaths per 1,000,000 in 1992 to 61.2 deaths per 1,000,000 in 2003) and of 40.8% in women (from 38.7 deaths per 1,000,000 in 1992 to 54.5 deaths per 1,000,000 in 2003) [28].

Pulmonary fibrosis itself was reported to be an underlying cause of death in 60 ± 2.2% of deaths, with ischaemic heart disease being a case in 8.5 ± 0.6%, lung cancer in 2.9 ± 0.4%, pneumonia in 2.4 ± 0.5%, cerebrovascular disease in 1.3 ± 0.2%, congestive heart failure in 1.3 ± 0.3%, pulmonary embolism in 0.37 ± 0.05% and other causes in 23.4 ±1.3% [28].

Male gender and increasing age are both important determinants of survival (28,29,30,31) with HR of 1.4 (95% CI 1.15 to 1.7, p=0.001) for male gender and 8.75 (95% CI 4.98 to 15.36, p<0.0002) for the age >85 [30]. A statistically significant advantage for females was demonstrated not to be related to the severity of the disease in a multivariate analysis evaluating gender differences adjusted for age, smoking history, DLco % predicted and desaturation on 6 minute walk [72].Seasonal variation in mortality, with an increased winter incidence of pneumonia and in chronic obstructive airway disease, is well documented. On the basis of analysis of the underlying cause of death in pulmonary fibrosis from National Centre for Health Statistics between 1992 and 2003 Olson et al. observed the same seasonal variation with mortality rates in patients dying from PF being 15.9% higher in winter (p<0.0001), 12.7% higher in the spring (p<0.0001) and 5.1% higher in autumn (p=0.0008) than in the summer. It is hypothesised that the winter increase is related to an infectious trigger[73].

1.10.2 Disease Progression

A number of recent clinical trials demonstrated that a rate of annual decline of PFT is not that high. A randomised placebo controlled trial of Interferon-1γb showed that patients who survived till week 72 had a decrease in mean % FVC predicted from 64.5% to 61%, and a decrease in

mean DLCO predicted from 37.8 to 37%. In a randomised placebo controlled trial of N-acetylcysteine during 12 months in placebo arm a mean reduction in Vital Capacity was 190ml (7.5 % from baseline) and mean decline in DLCO of 0.7 mmol/min/kPa (13.3% from baseline).

The discordance between the rate of decline in PFT and mortality suggests that the clinical course of IPF may be less a gradual decline and more a step like process, with periods of relative stability punctuated by periods of acute decompensation that may be associated with high mortality, Figure 1.8 [70].

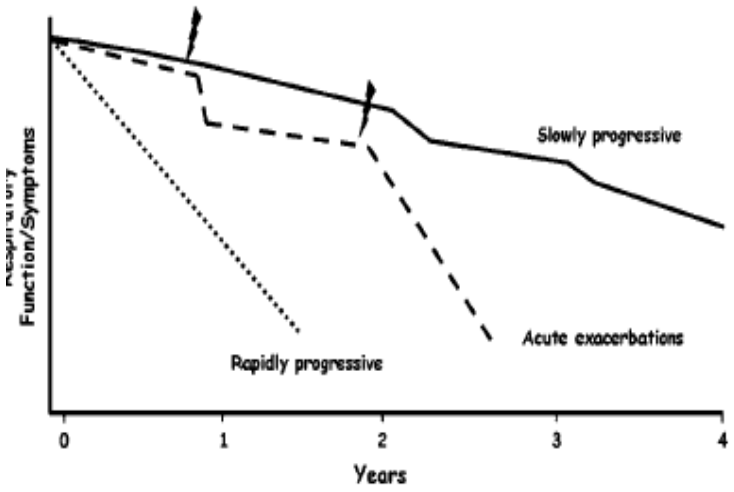


Figure 1.9 Schematic drawing of the potential clinical course of patients with IPF. The majority show a relatively slow decline in functional status after the diagnosis. Others appear to have episodes of acute clinical deterioration (acute exacerbation) that precede and possibly initiate the terminal phase of their illness. A minority of patient appear to have a short duration of illness with a more rapidly progressive course. Jagged mark = acute exacerbations[70].

1.10.3 Accelerated Decline

Accelerated decline is characterised by unexpected worsening of the underlying disease over a short period of time which leads to death in the vast majority of cases. While at times the cause of it could be identified (infection, pulmonary embolism, pneumothorax and heart failure) and therefore treated, quite often there is no identifiable cause and this episodes are called acute exacerbations. In order to call an episode an acute exacerbation it is important to exclude any identifiable cause as above.

1.11 Assessment of disease severity

Assessment of disease severity is required at initial presentation and at subsequent follow up of each patient with IPF. This will help to decide on the time and appropriateness of commencement of medical treatment as well as on the need for referral for a transplant assessment and to support services including breathlessness clinic and Macmillan nurse, and could be done using a combination of parameters including the results of PFT, exercise testing, HRCT along with taking into account presence or absence of complications.

It was demonstrated recently that the disease severity could be defined as advanced and limited on the grounds of pulmonary function tests. Mogulkoc et al. studied PFT of 115 patients referred for a lung transplant assessment in a tertiary centre and related it to two year survival. A multivariate stepwise regression analysis identified that only DLCO % predicted and HRCT fibrosis score are independent predictors of 2 year survival. Receiver operator characteristic analysis showed that a DLCO of 39% predicted and HRCT fibrosis score of 2.25 have an 80% sensitivity and specificity for predicting death within 2 years [48]. DLCO of 39% could be used as a discriminator between advanced and limited disease and trigger a referral for a transplant assessment accordingly. In tune with the above study Latsi et al showed that patients with reduction in DLCO to <35% had a survival time of less than 2 years irrespectively of whether they had a histological diagnosis of UIP or NSIP [23].

As described above a number of parameters have been shown to predict survival in IPF, this is summarized in Table 1.4.

Parameters associated with more severe disease	Degree of impairment reflecting more severe disease
Demographic	Male gender Age above 75 years old Current or former smoking
Physiologic	DLCO < 39% predicted 6 minute walk distance < 207 m in patients referred for transplant assessment 24-45 m decline in 6 minute walk distance over 6 months Desaturation below 88% on 6 minute walk
Radiographic (HRCT)	UIP pattern Fibrosis score of > 2
Histological	UIP pattern Fibroblastic foci
Clinical	Evidence of respiratory failure at rest Pulmonary Hypertension Emphysema

Table 1.4 Parameters associated with severe IPF

1.12 Who to treat?

Current joint committees IPF guidelines suggest selected features commonly observed in clinical practice that are associated with increased risk of mortality within 2 years in an attempt of identifying patients who should be considered for lung transplantation (Table 1.5)[16].

Baseline factors
Level of dyspnoea*
DLCO < 40% predicted
Desaturation ≤ 88% during 6MWT
Extent of honeycombing on HRCT*
Pulmonary hypertension
Longitudinal factors
Increase in level of dyspnoea*
Decrease in forced vital capacity by ≥ 10% absolute value
Decrease in DLCO by ≥ 15% absolute value
Worsening of fibrosis on HRCT*

Table 1.5 Selected features associated with increased risk of mortality in IPF[16]. *Currently, there is no uniformity in approach to quantification.

Presence of a number of parameters developed based on data from clinical trials is consistent with progressive disease in the absence of another identifiable cause and helps to guide appropriate treatment interventions including consideration of lung transplant[16].

- Progressive dyspnoea (objectively assessed)
- Progressive sustained decrease decline from baseline in absolute FVC
- Progressive sustained decrease decline from baseline in absolute DLCO (corrected for hemoglobin)
- Progression of fibrosis form baseline on HRCT
- Acute exacerbation
- Death from respiratory failure

It is suggested that a combination of FVC and DLCO is useful in assessing disease progression rather than each of this measures individually as the presence of significant emphysema impacts FVC results[16].

It is recommended that on average progression of disease is monitored over periods of 3 to 6 months but sustained changes in symptoms, physiology, and radiology over shorter periods of time may also identify disease progression in which case follow up measurement should be done earlier[16].

The following schematic pathway is currently recommended for clinical management of IPF patients (Figure 1.9)[16]:

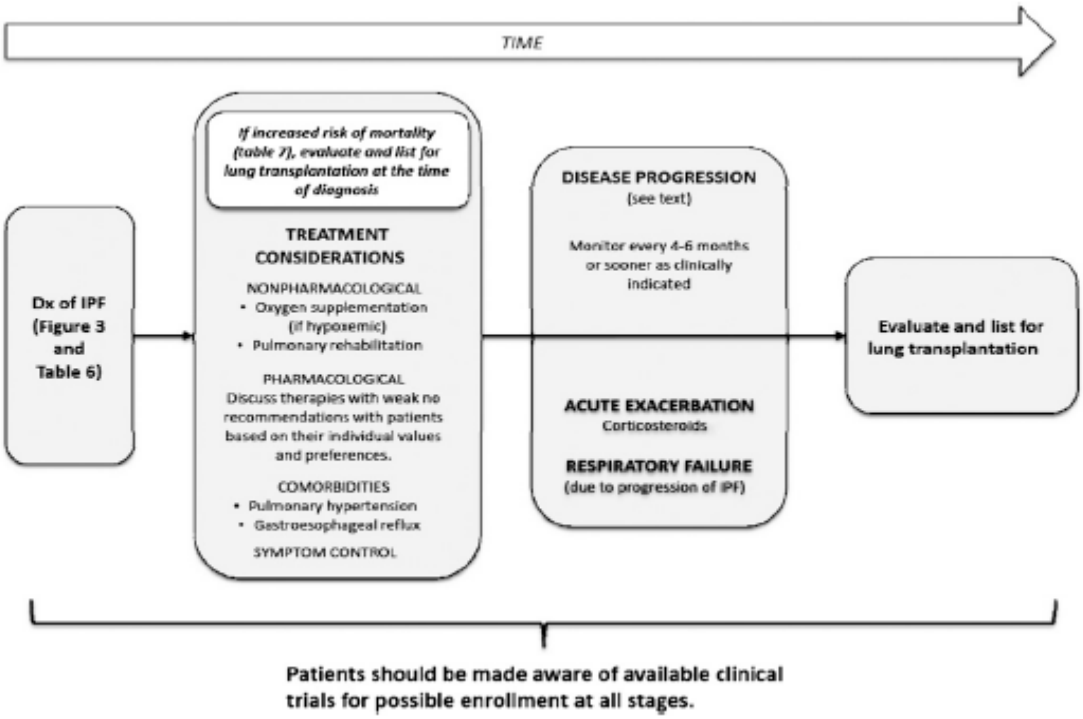


Figure 1.10 Schematic pathway for clinical management of patients with IPF. Clinicians are required to spend adequate time with patients to discuss patients' values, preferences, and prognosis. All patients should be made aware of available clinical trials for possible enrollment. Patient at increased risk of mortality should be considered for lung transplantation. Pharmacologic treatment should be limited to a carefully selected minority of patients who are willing to accept possible adverse consequences even if expected benefits are small. See text for specific recommendations of pharmacological therapies. Oxygen supplementation (if hypoxemic) and pulmonary rehabilitation are recommended treatments (strong yes and weak yes, respectively). All patients should be monitored for disease progression and identification of complications at 4 to 6 months or sooner as clinically indicated. Corticosteroids are an appropriate treatment option for acute exacerbation. Mechanical ventilation is not recommended for the majority of patients with respiratory failure due to progression of their disease. Symptom control (palliative care) focuses on reducing symptoms (e.g., cough and dyspnoea) and providing comfort to patients, rather than treating patients' disease. Advanced directives must be discussed in the ambulatory setting.[16]

1.13 Quality of life in patients with IPF

Though slowing of the disease progression and improvement in survival are crucial targets in IPF optimising the quality of life is judged by some patients with IPF to be as much or more important than their length of survival[74]. Quality of life is defined as a person's "holistic" evaluation of satisfaction with his own life in areas (domains) that he considers to be important[75]. Health-related quality of life (HRQL) incorporates the subjectively perceived impact of one's health – including aspects of well-being (or lack of thereof) in the physical, mental, emotional, social, and spiritual facets of life – on life domains of perceived importance[76]. HRQL is being measured by generic instruments or condition-specific instruments with the latter ones being tailored to patients with the disease of interest

which makes them more sensitive to underlying change than generic instruments [77].

Studies assessing HRQL in IPF as well as interventional trials in IPF assessing HRQL as secondary endpoints used generic or non-IPF respiratory specific instruments as there was no IPF-specific instruments available. Respiratory specific instruments included obstructive lung disease specific HRQL questionnaires: Chronic Respiratory Questionnaire, CRQ (assessing domains of dyspnoea, fatigue, emotional function and mastery) and Saint George Respiratory Questionnaire, SGRQ (assessing symptoms, activity and impact domains). Impairment in HRQL was demonstrated in many life domains of IPF patients but physical health was most negatively impacted; other domains were rated consistently lower compared to healthy controls or large sample of the general population including those that assess respiratory symptoms, energy levels, and degrees of independence[78].

Patients' views on how IPF affects their lives have been assessed in two studies. In a study the primary aim of which was assessment of the relevance of two instruments (SGRQ and WHOQOL-100) in IPF De Vries et al in three focus groups asked 10 patients with IPF (no definition of IPF cases given) directly of their views on how IPF affects their lives[79]. Swigris et al through focus groups and interviews performed a study in 20 patients of varying age with IPF with broad range of disease duration (from a short time prior to enrolment into the study to those listed for transplantation or those in hospice care) with all patients but one taking at least one medication specifically for IPF and 50% patients using continuous supplemental oxygen. The study specifically aimed at gaining further insight into the effects of IPF on patients' lives from their own prospective and at organising those effects into a structured conceptual framework along with assessing if the existing instruments adequately covered the elements of this framework and if they included items that might be irrelevant to patients with IPF. The results of both studies were consistent but due to possibly a larger number and more systematic and detailed analysis used by Swigris et al the additional effects of IPF were identified that were not previously reported. Patients noted that symptoms of breathlessness and cough were extremely bothersome and limited physical activity, social participation, travel, and sexual relations. Most patients had to rearrange their lives extensively because of the effects of IPF and were taking more time to prepare for the day, used a lot of mental

energy examining tasks to determine if they could complete them and were fearful of the impending need to depend on other people[76].

SGRQ

SGRQ is a self administered respiratory specific instruments designed for obstructive lung disease. It has 50 items which are used to calculate Total and three domain scores including Symptoms (distress caused by respiratory symptoms), Activity (physical activities that are caused or limited by breathlessness) and Impact (social and psychological effects of the disease). It is scored from 0 to 100 with 0 indicating the best health and 100 indicating the worst health; an increase in score over time shows worsening of health status. In 750 healthy adult control population the following scores were shown to be normal (mean ± SD): Total 7±7, Symptom 12±15, Activity 11±13, Impact 3±5[80]. A change in score of four units was shown to be consistent with clinically significant change in patient's health.

SGRQ has been used in a number of studies assessing HRQL and interventional trials in IPF. Chang et al in their study of 50 patients with ILD (24 patients with IPF) showed that SGRQ scores were particularly impaired in symptoms and activity domains (median 50.5 and 54.4 respectively reflecting a moderate rate of impairment) and that total score had a strong correlation (Pearson correlation coefficient of 0.45 to 0.66, $p<0.01$) with physiological parameters (in particular FEV1, FVC, DLCO, 6MWD and dyspnoea score)[81]. The degree of impairment was similar in 10 IPF patients in the study of De Vries et al and 41 IPF patients in the study of Nishiyama (Symptoms domain 47 and 40 respectively, Activity domain 55 and 45 respectively)[79, 82]. In the latter study TLC, DLCO, arterial partial pressure of oxygen at rest, the lowest oxygen saturation during exercise test, and the baseline dyspnoea index (BDI) score were significantly correlated with the total SGRQ score with a similar tendency being observed in each component. Nevertheless in stepwise multiple regression analysis, the BDI score was selected as the only factor significantly contributing to the total SGRQ score[82]. This is not unexpected as clinical observations show that patients with objectively equal physiological parameters can have different quality of life[78]. Of four HRQL questionnaires (SGRQ, CRQ, QWB and SF-36) SGRQ total score showed the strongest correlation with all objective parameters of

disease progression used in routine clinical practice – FVC % predicted (r=-0.45), DLCO % predicted (r=-0.55), 6 MWD (r=-0.66)[74].

Recently the first systematic examination of the longitudinal performances (over 6 months) of SGRQ in 129 patients with IPF (recruited into BUILD-1 study) was performed to establish if the scores are responsive to the change in the condition over time and if they can discriminate between patients whose status improves, deteriorates or remains unchanged over time. The authors found that subjects whose clinical status changed most (FVC ≥ 12%) had the greatest changes in SGRQ scores, subjects whose clinical status did not change (FVC change within 7%) had no change in the scores and those whose clinical status changed minimally (FVC change between 7 and 12%) had minimal changes in scores. This results support the validity of SGRQ for longitudinal use in IPF and allow to apply meaning to the changes in the scores[83].

It has also been assessed if SGRQ score could predict mortality in IPF. In a study of 87 IPF patients over an observation period of 44 ± 30 months univariate regression analysis showed that FVC % predicted, DLCO% predicted, baseline pO2 and the activity score of SGRQ (HR1.016, 1.004-1.029, 0.01) were significantly predictive of mortality; in multivariate analysis however only FVC % predicted was a significant predictor of survival therefore mortality can not be predicted from the SGRQ score (data in an abstract form only)[84].

Compared to IPF 736 patients with COPD were shown to have more significantly impaired Symptoms (67 units) and Activity (62 units) scores (the total score was 50)[80]. This is as opposed to the results in 28 patients with Scleroderma associated ILD (in the absence of pulmonary vascular disease) who showed total SGRQ score of 35 with Symptoms domain score of 27 and Activity of 51[85]. The latter study confirmed the validity of SGRQ in assessing the HRQL in patients with Scleroderma associated ILD and its good correlation with the 6MWD, HRCT scores and MRC though not PFT[85]. The use of SGRQ has been validated in asthma[86] and it has been shown that patients with asthma have a better QOL as indicated by a lower total SGRQ score of 37[87].

It is accepted that HRQL instruments provide information about IPF patients that is unique from that generated by the other measures of disease severity (both physiological and radiological)[74]. As a result investigators see HRQL as an important outcome to use when assessing the effectiveness of a particular intervention[83].

1.14 Treatments

Current best medical practice approach is suggested to be relying on clinical guidelines which are supported by evidence based recommendations. The best evidence comes from well designed prospective placebo controlled blinded clinical trials. Current evidence of treatment of IPF is difficult to interpret particularly when it refers to earlier studies prior to a new classification of IIP when a group of patients with the diagnosis of IPF was heterogeneous as included patients with other conditions which could be more responsive to treatment than true IPF with UIP histology. The interpretation was also hampered by methodological issues including study design problems: uncontrolled, not blinded type, inadequately powered, use of small number of patients, varying primary and secondary end points which are poorly reproducible or not standardised. Another issue is a selection bias which along with security of diagnosis at recruitment mentioned previously includes disease severity (mild/moderate versus severe) and its duration (recruitment of patients with disease duration of more than 3 years means representing a prevalent rather than incident group considering median survival of 3 years only) [88, 89]. The next problem was understanding of pathophysiological mechanisms involved in IPF and its transition from a hypothesis associated with inflammatory alveolitis to a hypothesis of fibroproliferation disorder. As a result most of conventional therapy approaches do not have sufficient evidence under it and in fact at present there is no therapy proven to improve survival or otherwise significantly modify the clinical course of IPF [14].

The above issues are being addressed in more recent studies designed and conducted in the last 10 years which are also more stringent in diagnostic inclusion criteria requiring either evidence of confident clinical-radiological diagnosis of IPF based on ATS/ERS consensus criteria [6] or in case of probable IPF – surgical lung biopsy compatible with UIP pattern. An important question here is timing of a central HRCT and histology review as it can divert diagnosis away from IPF in ≤25% of cases suggesting that ideally the review should occur before the enrolment into a trial [89].

It is now appreciated that the appropriateness of outcome measure should be judged according to its clinical relevance in its ability to identify either

improvement or a progression of the disease [89] and the likelihood that it could be used to detect statistically significant effects [90]. The importance of identifying the primary and secondary outcome measures in advance of trial commencement is emphasized to avoid misinterpretation of results.

Outcome measures include physiological measures, measures of mortality (defined as time until death; progression–free survival defined as time until a prespecified decline in a prespecified parameter, though does not measure mortality uses survival analysis methodology), measures of morbidity (acute exacerbations which have been shown to precede death and therefore are clinically relevant; hospitalisations; adverse events including pulmonary embolism, pneumonia and respiratory failure with changes in oxygen requirements; degree of dyspnoea), changes in radiological scores, measures of quality of life, composite measures which combine two or more measures [90]. Outcome measures that are able to demonstrate clear benefit to patient well-being should be given primary importance in later stage definitive trials (phase III trials) and while survival benefit would be clinically relevant and beneficial to patient well-being, achieving such a result would require well-designed, long-term studies with a large number of well-defined IPF patients [90].

Physiological measures are based on validated and reproducible pulmonary function testing the procedures for which are well defined and standardised in relevant guidelines. These measures in IPF include FVC, TLC, DLCO, measures of oxygenation (oxygen saturation measured by pulse oximetry, arterial blood gases, 6 minute walk distance and desaturation.

Lack of effective and proven treatment options in IPF leads to a constant search for new treatment options. This involves either search among already existing medication or a dedicated development of new agents. According to most recent ILD guidelines of the British Thoracic Society Interstitial Lung Disease Guideline Group form 2008 it is now recommended that all patients be considered for recruitment to high quality clinical trials of therapy and/or for lung transplantation if appropriate [14].

Overall current treatment strategies involve the following areas: conventional therapy (anti-inflammatory therapy with corticosteroids or its combination with immunosuppressive drugs), antifibrotic drugs, novel therapies, pulmonary rehabilitation, lung transplant, best supportive care

and symptomatic treatment (of cough, breathlessness, gastro-oesophageal reflux).

1.14.1 Conventional – Historical Treatments

Corticosteroids suppress neutrophil and lymphocyte migration into the lungs, decrease the level of immune complexes, and alter alveolar macrophage function [88]. The hypothesis of inflammatory alveolitis as a main pathophysiological mechanism in IPF led to use of prednisolone as first line treatment following its release for clinical use in 1948. This was also supported by trials data showing that up to 30% patients showed physiological and radiographic response with prednisolone in older studies. Nevertheless it was subsequently acknowledged that those trials involved heterogeneous group of patients including those who did not have IPF but a more inflammatory conditions with a higher degree of cellularity on biopsy. A Cochrane review of the role of corticosteroids alone in IPF identified no suitable randomised controlled or case-controlled trials and therefore there was no data available for inclusion in meta-analysis (all studies had inadequate methodologies); it concluded that there was no evidence that steroids prolonged survival or improved quality of life in patient with IPF [91]. Main adverse events with the use of corticosteroids include weight gain, hyperglycaemia, osteoporosis.

Corticosteroids have been assessed in combination with another immunosuppression drug with the greatest clinical impact being produced by its combination with Azathioprine. Azathioprine is a purine analogue converted into mercaptopurine which inhibits adenine deaminase which leads to impairment of proliferation of cells especially lymphocytes. Cochrane analysis identified only 2 case-controlled and 1 randomised controlled studies assessing the role of Azathioprine [92]. A randomised controlled study of Raghu which compared the addition of Azathioprine (3 mg/kg) to high dose prednisolone showed that there was no difference on lung function at 1 year of treatment but there was a statistically significant improvement in survival in the Azathioprine/Prednisolone group (14 patients) when adjusted for age (57% vs 23%, $p<0.05$) but only after 9 years of follow up and the survival curves did not diverge until 4 years [93]. Nevertheless the changes in lung function tests were not significant between the two groups and a longer than median survival could reflect patients with milder disease. Main adverse events of Azathioprine include

gastrointestinal side effects, myelosuppression, hepatotoxicity, increased risk of infection and skin cancer.

Cyclophosphamide is another immunosuppression drug that has been tested as an add on therapy to corticosteroid. It is an alkylating agent which suppresses lymphocyte function. There are no prospective randomised placebo controlled trials using Cyclophosphamide in a well defined IPF population. The most recent retrospective study of 82 patients with IPF by Collard et al showed no survival difference between patients treated with a combination of prednisolone and cyclophosphamide compared to untreated patients (median survival 1,431 days in treated group vs 1,665 days in untreated group ($p = 0.58$). Subgroup analysis in patients with presumed milder disease (FVC ≥ 60% predicted) or in patients with biopsy proven diagnosis showed no difference in mortality [94]. Main adverse events include myelosuppression, hepatotoxicity, increased risk of infection and of several cancers, haemorrhagic cystitis.

Colchicine inhibits fibroblast collagen formation and possibly increases collagen degradation. Though some in vitro and animal model studies suggested that it may slow fibrotic process several clinical studies failed to show significant difference in the rate of decline of lung function or improvement in survival. In the most recent randomised open-label parallel group efficacy study comparing a group of 32 patients treated with interferon gamma-1b and a groups of 18 patients with colchicine over 2 years no survival benefit was found with colchicine, with significant difference in FVC %predicted detected after 24 months treatment in favour of interferon gamma-1b (though not at 6 and 12 months of treatment) [95]. The main adverse events include gastrointestinal upset.

The literature on cyclosporin, methotrexate, chlorambucil, and D-penicillamine contains only case reports or small case series.

In summary there is no evidence to support the use of high dose corticosteroids, cyclophosphamide and colchicine in IPF as it does not improve survival or modify the clinical course of the disease. BTS ILD guidelines from 2008 suggest that prednisolone and azathioprine without N-acetylcysteine (see further) are not recommended; lower dose steroids (20 mg or less) or omission of azathioprine are very likely to be better tolerated but are entirely without evidence base [14].

1.14.2 Novel therapies

Current pathophysiological hypothesis suggests that IPF is a result of continuing patchy alveolar epithelial injury due to unknown agent followed by an abnormal wound healing. Therefore new treatment strategies have included agents that inhibit, the proinflammatory and profibrotic effects of oxidants and endothelins, blood coagulation and chemokines, tumour necrosis factor-alpha, transforming growth factor-ß, connective tissue growth, platelet-derived growth factor, tyrosine kinases. Phase I, II and III have utilised the following novel groups of treatment: antioxidant (N-acetylcysteine), immunomodulators (interferon-γ-1b), antifibrotic agents (pirfenidone), endothelin receptor 1 antagonists (bosentan), anticoagulants (Warfarin), tumour necrosis factor-alpha antagonist (etanercept), transforming growth factor-ß antibody, tyrosine kinase inhibitor (imatinib) (Table 1.6).

Trial, drug used	Drug action	Study design	Number of patients	Primary endpoint	Results (primary and secondary endpoints)	Reference
IFIGENIA N-acetylcysteine 600 mg tds	Antioxidant	Multinational, double-blind, randomised, placebo-controlled trial, 12 months,	182	Absolute change in VC and DLco at 12 months of treatment	Reduction in the rate of decline of both VC and DLco with the use of NAC. No difference in CRP score, dyspnoea, HRCT and SGRQ score.	[96]
Interferon-γ-1b	Cytokine with antifibrotic, antiproliferative, immunomodulatory effect	Multicentre double-blind, randomised, placebo-controlled trial, median 58 weeks	330	Progression free survival	No significant difference in the duration of progression free survival.	[97]
		INSPIRE multinational double-blind, placebo-controlled trial, 96 weeks	826 (ratio 2:1 IFG to placebo)	Survival time	No significant difference in survival at 64 weeks treatment. No effect on FVC, DLco, survival without lung transplantation, dyspnoea, QOL. NO significant difference in deaths	[98]
Bosentan	Dual endothelin receptor antagonist (Eta and ETb) which reduces collagen deposition in the lungs	BUILD-1 multinational double-blind, placebo-controlled trial, 12 months	158	6 minute walk distance	No significant difference in 6 minute walk distance. A trend in favour of Bosentan in time to death or disease progression and in dyspnoea and QOL	[99]
		BUILD-3 mean duration 19.9 months (event driven study)	616	Time to IPF worsening/acute exacerbation or death	No effect	[100]
Pirfenidone	Anfibrotic, antiinflammatory and antioxidant properties	Multicentre double-blind, randomised, placebo-controlled trial (Japan), 9 months	107	Change in the lowest oxygen saturation (SaO2) during 6 minute walk	No significant difference in change from baseline of the lowest SaO2. Statistically significant difference in VC at 9 months and in frequency of acute exacerbations; no difference in TLC. DLco, resting PaO2. No difference in dyspnoea or QOL.	[101]
		Multicentre, double-blind, placebo-controlled, randomised phase III clinical trial (Japan), 52 weeks	275	change in VC at 52 weeks Change in FVC %	Significant differences were observed in VC decline and in PFS (the secondary end-point)	[102]

		CAPACITY 2 if published by then, 72 weeks	779	predicted	Significant difference in percent predicted FVC change Treatment effect favouring Progression free survival, categorical FVC change and 6 minute walk distance.	[103]
Etanercept	Recombinant soluble human tumour necrosis factor-alpha receptor	Multinational double-blind, exploratory trial, 48 weeks	87	Change in FVC %predicted, DLCO %predicted, P(A-a)O2	No significant difference in change from baseline of FVC %predicted, DLco %predicted, P(A-a)O2. No difference in dyspnoea, HRCT scores, QOL, SGRQ scores	[104]
Imatinib	Tyrosine kinase inhibitor	Multinational double-blind, randomised, placebo-controlled trial, 96 weeks,	119	Time to disease progression or time to death	No significant difference in time to disease progression or time to death. No effect on change in FVC or DLco	[105]
Warfarin	Anticoagulant	Multicentre nonblinded randomised placebo controlled trial, median follow up 347 days	56	Overall survival time to death and hospitalisation free period	Survival to death was significantly better in an active group; no difference in hospitalisation free period	[106]
Sildenafil	Phosphodiesterase-5 inhibitor	Multicentre double-blind, randomised, placebo-controlled trial in patients with advanced IPF, 3 months	180	20% improvement in 6 minute walk distance at 3 months	No significant difference in a number of patients with 20% improvement in 6 minute walk distance. Significant improvement in degree of dyspnoea and quality of life, arterial oxygenation and DLCO. NO significant difference in deaths or rate of acute exacerbations.	[107]
Everolimus	A macrocyclic proliferation signal inhibitor with anti-fibroproliferative activity	Placebo-controlled, double-blinded, multicentre study, 3 years	89	Disease progression or death	more rapid disease progression in a everolimus group	[108]
BIBF1120	Tyrosine kinase inhibitor	Multicentre double-blind, randomised, placebo-controlled trial	432	Annual rate of decline of FVC	Trend towards a reduction in decline in FVC (p=0.06). Reduction in a number of acute exacerbations and improvement in quality of life (SGRQ), no change in TLC, DLCO and 6MWD (as secondary endpoints). NO significant difference in deaths.	[109]

Table 1.6 Recently conducted clinical trials in IPF

Antioxidant (N-acetylcysteine)

The rational for the use of N-acetylcysteine (NAC) in IPF is based on the evidence that patients with IPF have depleted levels of glutathion in the BAL fluid and in the epithelial fluid lining and that the depletion could be corrected by treating patients with oral NAC, this being associated with improvement in PFT [110]. Activated inflammatory cells release increase amount of reactive oxygen species which could contribute to parenchymal injury and interstitial fibrosis [111]. Glutathion is an important antioxidant in all tissues and is vital for cell metabolism and survival and tissues depleted of it are more susceptible to injury. NAC is used to increase the production of glutathione as it is capable of crossing cell membranes easily and can be converted to cysteine.

In the IFIGENIA trial (a multinational, double-blind, randomised, placebo-controlled trial) 182 patients were randomised to receive NAC 600 mg tds or placebo in addition to prednisolone and azathioprine over 12 months, of these 155 qualified for final analysis and 108 completed 12 months treatment. The primary end points were the absolute changes in vital capacity and DLco between baseline and month 12. The results showed that both parameters declined over time in both groups but NAC slowed the rate of loss of vital capacity by 180 ml (or 9%, p=0.02) and of DLco by 0.75 mmol/min/kPa (or 24%, p=0.003) [96]. Therefore it was a positive study in its primary end point, though there was no difference in the mortality between the two groups (though the study was not powered to detect a difference in mortality). NAC was well tolerated and the level of adverse events was similar in both groups. The study did not have a true placebo arm or an NAC alone arm but the study using these two additional arms is on the way at the USA at present.

This study has generated a weak recommendation (grade C) for the BTS ILD guidelines from 2008: prednisolone (tapering from 0.5 mg/kg to 10-20 mg/d) with azathioprine (2 mg/kg, maximum 150 mg/day) and NAC (600 mg three times a day) has been shown to have a significantly better treatment effect than prednisolone and azathioprine alone; prednisolone and azathioprine without NAC are not recommended [14]. 2011 Joint IPF guidelines recommend that the majority of patients should not be treated with this combination though it might be a reasonable choice in a minority [16] .

Immunomodulators (interferon-γ-1b)

Interferon-γ-1b is known to down-regulate the gene for transforming growth factor-ß (TGF-ß) and to inhibit proliferation of fibroblasts. As shown by Zeische et al in a preliminary study of long-term (1 year) treatment of 18 patients with IFG, exogenous IFG administered subcutaneously leads to a marked reduction of the levels of transcription of the genes for TGF-ß and connective tissue growth factor; this was associated with an increase in Total lung capacity and partial pressure of oxygen [112]. Subsequent multicentre double-blind, randomised, placebo-controlled trial of Raghu et al of 330 patients with IPF unresponsive to corticosteroid therapy alone showed a trend toward improved survival in the IFG group but the results did not reach statistical significance (median time to death or disease progression was 439 and 344 days in active and placebo group respectively, p=0.5). No treatment effect was observed on FVC(-0.2 litre in active and -0.16 litre in the placebo group), P(A-a)O2 (3.3 and 2.9 mm Hg respectively), DLco (-1.0 and 0.7 ml/min/mmHg respectively). However among patients with less severe impairment of FVC (≥ 62 % predicted) there was significant difference in survival in active group compared to placebo (12 versus 4%, p=0.04) [97].

Subsequent large scale multinational study by King et al enrolled 826 patients with moderate to mild IPF; patients were randomly assigned in a 2:1 ratio to receive 200 µg interferon gamma-1b (n=551) or equivalent placebo (n=275) subcutaneously, three times per week. The primary endpoint was overall survival time from randomisation measured at the second interim analysis; then the hazard ratio for mortality in patients on interferon gamma-1b showed absence of minimum benefit compared with placebo (1·15, 95% CI 0·77—1·71, p=0·497), that indicated that the study should be stopped. In terms of side effect profile constitutional symptoms occurred more frequently in an active group (6% versus 1%), none of them were graded as life threatening[98].

Endothelin receptor 1 antagonists (bosentan)

Endothelin-1 is an endogeneous vasoconstrictor with profibrotic properties that can modulate matrix production and turnover resulting in increased collagen synthesis and decreased interstitial collagenase production [99]. BUILD-1 study recruited patients with mild-moderate disease with a disease duration of under 3 years who were able to produce a 6 minute

walk distance of at least 150 m (and did not desaturate below 80%), and prescribed 158 patients with either 125 mg of Bosentan or placebo. Though the primary endpoint of 6 minute walk distance did not demonstrate significant difference (with median treatment effect of -17 m, p=0.226), a trend in favour of Bosentan was shown in secondary end-point of time to death or disease progression up to 12 months (HR 0,613; 95% CI 0.328-1.144, p=0.119); in patients with biopsy proven disease this reached statistical significance (HR 0.315; 95% CI 0.126-0.789, p=0.009). In terms of tolerability of bosentan the main difference was in higher frequency of hepatic aminotransferase elevation with 12.2% of active arm group needing to discontinue treatment as a result (versus none in placebo group) [99]. Subsequent event driven BUILD-3 study of 616 patients with IPF with mean duration of follow up of 19.9 months showed no effect on time to IPF worsening/acute exacerbation or death and no effect on quality of life[100].

Antifibrotic agents (pirfenidone)

A novel compound with combined anti-inflammatory, antioxidant and anti-fibrotic properties which was previously tested in experimental models of pulmonary fibrosis has been a part of 2 studies one of which was conducted in Japan and another one was multinational the final results of which are awaited.

The study conducted in Japan enrolled 107 patients with mild to moderate disease for 9 months. The study did not meet its primary end point of improvement of the lowest oxygen saturation during 6 minute walk (a mean increase from baseline of 0.47% in active group compared with a mean decrease of 0.94% in placebo arm, p=0.0722). However there was a significant difference in the change of vital capacity (-0.03 litre in active versus -0.13 litre in placebo group, p=0.0366) and a number of acute exacerbations (none in active group versus 5 in placebo group, p=0.0031) the latter leading to premature termination of the trial. A significant number of patients in active group had adverse events but only 15% discontinued treatment; a larger scale study was expected to clarify the safety aspect further. [101].

In subsequent large multinational study (CAPACITY programme consisting of two studies) of pirfenidone which used a variety of dose regimens its part where patients were assigned in a 2:1:2 ratio to pirfenidone 2403 mg/day (435 patients), pirfenidone 1197 mg/day (87 patients), or placebo

(174 patients) pirfenidone reduced decline in FVC (primary endpoint, (a mean 76 mls less decline than in placebo group)p=0.001). Mean FVC change at week 72 was -8.0% (SD 16.5) in the pirfenidone 2403 mg/day group and -12.4% (18.5) in the placebo group (difference 4.4%, 95% CI 0.7 to 9.1); the drug was shown to be safe and well tolerated[103]. A subsequent Cochrane review of the three studies using pirfenidone (including the CAPACITY study and study by Taniguchi[102]) suggested that pirefenidone reduced the risk of disease progression by 30% (HR 0.7, 95% CI 0.56-0.88).

Tumour necrosis factor-alpha antagonist (etanercept)

Tumour necrosis factor-alpha (TNFα) is a cytokine with proinflammatory and profibrotic properties the elevated levels of which were detected in the lungs of patients with IPF; pulmonary fibrosis develops in a mice expressing high levels of TNFα; in animal models of pulmonary fibrosis TNF antagonists inhibit pulmonary inflammation and fibrosis [104]. Etanercept, recombinant soluble human tumour necrosis factor-alpha receptor which binds to TNF and neutralises its activity, was used in a multicentre double-blind, exploratory trial of 87 patients over 12 months where all other treatment for IPF was forbidden. No statistically significant difference was achieved for any of the primary end points (Change in FVC %predicted, DLCO %predicted, P(A-a)O2); nevertheless subjects in the etanercept group showed a tendency toward reduced disease progression in multiple physiologic and functional endpoints (FVC % predicted, DLCO % predicted, PA-a gradient, TLC % predicted, O2 saturation). Etanercept was well tolerated and the rate of adverse events were similar between the two groups [104].

Tyrosine kinase inhibitors

Two tyrosine kinase inhibitors have been assessed in clinical practice. Imatinib is a tyrosine kinase inhibitor with activity against the platelet-derived growth factors (PDGFR-α and –ß), discoidin domain receptors (DDR1 and DDR2), c-kit and c-Abl; it was defined as a potent inhibitor of lung fibroblast-myofibroblast transformation and proliferation as well as extracellular matrix production through inhibition of PDFG and transforming growth factor-ß signalling; it was also shown to inhibit lung fibrosis in bleomycin models of lung fibrosis [105]. BIBF 1120 is a potent intracellular tyrosine kinase inhibitor and also targets platelet-derived

growth factors (PDGFR-α and –ß) as well as vascular endothelial growth factor receptors and fibroblast growth factors receptors. Since signalling pathways activated by these tyrosine kinase receptors were shown to be involved in lung fibrosis it was suggested that inhibition of receptors might slow the progression of IPF.

The trial by Daniels et al was an investigator initiated multinational double-blind, randomised, placebo-controlled study of 119 patients with IPF for the duration of 96 weeks. No significant difference in primary endpoint which was time to disease progression or time to death was identified. There was a difference in resting pO2 at 48 weeks but not at 96 weeks. There was also no effect on change in FVC or DLco, SGRQ score, overall mortality or CRP score. More imatinib treated patients discontinued treatment because of perceived drug related adverse event[105]. A phase 2 trial by Richeldi of 432 patients randomised to receive one of three doses of BIBF1120 (50, 100 or 150 mg twice a day) or placebo for the duration of 12 months showed that the group receiving 150 mg twice a day demonstrated preservation in lung function compared to placebo group (0.06 l versus 0.19 l annual decline respectively (p=0.06 with the closed testing procedure for multiplicity correction; p=0.01 with the hierarchical testing procedure); this was also associated with a lower incidence of acute exacerbations (2.4 vs 15.7 per 100 patient-years, p=0.02) and a decrease in SGRQ symptoms and activity score. Thus from a group of tyrosine kinase inhibitors there is a potential clinical benefit from BIBF 1120 that warrants its assessment in phase 3 clinical study.

<u>Phosphodiesterase inhibitor</u>

On the basis that patients with severe IPF have abnormalities in their pulmonary vasculature leading to decreased levels of resting and exercise induced production of nitric oxide and hence to pulmonary vasoconstriction and impaired gas exchange it was hypothesized that treatment with sildenafil (a phosphodiesterase-5 inhibitor which leads to vasodilatation) would improve walk distance, dyspnoea and quality of life in patients with severe IPF (mean DLco 26% and 27% predicted in active and placebo arms respectively). There was no significant difference in a proportion of patients with 20 or more % increase in 6 minute walk distance as a primary endpoint over 12 weeks of treatment. There was small but significant improvement in DLco, the degree of dyspnoea and total and symptoms domain score of SGRQ with the latter two being an important outcome for

a patient with advanced disease where no therapies are known to improve survival[107]. This study did not assess involve right heart catheterisation to exclude severe pulmonary hypertension. Symptomatic improvement in the absence of change in physiological parameters might still be important for the patients.

Anticoagulants (Warfarin)

Pulmonary thromboembolic disease can cause progression of IPF and could be clinically subtle, therefore it should be excluded as a cause of disease progression by the means of additional imaging (CT pulmonary angiogram). It is suggested that vascular injury with subsequent increased profibrotic state can contribute to the pathological process in IPF even in the absence of classical pulmonary artery thrombi. Kubo et al conducted a nonblinded trial comparing the effects of Warfarin and placebo in 56 patients treated with prednisolone (patients were switched onto the low molecular weight heparin daltaparin during hospital stay). The study showed significant improvement in survival in an active group (mortality hazard ration of 2.9, p=0.04) with a significant reduction in mortality associated with acute exacerbations (18 versus 71% respectively, p=0.008), though the incidence of acute exacerbations was similar [106]. Though this outcome is encouraging a number of methodological issues prevents the results of this small study being suggested for the use routine clinical practice: nonblinded nature of the trial, absence of the intention to treat analysis with a quarter of patients in placebo group withdrawing following randomisation but before treatment (it is possible these patients had a more severe disease with potentially higher mortality).

In summary only a few studies met their primary end-points, some of them demonstrated statistically significant results and trends in secondary end-points. This suggests that either a treatment broadly lacks efficacy but achieves a low average effect or, alternatively, is very selective but achieves important efficacy in selected subgroups [89]. Only the use of NAC (as an add on to prednisolone and azathioprine) and Pirfenidone led to statistically significant change in pulmonary function tests over time.

Current IPF guidelines based on review of evidence available by 30 May 2010 demonstrate no sufficient evidence to support the use of any specific pharmacologic therapy for patients with IPF though trials of some agents

suggested a possible benefit[16] .The implication of the guidelines recommendation for the patient is listed in the Table 1.7[113].

Strong yes

Implication for the patient: *most patients would want the following treatment intervention and only a small proportion would not.*

1) Long-term oxygen therapy in patients with IPF demonstrating clinically significant resting hypoxaemia
2) Lung transplantation in appropriate patients

Weak yes

Implication for the patient: *a majority of patients would want the following treatment intervention, but many would not. Not using them may be a reasonable choice in a minority.*

1) Corticosteroids for acute exacerbation of IPF
2) Treatment of asymptomatic gastro-oesophageal reflux
3) Pulmonary rehabilitation

Strong no

Implication for the patient: *most patients would not want the following treatment intervention and only a small proportion would.*

1) Monotherapy with corticosteroids
2) Colchicine
3) Cyclosporine A
4) Combined corticosteroid and immune modulator therapy
5) Interferon-γ
6) Bosentan
7) Etanercept

Weak no

Implication for the patient: *the majority of patients would not want the following treatment intervention, but many would, i.e. the following treatment interventions should not be used in the majority of patients with IPF, but may be a reasonable choice in a minority.*

1) Combined prednisone, azathioprine and NAC
2) Monotherapy with NAC
3) Anticoagulation
4) Pirfenidone
5) Pulmonary hypertension associated with IPF
6) Mechanical ventilation in patients with respiratory failure due to IPF

Table 1.7 Evidence based treatment recommendation for patients with IPF. "Yes" is for the use of specific treatment, "No" is against the use of specific treatment[113].

1.14.3 Current trials

A number of high quality interventional studies are now recruiting patients. Information about these studies could be obtained from a database located on a website called www.clinicaltrials.gov . This involves the assessment of effectiveness of NAC in a four arm interventional study (also including prednisolone/azathioprine/NAC arm, NAC alone arm and placebo alone arm) including 390 patients; and the assessment of effectiveness of Warfarin in 256 patients over a period 48 weeks by assessing the time to disease progression. There is also a number of small phase I and II pilot studies assessing the effects of already known drugs like Losartan, somatostatin analogue Octreotide, antifibrotic and anti-inflammatory drug thalidomide, as well as of new compounds like BIBF 1120 (triple angiokinase inhibitor that inhibits vascular endothelial growth factor receptor, platelet derived growth factor receptor and fibroblast growth

factor receptor) , CNTO 888 (an experimental drug currently being studied in cancer patients with solid tumours), IW001 (a drug designed to treat anti-Col (V)-mediated autoimmune diseases). Some studies are looking at the efficacy of certain drugs in patients with IPF associated with pulmonary hypertension as its complications (ambrisentan and treprostenil).

1.14.4. Lung transplantation

None of the existing medical treatment has been proven to improve survival in IPF. Unlike lung transplantation which at the moment is the only treatment that offers survival benefit [114]. IPF is the most frequent indication for a lung transplant among all patients with ILD and since it has the worst prognosis among the rest of IIP it is crucial to differentiate it from the other forms. According to the Registry report of the International Society for Heart and Lung Transplantation from 2008 [115] IPF was registered to be the second indication (20%) for transplantation between January 1995 and June 2007 after chronic obstructive pulmonary disease, COPD, (36%) and before cystic fibrosis (16%), α1-antitripsin deficiency emphysema (8%) and pulmonary hypertension (3.5%). At the same time with the introduction of the Lung allocation Score in 2005 a redistribution of indications was observed in North America with IPF becoming a leading indication (38%) followed by COPD (31%) according to the United Network for Organ Sharing [116].

Ideally, listing for lung transplant should occur when life expectancy is greatly reduced but nonetheless greater than expected waiting time for a suitable organ, and transplantation should be performed when life expectancy after transplantation exceeds life expectancy without the procedure [117]. Based on previous studies a range of prognostic factors for poor survival and indicating the reason for earlier referral for a transplant assessment for patients with IPF has been identified. This includes histological, physiological parameters at baseline and its subsequent change over time, radiological evidence of honeycombing. International guidelines for the selection of lung transplant candidates were updated in 2006 [117] and suggest the following guidelines for the referral and for transplantation:

Guideline for Referral

- Histologic or radiographic evidence of UIP irrespective of vital capacity.
- Histologic evidence of fibrotic NSIP.

- Histologic or radiographic evidence of UIP and any of the following:
  - A DLCO of less than 39% predicted
  - A 10% or greater decrement in FVC during 6 months of follow-up
  - A decrease in pulse oximetry below 88% during a 6-MWT
  - Honeycombing on HRCT (fibrosis score of > 2)
- Histologic evidence of NSIP and any of the following:
  - A DLCO of less than 35% predicted
  - A 10% or greater decrement in FVC or 15% decrease in DLCO during 6 months of follow-up

It is now recognised that since current medical therapies do not offer survival benefit the referral for transplant assessment should not be delayed by waiting for an assessment of response to traditionally used therapeutic trials.

Risk-unadjusted survival after transplantation for IPF is 73%, 56%, 44% and 36% at 1, 3, 5 and 7 years respectively which is similar to 81%, 61%, 48% and 38% for the same intervals for non-IPF indications according to the analysis of 469 patients from Cleveland clinic in a period between February 1990 and November 2005 [118].Nevertheless in propensity-matched patients the risk-adjusted survival was worse [118] among patients with IPF which has been observed in a number of other studies too.

Procedure type in patients with IPF, in other words single- or bilateral-lung transplant (SLT and BLT respectively) is a reason for a continuous discussion and institutional practices are variable. Since IPF patients often present acutely ill it was historically felt that SLT as more limited operation with less cardiac manipulation would provide a better perioperative morbidity and mortality, but as surgical techniques have been refined BLT has been increasingly used in patients with nonsuppurative lung disease with potential therapeutic benefits including a reduction in alveolar damage during reperfusion, improved pulmonary compliance and mechanics and avoidance of native lung pathology (with native lung demonstrating disease progression following SLT) [116] . There is a legitimate concern that BLT is not an optimal use of a limited resource [116] though at the same time it is suggested that the primary focus should be on an improvement of individual patient outcome [118]. The results of some earlier studies suggested that BLT was a risk factor for mortality in IPF patients (a study of Whelan et al of 830 patients transplanted between January 1995 and June 2002, [119]. More recent studies (since the BLT

started being used more frequently for IPF) have shown the opposite trend[116, 118].

In summary lung transplantation offers survival benefit to those patients suitable for a transplant. Careful assessment of disease severity and comorbidities is crucial and in suitable candidates the referral should take into account a number of physiological and radiological factors rather than a diagnosis alone and not be delayed while waiting for the effects of medical treatment.

1.14.5 Best supportive care

Best supportive care is a term originating from palliative care approach adopted in oncology. In IPF it could be used either alone or along side with medical therapy and referral for a lung transplant. It involves smoking cessation, treatment of breathlessness with and without resting or exercise induced hypoxia (with long term oxygen therapy in case of resting hypoxia or with nocturnal oxygen therapy in case of nocturnal desaturation, or with ambulatory oxygen in mobile and active patients with exercise induced hypoxia; this should be considered after an adequate formal assessment), treatment of cough (with opioids), antireflux therapy, withdrawal of treatment that does not provide benefit while could potentially cause harm, use of pulmonary rehabilitation. A recent Cochrane review showed that pulmonary rehabilitation in IPF is safe and that functional exercise capacity as measured by 6 minute walk distance improved significantly after a course with improvement in perception of dyspnoea and quality of life though long term benefit of the rehabilitation is not clear [120].

1.15 Complications/Associations

1.15.1 Lung cancer

There is an association between IPF and lung cancer and current evidence suggests that this might be independent of the effects of the cigarette smoking. Two large studies by Hubbard et al [121] and Le Jeune [122] both using GP databases and involving 890 and 1064 (incident cases) patients with IPF respectively (along with 1:4-6.6 control subjects) demonstrated an increased overall risk of cancer in an IPF population compared to the general population which was a result of an increased risk of lung cancer. The results of most recently published BTS study of CFA and lung cancer [123] with the follow up time of 11 years (between 1990 and 2001)

confirmed that the mortality rate from the lung cancer was much higher among IPF cohort compared to the number of expected deaths based on age-, sex- and period specific national lung cancer mortality rates with the standardised mortality ratio of 7.40 (95% CI 5.42 to 9.88), this was similar to the results of the study by Hubbard et al. – 7.31 (95% CI 4.47 to 11.93) [121]. In BTS study stratified lung cancer mortality analysis identified an increased risk among younger subjects, men, smokers (particularly current smokers) and those who reported asbestos exposure [123]. In both studies the observed increase remained when the analysis was restricted to current smokers only (RR7.46 CI 1.54 to 35.19). Thus the mechanisms for increased risk of lung cancer in IPF are unclear but may be related to the presence of fibrosis itself or other exposures associated with IPF including immunosuppression. Although the risk of lung cancer in IPF population seems to be independent of the smoking status smoking has been identified as a potential risk factor for IPF hence the implication for the smoking cessation. It has been suggested that taking into account the higher risk of lung cancer in IPF patients this cohort might be suitable for lung cancer screening [122].

1.15.2 PE

There is limited clinical data on the role of coagulation cascade in patients with IPF. There are reports of pulmonary embolism (PE) being a cause of death in patients with IPF in 0.37% [28] to 3.4% cases [124]. Danish nationwide study by Sode et al. showed that in the general population, ever-diagnosed venous thromboembolism was associated with idiopathic interstitial pneumonia, particularly among those never treated with anticoagulants: multivariate-adjusted hazard ratios for idiopathic interstitial pneumonia were 1.8 (95% confidence interval [CI], 1.7-1.9) in those ever diagnosed with venous thromboembolism, 2.4 (95% CI, 2.3-2.6) in those ever diagnosed with pulmonary embolism, and 1.3 (95% CI, 1.2-1.4) in those ever diagnosed with deep venous thrombosis only, compared with control subjects; corresponding hazard ratios in those ever diagnosed with venous thromboembolism stratified in those ever and never treated with anticoagulants were 1.4 (95% CI, 1.2-1.6) and 2.8 (95% CI, 2.4-3.1) [125]. The study by [106]. Kubo assessing the role of anticoagulant therapy in IPF showed no cases of PE or deep vein thrombosis among 56 patients admitted with IPF [106]. There is a report of a higher rate of PE in IPF transplant recipients with PE occurring in 27% (6/23) of patient with IPF

compared to 0 among all other (49 patients) with no apparent difference in patients functional status not any predisposition to embolic events through lack of activity or prolonged hospital stay [126].
Pulmonary embolism needs to be excluded as a cause of IPF exacerbation the nature of which is not clear since it is a treatable condition.

1.15.3 Pulmonary hypertension

Pulmonary Hypertension (PH) is diagnosed if the following haemodynamic parameters are present on right heart catheter: mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest or ≥ 30 mmHg on exercise, pulmonary capillary wedge pressure ≤ 15 mm Hg and pulmonary vascular resistance (PVR) ≥ 3 Wood units/m2. [127].
The majority of studies of PH in IPF involve patients referred for lung transplantation, where the prevalence is reported to be between 31.6 and 40.7% [128, 129]. Nevertheless even in this group of patients there is no correlation between the severity and extent of the underlying lung disease (as evidenced by the PFT measurements and composite physiological index) and the presence and severity of PH [128, 129]. In current classification of PH [127] PH associated with ILD is a part of the group called PH associated with lung disease and/or hypoxemia. Nevertheless there is a group of patients who have haemodynamic evidence of PH in the presence of only mild to moderate disease and in the absence of hypoxia[130].
Presence of PH is a negative prognostic factor for patients with IPF. Hamada et al. showed that 5 year survival in IPF patients with mPAP > 17 mmHg is lower (16.7%) than in those with mPAP < 17 mmHg (62.2%) [131].
There is a negative association between DLCO and the risk of PH as shown in studies by Lettieri and Hamada [128, 131]. Transthoracic echocardiogram (TTE) when used in patients with IPF has been shown to overestimate systolic PAP in patients with normal pressures and underestimate sPAP in patients with raised pressures [132], therefore the results should be interpreted with caution. Contrast enhanced computed tomography (combined with HRCT) is a convenient modality since it is able to demonstrate both lung parenchima, the size of right ventricle and a ratio of pulmonary artery to ascending aorta diameter.
Treatment of PH in IPF involves treatment of underlying lung disease and correction of hypoxia as well as potential consideration of drugs used for

the treatment of idiopathic PH, but so far only small studies have been performed in patients with a combination of PH and IPF therefore larger studies are required before definite recommendations are provided.

1.15.4 Respiratory Failure

Respiratory failure in IPF could be a consequence of a natural cause of the disease and its progression and be present only on exercise or on exercise and at rest (and in this case contribute to the development of right heart failure), or be acute. Management of respiratory failure depends upon the clinical context. In patients with chronic respiratory failure there is no evidence according to Cochrane review that oxygen therapy improves quality of life or long-term survival [133]. According to BTS guidelines [14] in the absence of suitable controlled studies of long-term, short burst or ambulatory oxygen therapy in ILD recommendations are consistent with those published by the BTS Working Group and involve the following: patients with persisting resting hypoxaemia PaO2 at or below 7.3 kPa (55 mm Hg) or below 8 kPa with clinical evidence of pulmonary hypertension and who are breathless should be considered for palliative oxygen at home delivered by oxygen concentrator. Patients with exercise induced hypoxia blow 90% who are mobile and breathless should be considered for ambulatory oxygen if improvement in exercise capacity and/or less breathlessness could be demonstrated by formal ambulatory oxygen assessment. Nocturnal hypoxaemia is common, its role in development of pulmonary hypertension is not clear and there is no evidence that supplemental oxygen is useful.

Patients with IPF can present with acute respiratory failure which could be due to respiratory infection, pulmonary embolism, pneumotorax or congestive cardiac failure, or could be a result of acute exacerbation. Current diagnostic criteria of acute exacerbation include previous or concurrent diagnosis of IPF, unexplained worsening or development of dyspnoea over 30 days or less, new bilateral radiographic opacities, no evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage, exclusion of another identifiable aetiology. Irrespectively of the cause such patients are often considered for referral to the intensive care unit (ICU). Case series in IPF have demonstrated a nearly 100% hospital mortality rate in intubated patients in the short term even if discharged from ICU irrespectively of the cause of admission [14, 134].

1.17 Mechanisms of Pulmonary Fibrosis

The pathogenesis of IPF is complex and three major hypotheses for the pathogenesis of IPF have emerged: dysregulated epithelial-mesenchymal interactions, aberrant angiogenesis and the TH1/TH2 cytokine imbalance [135]. Phenotypic changes in alveolar epithelial cells are early and consistent features of IPF, suggesting that alveolar epithelial cell injury and apoptosis are key to the pathogenesis of IPF. Epithelial-mesenchymal interactions between altered epithelial and mesenchymal phenotypes results in dysregulated interactions between these cellular compartments. The cause(s) of alveolar epithelial cell injury associated with IPF is unknown, and host responses to tissue injury are likely to involve a combination of host-specific, genetic and environmental factors including latent viral infections and cigarette smoke; genetic factors such as mutations in surfactant protein C and polymorphisms of tumour necrosis factor-alpha (TNF-α) are seen with increased frequency; polymorphisms in transforming growth factor-β1 (TGF-β1) are associated with more rapid progression of IPF. In response to an unknown stimulus, alveolar epithelial cells in IPF develop a phenotype characterized by increased apoptosis, dysregulated proliferation, impaired regeneration/differentiation and perhaps impaired migration. atypical and apoptotic epithelial cells are fibroblastic foci containing activated contractile myofibroblasts. Alveolar epithelial cells elaborate increased TGF-β1 and endothelin-1 along with decreased levels of PGE2. Mesenchymal cells in this alveolar microenvironment acquire a contractile, synthetically active myofibroblast phenotype. Myofibroblasts retain the capacity to proliferate and are resistant to apoptosis while secreting large amounts of extracellular matrix proteins, soluble growth factors/cytokines and extracellular oxidants, its differentiation could be induced by such soluble factors as endothelin-1, thrombin, and thrombospondin-1. Soluble mediators and the insoluble matrix elaborated by these myofibroblasts may, in turn, lead to aberrant reepithelialization that perpetuates a feed-forward cycle. IPF fibroblasts/myofibroblasts and alveolar epithelial cells contribute to an imbalance in angiogenic chemokines that may promote neovascularization and aberrant angiogenesis in IPF.

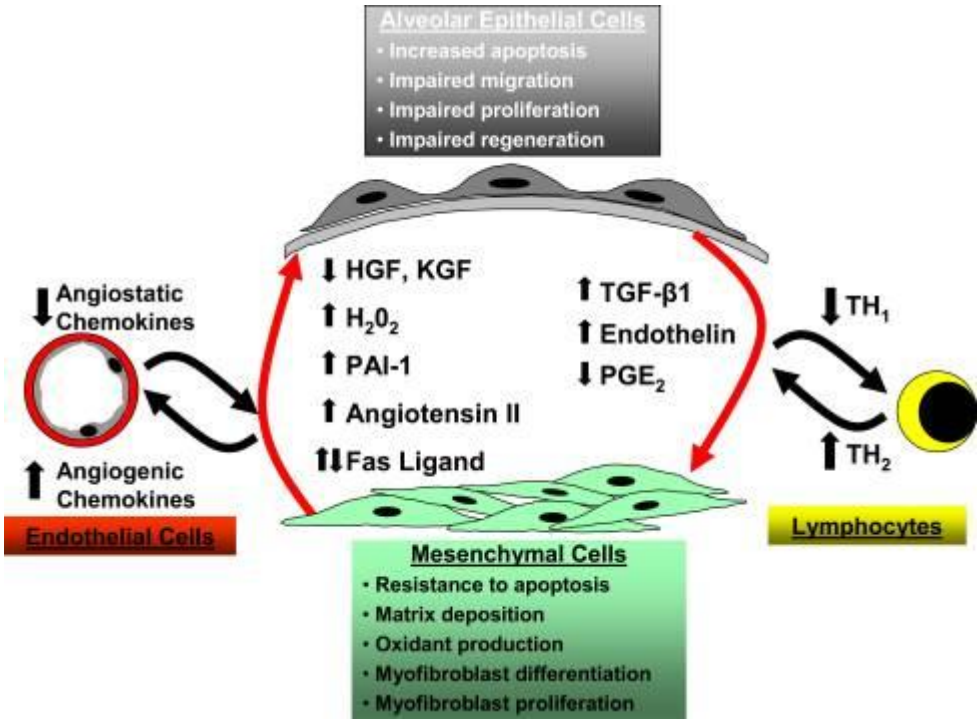


Figure 1.11 Though the leading theory is the one of fibroproliferation there is evidence of inflammatory cell involvement with an alveolar septal infiltrate of lymphocytes, plasma cells, and histiocytes associated with type II pneumocytes hyperplasia (ATS/ERS consensus Classification). One of the new hypotheses regarding the role of inflammation now focuses more on the balance between a “pro-inflammatory” TH1 cytokine profile (such as interferon gamma (IFN-γ) and interleukin (IL)-12 which tend to suppress fibrotic responses) and a “pro-fibrotic” TH2 cytokine profile (such as IL-4, IL-10, IL-13 that promote fibrotic response) suggesting an inappropriate shift in the TH1/TH2 cytokine balance, favoring the TH2 profile, results in the development of fibrotic disease in response to a chronic or persistent pathogen/antigen stimulation. It is thought that free radicals are involved in the role of fibrogenesis of human lungs in ILD and the activation of inflammatory cells leads to the production of reactive oxygen species: a strong expression of nitrotyrosine (a byproduct of protein nitration caused by a potent oxidant peroxinitrate) and nitric oxide synthase is seen in macrophages, neutrophils and alveolar epithelium of lungs of patients with early to intermediate stage of IPF compared to normal control subjects [135].

1.18 Biomarkers for IPF and the role of angiogenesis

Diagnosis of IPF, monitoring of disease activity and assessment of prognosis is based on the use of clinical, radiological, lung function and pathological data. Along with this some soluble markers detected in serum have been studies including enzymes, cytokines, adhesion molecules, collagen-related products and products of type II epithelial cells. Type II epithelial cells are a major source of KL-6, surfactant protein-A (SP-A) and surfactant protein-D (SP-D). Studies showed that serum SP-A and SP-D were significantly elevated in patients with IPF and could distinguish patients with IPF from patients with sarcoidosis, beryllium lung disease and healthy controls and that SP-D correlated with radiographic abnormalities in patients with IPF [2](Greene et al.). Studies by Yokoyama and Satoh demonstrated KL-6 to be a predictor of survival with levels above 1000 u/ml at diagnosis to be a negative predictor; KL-6 levels inversely correlated with DLCO and FVC [136, 137].

Angiogenesis, defined as a process of new blood vessels growth[138], is an important part of wound healing process and is affected by the balance between various factors – mainly chemokines that promote or inhibit angiogenesis[139]. The role of angiogenesis in IPF is controversial. In lung tissue increased angiogenesis can aggravate pulmonary fibrosis but prevent pulmonary hypertension[140]. On the other hand it is not clear if angiogenesis is an essential part of fibrogenesis or a necessary compensatory mechanism to prevent excessive fibrosis[141]. In rodent models angiogenesis was shown to be a result of lung injury [142] and to contribute to fibroproliferative and extracellular matrix deposition observed in IPF[143]. Mice deficient of angiogenic chemokine CXCL10 develop increased pulmonary fibrosis following bleomycin-induced lung injury[144]. An aberrant vascular remodelling occurs in lungs affected by IPF but fibrotic areas have fewer blood vessels, whereas adjacent nonfibrotic tissue is highly vascularised[145]. Capillaries within the fibroblastic foci are almost absent suggesting that the fibrotic process in IPF does not require neovascularisation[146]. The levels of potent angiostatic factors in patients with IPF are increased[147]. Therefore it is possible that an imbalance between angiogenic and angiostatic factors contributes to the development of IPF[138].

Angiogenesis as one of multiple pathways of pathogenesis of IPF was targeted in clinical trials using tyrosine kinase inhibitors (imatinib[105] and BIBF 1120[109]) which affect platelet-derived growth factor receptors α

and β, vascular endothelial growth factor receptors and fibroblast growth factor receptors. Whilst treatment with Imatinib over 96 weeks failed to demonstrate the effect on disease progression, treatment with BIBF1120 in a dose of 150 mg twice a day for 12 months led to preservation in lung function compared to placebo group (as described in section 1.14.2). Vascular endothelial growth factor (VEGF) is a potent mediator of vascular regulation in angiogenesis and vascular permeability [148]. Plasma concentrations of VEGF correlate with HRCT thoracic scan fibrosis scores [149]. In support of its role in the development of pulmonary fibrosis, a VEFG receptor antagonist attenuated bleomycin-induced lung fibrosis in a murine model [150]. Although its concentration is higher in patients with progressive disease (defined as those with a 10% change in FVC after 6 months)[149], the usefulness of VEGF as a survival indicator has not been evaluated. Along with the use for assessment of diagnosis and disease progression biomarkers have also been used as a marker of response to treatment when the levels of KL-6, SP-A and SP-D decrease slowly indicating favourable response with regard to down regulation of lung inflammation but not necessarily a relief in patient's symptoms [151].

1.19 Health economics analysis

During the past 30 years, health care expenditures have risen dramatically throughout the world[152]. In the UK total expenditures as a percentage of gross domestic product have increased from 4.6% in 1972 to 7.7% in 2003; during the same time period it increased in the USA from 7.4 to 15%, in France from 6.2 to 10.1% and in Germany from 7.1 to 11.1%[153, 154]. In response to these increases, countries around the world have been investigating methods to control health care cost. It is important to undertake analysis of the costs and savings of implementing a new medication or an existing medication for a new indication; this information could be obtained from clinical trials that establish the efficacy and effectiveness through the economic evaluation of medical therapies. The UK Medical Research Council and US National Institute of Health routinely request the inclusion of economic assessments prior to funding large scale multicentre trials[152].

Economic evaluation (in other words efficiency evaluation) is defined as the comparative analysis of alternative courses of action in terms of both their costs (inputs) and consequences (outputs); therefore, the basic tasks of any economic evaluation are to identify, measure, value, and compare

the costs and consequences of the alternatives being considered[155]. The economic evaluation is considered to be full if it includes each of the following three analyses: cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA).

The resources consumed by health care programmes are considered to comprise four components – health care sector, patient/family sector, productivity losses, other sectors[155], the latter three could be looked at as societal costs. The health care sector would consist of the items like medications, equipment, hospital admissions, physician visits. The patients and family resources would consist of out-of-pocket expenses in travelling to hospital, expenditures in the home (for example adapting a room to accommodate an oxygen concentrator), and time spent by a patient on receiving care or by a family member on providing care. This links with associated loss of productivity. The resources in other sectors depend upon the nature of the health care programme and an example could include nursing home care.

CEA is of most use in situations where a decision maker, operating with a given budget, is considering a limited range of options within a given field; both costs and consequences of health programmes or treatments are examined[155]. The Panel of Cost Effectiveness in Health and Medicine has recommended the use of quality-adjusted life years (QALYs) as the principal measure of effect in CEA[156]. At the same time physiological outcomes could also be used as measure of effectiveness. There are two methods for developing point estimates for the difference in cost and effect – the cost-effectiveness ratio and net monetary benefit.

The incremental cost-effectiveness ratio is defined as:

ICER = CostA – CostB / EffectA – EffectB

Where cost A and B are the arithmetic mean costs for treatment groups A and B, and Effect A and B are the arithmetic mean effect for treatment groups A and B[152]. Costs are usually described in monetary units while benefits/effect in health status is measured in terms of quality-adjusted life years (QALYs) gained or lost. ICER provide policy makers with information on where resources should be allocated when they are limited[155]. ICER is the most popular method of CEA but since it does not give the information on the size or scale of treatments an alternative summary measure has been provided in a form of net monetary benefit where the value is being estimated by comparing the resulting cost-effectiveness ratio to the willingness to pay[152]. The therapies with a net benefit of greater than 0, in other words therapies with ICERs that are less than the willingness to pay, should be adopted[152] (Figure 1.11)

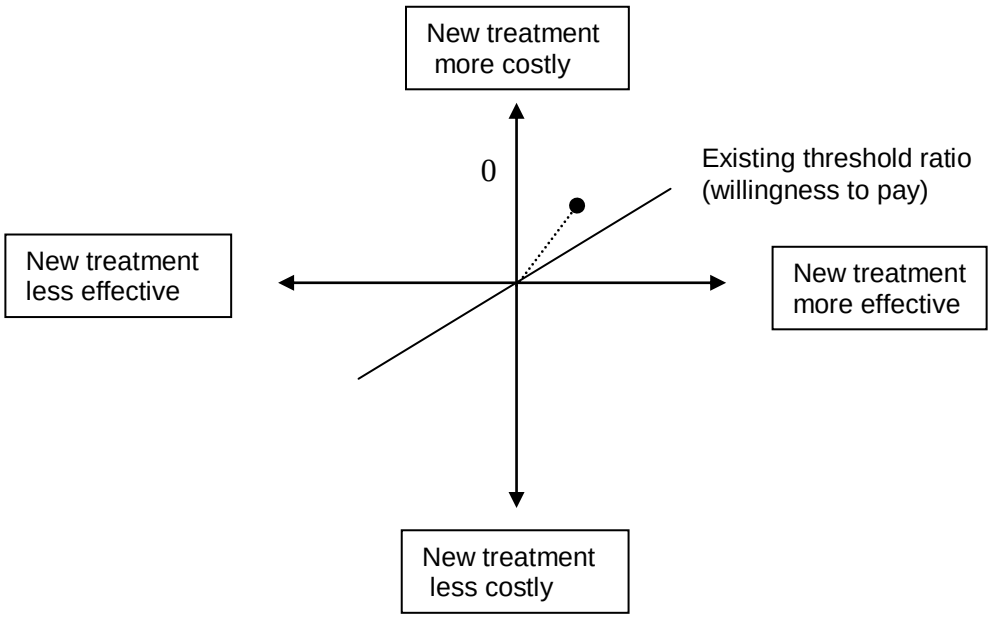


Figure 1.12 Threshold cost-effectiveness ratios on the cost-effectiveness plane[155]. Incremental cost-effectiveness ratio is a slope of the line joining the point determined by costs and effects of the new programme.

CUA is considered to be an especially useful technique as it allows for health-related quality of life adjustments to a given set of treatment outcomes, and at the same time provides a generic outcome measure

(usually expressed as QALYs) for comparison of costs and outcomes in different programmes. The term utility is a synonym to preference; the more preferable the outcome, the more utility is associated with it[155]. A widely used method of measuring preferences is the use of pre-scored multi-attribute health status classification systems. The most used are Quality of Well-being, Health Utilities Index, EQ-5D, and Short Form 6D. EQ-5D questionnaire includes 5 attributes (mobility, self-care, usual activity, pain/discomfort, anxiety/depression. Each attribute has 3 levels: no problem, some problem, major problem; thus there are 243 possible health states and with additional “unconscious” and “dead” it makes up a total of 245. Preferences for the scoring function were measured on a random sample of approximately 3000 adults in the UK[157]. The scoring system is between 0.0 (dead) and 1.0 (perfect health), this represents quality weights (that is used in the vertical axis of Figure 1.12). The advantage of the QALY as a measure of health output is that it can at the same time capture gains from reduced morbidity (quality gain) and reduced mortality (quantity gain), and integrate this two into a single measure[155]. Conventionally the quality adjustment weight for each health state is multiplied by the time in each state and then summed to calculate the number of QALYs. As per an example in Figure 1.13 without the health intervention an individual’s health-related quality of life would deteriorate according to the lower curve and an individual would die at time Death 1; with the health intervention the individual would deteriorate more slowly, live longer, and die at time Death 2; the area between the two curves is the number of QALYs gained by the intervention with part A being the amount of QALY gained due to quality improvement (that is the quality gain during the time that the person would have been alive anyhow) and part B being the amount of QALY gained due to quantity improvement (that is, the amount of life extension, but adjusted by the quality of that life extension)[155].

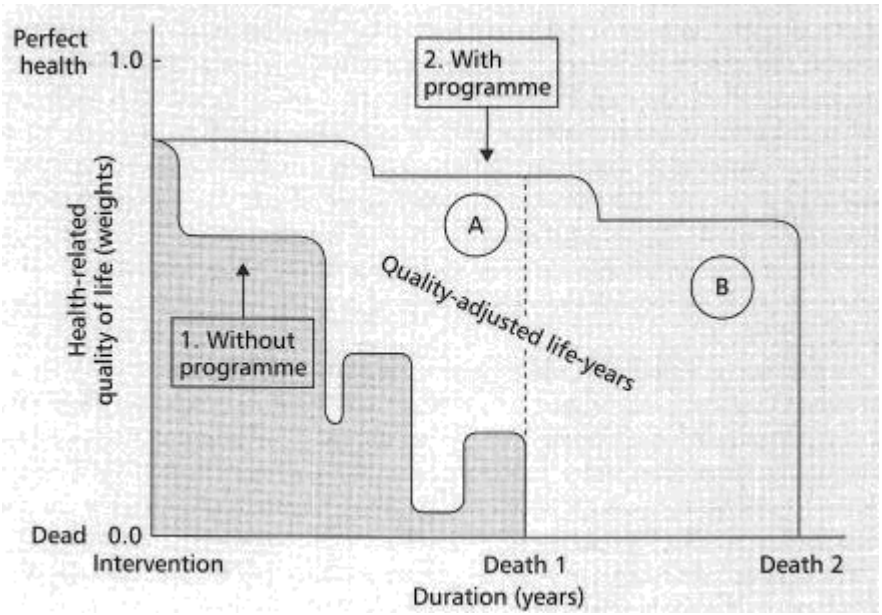


Figure 1.13 QALYs gained from an intervention[155]

Analysis that measures both costs and consequences of alternatives in monetary units is called cost-benefit analysis (CBA); CBA provides an estimate of the value of resources used up by each programme compared to the value of resources the programme might save or create[155]. A comprehensive CBA of health care interventions would use willingness-to-pay for health benefits approach to value health benefits[155].

In each of these components their quantities would be measures and the total cost calculated by multiplying the quantities by the relevant prices. If an economic study is being conducted alongside the clinical trial, data on the resource quantities could be collected in case report forms by asking patients or by providing them with a diary[155]. The pragmatic approach to costing is to take existing market prices. In the UK the data on outpatient visit fees is provided in NHS Reference Costs[158] which give average costs and dispersion statistics for the first and subsequent outpatient attendances by speciality[152]. The drug prices are obtained from the national formulary lists[159].

Economic evaluation can be performed by using either patient-level data (usually collecting data alongside randomised clinical trials) or decision analytic modelling. Many countries have a formal requirement for provision of safety and efficacy data for health care interventions including administration of drugs prior to product licensing; the accepted standard for such data collection is the randomised control trial[152]. It is an accepted practice to collect economic data alongside clinical data in a

clinical trial. The advantages would be that having patient-specific data on both costs and outcomes is potentially attractive for analysis and internal validity, also the cost of collecting the economic data is only modest compared to the cost of the main part of the trial[152]. When economic analysis is a part of a clinical study a number of limitations arise. The relevance of a placebo controlled study depends upon whether the new drug is an adjunctive therapy or a substitute to existing therapy; trials comparing against placebo to no therapy would not be a relevant comparison for the economic question as they do not reveal the incremental impact of the new therapy on population health[152]. Inadequate follow up data in patients who had to discontinue intervention prematurely with no record of longer term effect on health outcome and costs is another problem. Current statistical methods with missing data imputation help to resolve this problem. Another way of assessing patient-level data is designing a pragmatic trial specifically for economic evaluation of treatment/programme under the real world conditions that would dominate once the intervention was in routine use; these trials still use the concept of random allocation to treatment to minimise bias but patients and physicians are not blinded to treatment.

Analytic modelling offers a means of combining available evidence from a range of sources (including interventional and epidemiological studies) rather than relying on a single study[155]. It also helps to deal with another problem of patient-level data when a positive effect on an intermediate disease marker is not sufficient to show cost-effectiveness and impact on final health outcomes like morbidity and mortality have to be assessed indirectly by using epidemiological data in a decision model[155]. The main elements of the analytic modelling are probabilities and expected values. A probability is a frequency of an event in a given sample of population and is a number showing if an event will or will not occur. As prior to treatment it is not known which outcome (improvement/deterioration/no change) a specific patient is to follow the concept of probabilities is used to express the likelihood of each occurring[155].

One of the methods for summarizing information on uncertainty in cost-effectiveness is cost-effectiveness acceptability curve (CEAC) which is produced from the combined distribution of incremental costs and incremental effects. A CEAC shows the probability that an intervention is cost-effective compared with the alternative based on the observed data

for a range of maximum monetary values that a decision-maker might be willing to pay for a particular unit change in outcome. Cost-effectiveness acceptability curves were introduced as an alternative to producing confidence intervals around incremental cost-effectiveness ratios (ICERs), which can be statistically challenging; they are estimated by non-parametric bootstrapping of the observed data[160].

Public decision-making bodies like National Institute for Clinical Excellence (NICE) apply threshold cost-effectiveness ratios. NICE has generally enabled to keep the incremental cost per QALY below £30,000[155].

The formal use of economic evaluation in health care decision making is still quite limited though it has been used in a much wider range of situations both at a central level where a single agency or an organisation make decisions for the whole health care system or at a local level; the evidence of use and usefulness of economic evaluation is currently stronger for the local level[155]. It is shown that those responsible for formulating NICE guidance have to make judgements both about what is good and bad in the available science (scientific value judgements) as well as what is good and bad for society (social value judgements)[161].

1.20 Aims of the thesis

The aim of this thesis is to perform a number of studies to assess:

- The accuracy of diagnosis of IPF in clinical practice through an audit project
- The efficacy, safety and cost effectiveness of co-trimoxazole in patients with fibrotic interstitial pneumonia through interventional clinical trial
- The role of predictors of outcome in IPF (clinical, physiological and biomarkers) through an observational study analysing the role of exhaled nitric oxide and VEGF in IPF as well as through a study establishing predictors of death and FVC decline

Chapter 2

Methods

Study 1 – Audit (Chapter 3)

Study 2 – Clinical trial of the investigational medicinal product (CTIMP) using Co-trimoxazole (TIPAC) (Chapter 4)

Study 3 – The role of exhaled nitric oxide and plasma vascular endothelial growth factor in IPF study (Chapter 5)

Study 4 – Predictors of death or FVC decline study (Chapter 6)

2.1. Subjects

Study 1 was an audit project aimed at assessing the accuracy of the diagnosis of Idiopathic Pulmonary Fibrosis. The rationale for the audit was the following: Idiopathic pulmonary fibrosis (IPF) is a condition of unknown aetiology; ATS/ERS consensus statement on IPF includes the following statement as a major criterion for the diagnosis: exclusion of other known causes of interstitial lung disease, such as drug toxicities, environmental exposures, and collagen vascular diseases. Therefore a careful diagnosis is based on good history taking and exclusion of identifiable potential causes. Exclusion of occupational, drug induced lung disease is based on careful occupational history (including details of employer, duration of exposure, protection used), spouse employment and drug history taking. This should be documented in case notes. Exclusion of collagen vascular disease is based on clinical assessment and is supported by testing blood samples for the presence of autoantibodies. Therefore every patient with suspected IPF should have their autoantibodies checked to exclude collagen vascular disease as a cause of their pulmonary abnormality even in the absence of its clinical features. It was aimed at reviewing medical notes (the record of the initial visit after the referral to the respiratory clinic) of all patients with the diagnosis of IPF registered under the respiratory clinic care on 1st March 2008 at the Norfolk and Norwich, Ipswich and James Paget Hospitals.

Patients with clinical labelled diagnosis of fibrotic idiopathic interstitial pneumonia with HRCT scan features compatible with Usual Interstitial Pneumonia (UIP) or Fibrotic Non-specific Interstitial Pneumonia (NSIP) were invited to participate in studies 2 and 3. Assessment of eligibility of

diagnosis of IPF was based on the following criteria adapted from the ATS/ERS consensus statement on IPF [5]:

Major Criteria (All present):

- Exclusion of other known causes of interstitial lung disease, such as drug toxicities, environmental exposures, and collagen vascular diseases
- Abnormal pulmonary function studies that include evidence of restriction with or without impaired gas exchange
- Bibasal reticular abnormalities with minimal ground glass opacities on HRCT

Minor criteria (two out of three features):

- Insidious onset of otherwise unexplained dyspnoea on exertion
- Duration of illness 3 months
- Bibasal inspiratory crackles (dry or ‘‘Velcro-’’ type in quality)

All patients were recruited following provision of patient information sheet and at least 24 hours to consider participation.

2.2 Ethical approval

Study 1 was approved by each individual site audit department.

Study 2 REC reference 07/MRE05/45; The efficacy and safety of co-trimoxazole therapy in patients with idiopathic interstitial pneumonia, original approval 04/09/2007.

Study 3 REC reference 09/H0310/78; Are alveolar nitric oxide and plasma VEGF markers of disease severity and lung function decline in patients with idiopathic pulmonary fibrosis; original approval 07/12/2009.

Study 4 was performed alongside the study 2

For studies 2 and 3 an approval also was sought from the local Research Ethics committee and Research and Development department of each Trust. For study 2 an approval was sought from the Medicines and Healthcare products Regulatory Agency (MHRA) (2007-002324-15) and the study was registered on the International Standard Randomised Controlled Trial Number Register (ISRCTN22201583). All subsequent amendments to the protocols and patient information sheet were approved by the Ethics Committee and MHRA. Initial submission and submission of subsequent approvals and progress reports for study 3 was done by the MD student.

Studies 2 and 3 were performed according to the principles of Good Clinical Practice. In January 2011 co-trimoxazole study underwent a review of the Medicines and Healthcare products Regulatory Agency as a part of an inspection of its sponsor the University of East Anglia with no critical issues identified.

2.3 Blinding

In study 2, the double-blind placebo-controlled clinical trial of the investigational medicinal product (CTIMP), formulation and manufacture of the IMP placebo tablets to resemble Co-Trimoxazole 400/80 mg according to the rules and guidance for Pharmaceutical manufacturers and Distributors 2002 and the Medicines for Human Use (Clinical Trials) regulations 2004 was a responsibility of the Guys and St Thomas' Pharmacy department. Blinding of patients and investigators was provided by the use of tear off slips that were removed by pharmacy department at the stage of dispensing the IMP to a patient. Emergency unblinding procedures were put in place.

2.4 Instructions

In studies 2 and 3 patients were provided with patient information sheet describing the rationale for conducting the study, advantages and disadvantages of taking part in it and a comprehensive list of side effects and interactions was included as well based on Summary of Product Characteristics in CTIMP using Co-trimoxazole. On recruitment into study 2 (Co-trimoxazole study) patients were given a verbal instruction of how to take the study drug and instructed to discontinue it in case of experiencing sudden wheeziness, breathlessness; swelling of the eyelids, face or lips; or blisters and a skin rash. All patients were provided with a contact number for emergency situations. It was required from patients to exhibit at least 80% compliance with the study medication as assessed by the pharmacy drug returns in order for the data to be included into per protocol analysis.

2.5 Physiological outcomes

2.5.1 Pulmonary function tests

Change in FVC over 12 months treatment was a primary endpoints in the study 2 using Co-trimoxazole. Spirometry was measured according to the Standardisation of spirometry guidance [162]. Method used to measure lung volumes was depending upon the equipment and procedure used at individual study site and could involve body plethysmography, nitrogen washout or helium dilution. It is a standard approach to use the best out of three consistent measurements. Calibration of equipment was done according to the individual study site policy.

In study 3 (exhaled NO) lung volumes were measured by body plethysmography using a pneumotachograph (Jaeger Master Screen Body, Germany). Single breath breath-holding test was used for the measurement of diffusion capacity. Patients were seated wearing nose clip during the test. The pneumotachograph was calibrated daily using a 3 litre precision syringe.

2.5.2. 6 minute walk test

Changes in 6 minute walk test distance and desaturation over 12 months treatment were secondary endpoints in the study 2 using Co-trimoxazole and the test was performed according to the ATS Statement Guidelines for the Six-Minute Walk Test [163]. The test was self-paced and measured the distance that a patient could quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). Where possible (unless patients had progressive disease over 12 months of study drug intervention with progressively reducing physical capacity or had interventions that prevented them from performing the test, for example hip replacement) it was aimed at obtaining measurements at baseline, 6 months and 12 months. It was aimed at preserving the oxygen supplementation status throughout the study for the consistency of the results unless it was felt to be unsafe.

2.6. MRC breathlessness score

For study 2 and 3 Medical Research Council (MRC) dyspnoea scale was used for the estimation of impact of dyspnoea on daily activities and could be used for the assessment of the severity of IPF and of effect of treatment. The scale ranges from level 1 (Not troubled by breathlessness except on strenuous exercise) to level 5 (too breathless to leave the house or breathless when dressing or undressing).

2.7 Full blood count, Urea and Electrolytes and Liver function tests

For study 2 venous blood was taken for measurement of Full blood count, Urea and Electrolytes and Liver function tests and was analysed at local pathology departments for safety indication.

2.8 St Georges Respiratory Questionnaire (SGRQ)

For study 2 SGRQ was used which was a patient completed questionnaire consisting of two parts: part I produces the Symptoms score (the effect of

respiratory symptoms, their frequency and severity), and part 2 the Activity (activities that cause or are limited by breathlessness) and Impacts scores (social functioning and psychological disturbances). A Total score is also produced which summarises the impact of the disease on overall health status. Scores were expressed as a percentage of overall impairment where 100 represented worst possible health status and 0 indicated best possible health status. The threshold for a clinically significant difference between groups of patients and for changes within groups of patients was four units.

2.9 EuroQol (EQ-5D) Questionnaire

For study 2 EQ-5D was a one page self administered simple questionnaire, taking only a few minutes to complete with instructions to respondents included in the questionnaire. It used a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of three responses. The responses recorded three levels of severity (no problems/some or moderate problems/extreme problems) within a particular EQ-5D dimension. Quality Adjust Life Years (QALYs) were calculated by converting the EQ-5D questionnaire results into utilities using UK health state valuations, then measuring the resulting area under the curve.

2.10 A health and social care resource utilisation and costs questionnaire

In study 2 a health and social care resource utilisation and costs questionnaire was a 3 pages self administered simple questionnaire which reflected the use of primary (GP, nurse, other healthcare professionals), secondary and private healthcare resources, social services, personal expenditures for non-prescription medications and days off work. Quality Adjust Life Years (QALYs) were calculated as well as costs and outcomes (point improvement in FVC and QALYs gained) of treating a patient with or without co-trimoxazole.

2.11 Radiology review

For study 2 an independent retrospective radiological review was undertaken by two specialist respiratory radiologists using published criteria[164] where biopsy confirming usual interstitial pneumonia was not

available; study population included both patients with definite and probable UIP reflecting the range of disease in clinical practice. The HRCT scans of patients without honeycombing were also scored according to the degree of interstitial changes and the algorithm described by Fell et al[165]was used to predict a biopsy confirmation of IPF.

2.12 Review of causes of admission and death

For study 2 the reason for admission to hospital and the cause of death was obtained from death certificates and adverse event reporting forms. These were reviewed by two blinded physicians. Death was defined as respiratory related if resulted from respiratory failure, acute exacerbation or progression of IPF, pneumonia or respiratory tract infection, pulmonary empbolism, lung cancer,, pneumothorax or pulmonary embolism.

2.13 Vascular endothelial growth factor

In study 3 plasma samples were collected for future assays for the assessment of levels of Vascular endothelial growth factor by centrifuging EDTA blood sample for 10 minutes at 2500 revolutions, subsequent separation of plasma and storage in a freezer at -80 degrees C. Levels of VEGF in plasma were assessed using a commercially available validated VEGF ELISA kit.

2.14 Exhaled Nitric Oxide

In study 3 exhaled nitric oxide was measured using a NIOX hemiluminiscence nitric oxide gas analyzer (Aerocrine, Chicago, Illinois USA), with an expiratory flow rate of 50ml/sec according to American Thoracic Society guidelines [166]. In addition, measurements were taken at expiratory flow rates of 30, 100 and 200 ml/sec. The mean of three separate measures of nitric oxide were used in the analysis. The measurement technique was consistent with ATS/ERS guidelines (2005). Patient's dead space was exhaled unrestricted without flow regulation to assure correct fraction of exhaled NO (FeNO result). Visual aid for the patient was used and the patient was sitting in a chair for the duration of the measurement. Prior to measurement exhalation the patient was inhaling an NO-free air to total lung capacity to eliminate any contamination from high ambient NO levels. The analyser was calibrated every 2 weeks using a cylinder of nitric oxide at concentration of 205 ppb.

Alveolar concentration of nitric oxide (CaNO) and total flux of nitric oxide (JawNO) were estimated by using the model by Tsoukias and George[167].

2.15 Statistical analysis

Study 2 was powered as detailed. Study 3 was a pilot study therefore no power calculation was used. A value of $p<0.05$ was considered to be significant and 95% confidence intervals for mean treatment differences were calculated.

In study 2 (co-trimoxazole) the comparison of continuous outcome measures between treatment arms was based on a mixed effects model with treatment centre as a random effect and treatment arm and status as fixed effects. An adjusted analysis was also carried out by including the baseline value of the covariate as a fixed effect in the above model. These were fitted in Stata/SE 11.0 using the xtmixed command using restricted maximum likelihood treating centre and a random effect. A cost-effectiveness and cost-utility analysis were performed to determine the costs and outcomes (point improvement in FVC and QALYs gained) of treating a patient with or without co-trimoxazole, measured from the viewpoints of both the health service and society.

In study 3 (Exhaled NO) alveolar NO was calculated using a linear interpolation of the NO versus flow curve as described by George et al [167]. A T test was undertaken to compare the differences between baseline parameters in (1) patients with severe or mild/moderate IPF and (2) patients with or without a combined event defined as death, or a 10% decline in absolute FVC and/or 15% decline in absolute DLCO at 18 months after recruitment. Multiple linear regression analysis was used to evaluate an ability of alveolar NO as well as VEGF to predict a decline in absolute FVC, and a combined event as above.

In study 4 (Predictors of death or FVC decline) logistic regression analysis was used to identify independent predictors of all-cause mortality as well as of 5% and 10% decline in FVC at 6 and 12 months.

The rest of the details of statistical analysis are in relevant chapters.

Statistical analysis was performed by Allan Clark, statistician at the University of East Anglia for study 2 and 4, and by Ludmila Shulgina for study 3.

2.16 Investigational product

In study 2 using Co-trimoxazole patients were randomised to receive either of the following treatments for 12 months: Co-trimoxazole (non-proprietary) 960mg twice daily as 2 tablets of 480mg twice daily or placebo tablets (manufactured from pharmacy at Guy's and St Thomas's Hospital – to be identical to Co-trimoxazole 480mg) 2 tablets twice daily. Folic acid (non-proprietary) 5mg once daily was used to prevent potential haematological adverse events as a result of the use of Co-trimoxazole.

2.17 Study visits

Study visits description is as detailed in a relevant chapter.

2.18 Adverse events and adverse reactions

The local investigator at the study site was responsible for the detection and documentation of events meeting the criteria and definition of adverse events or adverse reactions (as below) including reporting to the sponsor.

"Adverse event" (AE) means any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

"Adverse reaction" (AR) means any untoward and unintended response in a subject to an investigational medicinal product, which is related to any dose administered to that subject.

"Serious adverse event" (SAE) or "serious adverse reaction" (SAR) or "unexpected serious adverse reaction" means an adverse event/reaction that fulfils at least one of the following criteria:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity or
- Consists of a congenital anomaly or birth defect

"Unexpected adverse reaction" means any adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product, or summary of product characteristics [SMPC] for an authorised product).

"Suspected Serious Adverse Reaction (SSAR)" means an adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question set out: in the case of a licensed product, in the summary of product characteristics (SMPC) for that product; in the case of any other investigational medicinal product, in the Investigator's brochure (IB) relating to the trial in question.

“Suspected Unexpected Serious Adverse Reaction (SUSAR)” means an adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out: in the case of a licensed product, in the summary of product characteristics (SMPC) for that product; in the case of any other investigational medicinal product, in the Investigator’s brochure (IB) relating to the trial in question.

Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, and vital signs) that are judged by the investigator as clinically significant were recorded as AEs or ARs if they met the definition’s above. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or were present at baseline and significantly worsen following the start of the study were reported as AEs or ARs. However, clinically significant abnormal laboratory findings or other abnormal assessments that were associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject’s condition, or that are present or detected at the start of the study and do not worsen, were be reported as AEs or ARs. The investigator exercised his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment was clinically significant.

Time Period, and Frequency of Detecting AEs and ARs

From the time a subject consents to participate in the study until he or she has completed the study (including any follow-up period), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) were reported promptly to the principle investigator.

Reporting of Adverse events

In compliance with Article 16 of the European Directive 2001/20/EC, the investigator was expected to report all SAEs promptly to the sponsor (Ms Sue Steel, RBS, UEA, Norwich Fax 01603 591550) within 24 hours of being identified. The immediate report was expected to be followed by detailed written reports. The immediate and follow-up reports would

identify subjects by unique code numbers assigned to the latter. The investigator was expected to report AE's to the sponsor within 3 months. For reported deaths of a subject, the investigator would supply the sponsor and the Ethics Committee with any additional information requested. The sponsor would keep detailed records of all adverse events which were reported to him by the investigators. These records would be submitted to the Medicines and Healthcare Products Regulatory Agency, UK if they so request.

Reporting of Serious adverse reactions

In compliance with Article 17 of the European Directive 2001/20/EC, the sponsor (Ms Sue Steel, RBS, UEA, Norwich) ensured that all relevant information about SUSARs that were fatal or life-threatening would be recorded and reported as soon as possible to the Medicines and Healthcare products Regulation Agency (MHRA), the Data Monitoring and Ethical Committee (DMEC) and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected serious unexpected adverse reactions would be reported to MHRA, DMEC and Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor (Ms Sue Steel, RBS, UEA, Norwich).

Once a year throughout the clinical trial, the sponsor (Ms Sue Steel, RBS, UEA, Norwich) was expected to provide the MHRA, DMEC and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

2.19 Quality control

Study 2 was managed by the East Anglia Thoracic Society (EATS) clinical fellow. The EATS fellow was trained in Good Clinical Practice. Prior to enrolment of a site, the EATS fellow contacted the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory and ethical requirements. When reviewing data collection procedures, the discussion included identification, agreement and documentation of data items for which the CRF served as the source document.

A monitoring committee was formed and monitored that the study was consistent with the demands of the study and to verify that:

• All outcomes and resource use data are authentic, accurate, and complete.

• Safety and rights of subjects are being protected.

• Study was conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

An independent trial steering committee was formed. It was comprised of an Independent Chairman (no direct trial involvement), two additional independent expert members, Chief Investigator and a patient/lay representative

A data monitoring and ethical committee comprised a statistician and a researcher with special interest in interstitial lung disease. This committee monitored the serious adverse events and mortality.

2.20 Data collection and validation

A password protected web based database was used for the data collection from the source documents and for the interim and final study analysis. Data validation was performed prior to the database lock and unblinding.

Assessments and checks performed prior to database lock:

1. Consort diagram collated
2. System allocation of Adverse events: Drug Analysis Print (DAP) for active ingredients of Co-trimoxazole (sulphamethoxazole and trimethoprim) from the MHRA website was used for system allocation of adverse events/reactions. DAPs give complete listings of all UK spontaneous adverse drug reactions (ADRs) reported through the Yellow Card Scheme to the MHRA and group together suspected ADRs by medical terms, broken down by more specific conditions. It uses terminology from so called MedDRA - Medical Dictionary for Regulatory Activities; its highest level grouping method is by System Organ Class which groups together reactions that affect similar systems/organs in the body.
3. Escalation analysis together with the Chief Investigator: Assessment of the Escalation of therapy is being done using the number of disease

deteriorations within 12 months, rather than a number of drug therapies being added. For example if a patient was prescribed with Prednisolone, Azathioprine and N-acetylcysteine this was approached as one escalation rather than 3 as was related to one disease deterioration rather than 3 separate episodes. Therefore Prednisolone, Azathioprine and antioxidants were grouped together and there was a separate assessment of the use of oxygen therapy due to a variety of causes of developing hypoxia in IPF.
Overall change in treatment requirement (judged as escalation or not) was assessed and documented by two assessors prior to unblinding procedure; an agreement was achieved if there is a discrepancy in assessment.

4. Source data validation: Dedicated electronic database was used for the data analysis in the TIPAC study. The data was entered on a database from the source documents (the list of which is according to the protocol) which will be stored at each site in individual patient case report forms. Data entry for the sites within East Anglia was performed by the study co-ordinator unless there was a research nurse or data entry manager available to assist with this in which case the study co-ordinator would check on all entries related to the primary end-point and one of secondary endpoints. 10% of data on primary end point and one of secondary endpoints in the sites where the data was provided solely by the study co-ordinator was validated by the Chief Investigator of the study. Entry error 0.9969%.
   Data entry for the sites outside East Anglia was performed by the study site team (usually a research nurse) and was validated by the study co-ordinator during monitoring and termination visits unless a termination visit predated an exit visit for some patients. In that case the study co-ordinator would validate all primary end point data and some of secondary endpoints (pending on the results of the termination visit data quality assessment).
5. Protocol deviation assessment by the Chief Investigator with a per patient assessment of suitability for per protocol analysis (spreadsheet with data available)
6. Primary end point (FVC) predicted value check against ECSC spirometry equations (This check revealed the following errors that were corrected:
   a. Wrong gender (2 patients)
   b. Wrong height (5 patients)

c. Different equipment used for different visits with vitalograph using different equations compared to Body box or other equipment, vitalograph predicted values corrected
d. Predicted in litres rather than % predicted entered (2 cases)
e. Obvious error of calculation of % predicted (10 patients) Spreadsheet with original and corrected data available.

Audit checks on completeness of secondary and tertiary endpoint data, including questionnaires as per eCRF.

1. consent date should be put in for all patients
2. demographic section - all fields should be filled in
3. section Medical history other than IPF if any entries are put in there should be a Yes or a No for the next box "ongoing"
4. in diagnosis section there should be there should be an entry for all 4 top lines and for the line saying Histological evidence of diagnosis available
5. there should be no blank fields for regular, alternative and prn medications (could say "uk" for unknown though)
6. in Current Medications in immunosuppression section for each of Prednisolone and Azathiprin if the statement is Yes there should be 4 items recorded: a dose, start date and last dose changed and how long on current dose inserted.
    a. there should be at least one field ticked for the PFT method (Body pletismography, helium or nitrogen washout) for visits 1,3 and 5 where the results are inserted
7. dates for blood tests are inserted (provided there is a result there), ie there should not be a missed date.
8. in bloods for all visits where at least one result is inserted WCC, Hb, Neutrophils, Lymphocytes, Platelets, Na, K, Creatinine, Bilirubin, ALT, ALP albumin should not blank (there will be an odd blank area but there would be a comment in additional info on that)
9. in bloods for visit 1 B12 and Folate should not be blank
10. for all patients who had PFT or a blood test done for any of the visits an MRC dyspnoea grade should be inserted.
11. in section ECG both answers should not be blank (should read Yes for both)
12. there should be Yes or No for all Q for visit 1

13. in_Lung function tests if an absolute number is inserted there should be a % predicted
14. in Randomisation and drug dispensing all fields should be filled
15. For subsequent visits:
    - adverse events should all have a close date or an "unresolved" box ticked; there should be grade, severity and details inserted for all.
    - for escalations for regular or PRN medications top 5 lines, bottom line and one of (previous or current does should be inserted)
    - for deaths all fields should inserted
    - all SAE entries should have all fields filled in and there should be no entries in "unresolved" box
16. all deaths should be allocated to IPF and non-IPF, have the place of death recorded.
17. Missing data in questionnaires should be checked to clarify if an error of entry or a true missing value
18. Ensure allocation of patients to a type of analysis (ITT, PP, Safety) performed

2.21 Compliance assessment for study 2

Adherence was assessed by a review of returns from accountability logs for each patient and was considered to be acceptable if each patient took at least 80% of their study medication doses.

Chapter 3

Study 1

Assessing the accuracy of the diagnosis of Idiopathic Interstitial Pneumonia

3.1 Introduction

The commonest fibrotic Idiopathic Interstitial Pneumonias are Idiopathic Pulmonary Fibrosis (IPF) and Nonspecific Interstitial Pneumonia (NSIP). These conditions can be difficult to differentiate as they present with similar respiratory symptoms. Whilst histological confirmation of UIP was considered the “golden standard” for the diagnosis of IPF, it has now been recognised that specific High Resolution Computer Tomography (HRCT) features can be diagnostic for UIP and this obviates the need for a surgical lung biopsy. Even in the presence of typical UIP radiological or histological pattern, it is important to integrate this with the clinical symptoms, exposure history, examination findings and pulmonary function tests to exclude other causes. This is because a histological or radiological pattern of UIP does not necessarily equate with an idiopathic disease as it has been reported with asbestosis, chronic hypersensitivity pneumonitis, ILD associated with connective tissue disease particularly rheumatoid arthritis, familial pulmonary fibrosis, and sarcoidosis[168]. However, in cases where there is uncertainty due to either atypical radiological features or clinical presentation, a surgical lung biopsy is required for histopathological evaluation. Nevertheless a proportion of these patients may not be suitable for a surgical lung biopsy either as a consequence of severity of their respiratory disease or co-morbidities. In this setting, the risk of biopsy may outweigh any potential benefits and the diagnosis of IIP is based on the integration of clinical and radiological information.

Thus, in order to distinguish between NSIP and IPF, the American Thoracic Society/European Respiratory Society devised major and minor criteria for the diagnosis of IPF[5]. An important major diagnostic criterion was the exclusion of other known causes of interstitial lung disease, such as drug toxicities, environmental exposures, and collagen vascular diseases[5]. Hence a careful and detailed clinical assessment is essential in the initial evaluation of a patient with ILD as it helps guide approaches to treatment and the information provided to patients regarding their disease and likely prognosis.

The aim of this audit was to assess the accuracy of data collection, in particular the aetiological factors which are associated with interstitial lung disease. The audit looks at the quality of predominantly history taking from patients with subsequent diagnosis of Fibrotic Idiopathic Interstitial Pneumonia during their first visit to the respiratory clinic following an initial referral with or without respiratory symptoms (on some occasions the referral was triggered by an abnormal Chest XRay).

The source of standard for the audit in patients with IPF was based on the international consensus statement on idiopathic pulmonary fibrosis[5] The standards included a 100% target compliance for the following data collection (Table 3.1).

Assessment of data record of patients with idiopathic NSIP was based on the similarities in assessment of idiopathic nature of the disease between IPF and idiopathic NSIP (subsequently called NSIP) and on the report of the ATS project on NSIP[22].

Aspect of care	Target % compliance	Instructions/comments
Patients with IPF should have drug history assessed at the time of diagnosis	100%	
Patients with IPF should have occupational and environmental exposure history assessed at the time of diagnosis	100%	
Patients with IPF should have family history of ILD and CTD assessed at the time of diagnosis	100%	
Patients with IPF should have a possibility of connective tissues disease assessed and autoantibodies tested at the time of diagnosis	100%	**This should be performed during initial clinical assessment unless already done by another health care professional prior to referral to a respiratory team (the results could be identified on the pathology system or in the referral letter)**

Table 3.1.Standards of aspects of care and a target compliance

3.2 Methods

Patients.

Patients registered under the care of respiratory physicians in respiratory clinic of three Trusts of East Anglia, on 1st March 2008 were included in the assessment. Patients were identified as a part of the patient identification process for the study 2.

Study design

This was an audit project involving retrospective review of medical notes of patients with the working diagnosis of IPF in three trusts in East Anglia - the Norfolk and Norwich, Ipswich and James Paget Hospitals (approved by an audit department of each trust) with subsequent descriptive analysis of findings. The adherence to the following standards of care was assessed: all patients with final working diagnosis of IPF and NSIP (assumed to be idiopathic) should have had their occupational history, past medical history including drug history checked at the time of diagnosis; all patients should have had connective tissue disease excluded by the means of history taking and antibody profile checking at the time of diagnosis. A data collection proforma was issued which became a basis for the web based database created by a data manager of the University of East Anglia, this was used for electronic data collection and subsequent analysis.

3.3 Results

Patients with a working diagnosis of IPF or NSIP, recruited for the interventional study assessing efficacy of Co-trimoxazole in IPF (Chapter 4), were identified from Respiratory clinics from three hospitals (James Paget Hospital, Ipswich Hospital and Norfolk and Norwich University Hospital) in East Anglia. Two of these hospitals are teaching hospitals and all have an access to a thoracic surgery service (1 hospital has a dedicated department of thoracic surgery and 2 hospitals have weekly input from a visiting thoracic surgeon). One hundred and forty cases of clinically diagnosed IIP (IPF or NSIP) were identified and medical case notes were available for 108 patients (26/32 James Paget Hospital, 40/48 Ipswich Hospital, and 42/60 Norfolk and Norwich University Hospital).

The baseline patient characteristics are presented in table 3.2. The majority (65%) were prevalent cases; however of the 108 cases assessed, 23 had been diagnosed within 6 months and 15 within 12 months of the date of the study. The mean time from diagnosis was 2.9 years (SD ±3 years) and 83 (77%) were males. All but one patient had a HRCT scan within 3 months of diagnosis. For the case without HRCT scan, the diagnosis of idiopathic pulmonary fibrosis was based on clinical and CXR data. In over 90%, integration of clinical and radiological information was used to establish the final working diagnosis. Overall 7 patients (6.5%) had a histopathololological diagnosis, which included 2 out of the 11 patients with a working diagnosis of NSIP.

	Number (%)
Cases assessed	108
Males	83 (77)
Age at diagnosis, years (mean ±SD)	74.5 ±8.6
Time from diagnosis, years (mean ±SD)	2.9 ±3
NSIP	11 (10.2)
IPF	97 (89.8)
Surgical lung biopsy (VATS)	7 (6.5)

Table 3.2 Baseline demographic characteristics

A smoking history was obtained for 104 (96%) cases. In contrast, less than 50% of patients had detailed occupational (including asbestos and other dust or chemicals) and domestic exposures. The main findings are summarized in table 3.3.

Audit Standard	% of cases (number) with data enquired and documented
Smoking History	96% (104)
Occupational history • Recorded • No record	 85.2% (92) 14.8% (16)
Asbestos exposure	44% (48)
Other exposures (inorganic dust, chemicals, drugs)	20% (22)
Spouse employment	1.9% (2)
Hobbies • Birds • Hobbies other than birds	 41% (44) 0.9% (1)
House dampness	0.9% (1)
Relevant past medical history and medication exposure • Malignancy and chemotherapy • Cardiovascular conditions and its treatment • Use of Nitrofurantoin • DMARD	 14.8% (16) 16.7% (18) 9.3% (10) 10.2% (11)
Family history of ILD/CTD	12% (13)
CTD • Record of enquiry on symptom of CTD • Auto-antibody screen	 15.7% (17) 61% (66)

Table 3.3 Audit Standards

Occupational history

A detailed occupational history, consisting of employer, duration of occupation and exposures, was present for 8 cases (7.4%), whilst 16 patients (14.8%, 7 male) had no occupational data documented. For the remaining cases, limited information, predominantly profession, was recorded in the medical notes. Overall a record of employer details was available for 19% (21) of the cases, and of these a description of the job duties was recorded for 19 patients.

Asbestos exposure

A history of asbestos exposure was enquired from 44% (48) of the patients reviewed in the audit. Nineteen patients had no evidence of exposure documented as “no history of asbestos exposure” and 9 cases had a record of “no occupational exposure/no known exposure/no occupational history”. Of the remaining cases with a positive history of asbestos exposure, 10 patients had no employment details (employer, duration, protection), 2 had a record of their employer only, and 4 had documentation of duration of the exposure (4-40 years) but no employer details. The use of respiratory protection was enquired from one patient. Furthermore, out of 10 patients, who had professions with potential exposure to asbestos (plumber, electrical/construction engineer, seaman, builder), only 7 had evidence of an enquiry of asbestos exposure. Twenty eight patients had occupations with low asbestos hazard (teacher, childminder, sales manager, police officer, lorry driver) and only 7 of this group had enquiries about non-occupational asbestos exposure. Spouse employment, including asbestos exposure, was recorded in 2 cases (1.9%).

Other potentially hazardous occupational exposures were identified in 22 (20%) cases. These exposures had the most comprehensive information on employer, substances exposed to and duration of the exposure. These included 2 leather workers, 2 bakers with flour dust, 3 welders, 2 farmers, 2 tobacco leaf factory workers, 1 each of poultry factory worker, cotton mill worker, wood cabinet maker, polyester fibre, nickel sulphate and copper in an electrolysis laboratory, paper and printing ink dust, organic solvents, abrasives in grinder industry, Benzene chlorine and acids in the pharmaceutical industry, organo-phosphates and pesticides, and upholstery adhesives.

Hobbies and domestic exposures

Forty four (41%) patients were asked about exposure to birds. Twelve (27%) reported having kept birds at some point in their life, but only 3 cases had a concise history including species of birds, duration of exposure and where the birds were housed. Avian precipitins were measured in five of the bird-keepers. One patient was reported to have a hobby other than bird keeping (dog breeder). Enquiry on house mould exposure was reported in one patient only.

Relevant past medical history

Out of the 16 patients asked about previous malignancy, radiotherapy and chemotherapy treatment, 6 cases were indentified: 1 case of groin lymphoma with local radiotherapy, 1 case of oesophageal adenocarcinoma treated with radiotherapy and chemotherapy prior to diagnosis of IPF, 3 cases of breast carcinoma (one treated by mastectomy alone; one treated with chemotherapy and radiotherapy 18 years before a diagnosis of IPF, and one treated with radiotherapy with no documentation of the time interval for diagnosis of IPF), and 2 cases of transitional cell carcinoma of bladder requiring local excision only.

Eighteen patients (16.7%) were questioned about cardiovascular conditions, which identified previous use of amiodarone in 2 cases, In both instances, amiodarone was stopped due to the development of ILD. However it was unclear if symptoms were related to drug use in one patient with a history of prolonged use (10 years) of amiodarone.

Of the 11 patients asked about exposure to methotrexate, 2 cases had a history of 9 and 40 years treatment for psoriasis respectively. In the case with a 9 year exposure, methotrexate had been discontinued 3 years prior to the occurrence of respiratory symptoms.

Family and personal history of connective tissue disease

A personal history of arthritis, skin rash, Raynaud's phenomenon or "history suggestive of connective tissue disease" was enquired in 17 (15.7%) patients. One patient with a history in keeping with Raynaud's phenomenon, was noted to have ANA HEp 2 strong positive (analysis performed in 2001), but did not develop any other systemic features. Rheumatoid factor and/or auto-antibody screen (antinuclear antibodies (ANA), extractable nuclear antibodies (ENA), cryoglobulin, lupus anticoagulant, anticardiolipin antibodies, anti-double-strandDNA (anti-dsDNA)) were assessed in 66 (61%) patients. Ten out of 51 patients tested had elevated Rheumatoid factor titres on one or more occasion. One patient, with a titre 10 times the upper limit of the normal reference range, was diagnosed with polymyalgia rheumatica/ inflammatory polyarthritis in the same year as IPF. Positive ANA was identified in 15 out of the 59 patients tested; 11 (9 weakly positive ANA) had no identifiable extractable nuclear antigen (ENA) although 2 cases had nucleolar and 2 cases had a homogeneous pattern. Two patients had anti-Ro antibodies and the

remaining 2 cases with a positive ENA had no detectable antigen. Lupus anti-coagulant was not assessed in any patient with elevated ANA titres. In the two patients that were tested, anti-cardiolipin antibodies were not present. Out of the 22 patients (20%) evaluated in this audit, 3 patients had a detectable anti-dsDNA (1 an isolated increase and 2 in combination with positive ANA and ENA negative).

A family history of connective tissue disease or pulmonary fibrosis was requested in 13 (12%) patients. Three patients had a history of pulmonary fibrosis in a first degree relative (affected sister in two cases and father in another). In one case, there was a history of scleroderma in first degree relative (mother), although the patient had no systemic features or serology supportive of connective tissue disease at presentation for ILD.

3.4 Discussion

One of the earliest studies to assess the approach to diagnosis and management of cryptogenic fibrosing alveolitis in three regions of the UK showed there was wide variations of practice, with the diagnosis based solely on clinical grounds in 60% of cases[169]. Subsequently, the British Thoracic Society undertook a questionnaire based evaluation of new incident cases of cryptogenic fibrosing alveolitis over a 2 year period (1990-92). This included a detailed assessment of symptoms (breathlessness, cough, arthritis), structured occupational, smoking and past medical histories, results of blood tests including ESR, rheumatoid factor, ANA, avian precipitins as well as lung function and CXR appearances[170]. They observed that dust exposure, including asbestos, was present in almost half of the cases and that 60% did not have a histological diagnostic procedure.

A number of studies have evaluated the sensitivity and specificity of clinical diagnostic criteria for IPF. One of the earliest studies compared the accuracy of the clinical diagnosis with subsequent histological diagnosis in 59 patients with IPF in an academic centre with recognised expertise in management of ILD[46]. This was performed prior to the IPF consensus statement[5]. It demonstrated that pre-defined clinical criteria (including absence of clinical features suggestive of identifiable cause of ILD, insidious onset of breathlessness of greater than six months duration, restrictive PFT defect, bibasilar reticular abnormalities on CXR and HRCT,

transbronchial biopsy excluding specific diagnoses) had a high specificity (97%) but low sensitivity (62%) for IPF. But for ILD other than IPF the clinical assessment, including HRCT scan and bronchoscopic findings, had low specificity (88%) and sensitivity (40%). A multicentre study by Hunninghake et al[45], using expert opinion rather than pre-defined clinical criteria, demonstrated that a confident clinical diagnosis of IPF had a positive predictive value of 80% (referring centre physician), which increased to 87% (specialist pulmonologists) and 96% (specialist radiologists). These studies suggested that clinical and radiological data supportive of a confident diagnosis of IPF may obviate the need for a lung biopsy. In addition, a study of 26 patients by three board-certified pulmonologists comparing the ATS/ERS clinical criteria for IPF[171] with subsequent lung biopsy results, showed that the sensitivity, specificity, positive predictive value and negative predictive value of the clinical criteria were 71, 75, 77 and 69% respectively, which means that 29% of cases would be missed if clinical criteria alone were applied . Hence, a lung biopsy is indicated when clinical and radiological data result in an uncertain diagnosis. All of these studies used a set of diagnostic clinical criteria and only those patients who qualified these criteria were included into the studies; the accuracy of data record and the number of patients excluded from the study, either as a result of incomplete data or not qualifying the inclusion criteria, was not provided.

Little is known about current practice for the diagnosis and management of IPF, in particular adherence to the ATS/ERS consensus recommendations for the diagnosis and treatment of IPF published in 2000. Two studies in the United States, using electronic questionnaires, assessed the level of acceptance of the ATS/ERS consensus statement and determined if the practice patterns were consistent with these recommendations. A survey of 272 academic physicians (33% response rate) by Collard et al. [172] and another of 814 academic and non-academic fellows of the American College of Chest Physicians (13 % response rate) by Peikert et al.[173] demonstrated similar trends regarding the use of HRCT for the diagnosis of IPF (90 and 73% respectively), surgical lung biopsy (< 30% of cases of IPF) and the lack of consensus regarding treatment of patients with IPF. The study by Peikert et al showed that 72% of the responders were familiar with the ATS/ERS consensus statement and 63% found it clinically

useful, whilst 28% were not familiar with the guidelines 7 years after their publication[173].

A benchmark exercise was performed among 370 consultant members of the British Thoracic Society (54% response rate) to compare the approach used for evaluating three clinical scenarios in ILD, two of which were cases of IPF. Responders were asked to choose from a range of diagnostic and treatment options, the management decision was subsequently compared to the consensus statement[174]. This exercise clearly demonstrated that there was a lack of consensus in both the decision for a lung biopsy and selecting appropriate treatment options.

Little is known about spontaneous record of the clinical history and risk factors data in clinic environment for patients with ILD. This audit evaluated the collection of aetiological factors associated with ILD. The results were analysed using the assumption that 100% of patients should have data on aetiological factors collected. It has demonstrated that there is considerable variability in the clinical assessment of patients with IIP across three hospitals in East Anglia. In this cohort of patients assigned a clinical diagnosis of IPF or NSIP, a smoking history was the only aetiological factor that was consistently obtained. Despite the ATS/ERS guidelines, occupational and domestic exposures, associated co-morbidities, potential pneumotoxic therapies, and assessment for connective tissue disease was undertaken in less than half of the patients. Incomplete data sets, in conjunction with radiology, were used to make a clinical diagnosis of either IPF or NSIP in more than 90% of patients. A histological diagnosis was only obtained in 7 cases, including 2 patients with NSIP. Nine patients had a clinical diagnosis of NSIP. However, in the absence of connective tissue disease radiology alone is not sensitive and a surgical lung biopsy should be performed.

Whilst the data on employment and profession was collected in the majority of patients (77%), there was no systematic enquiry. A full occupational history was only available for 8 cases (7.4%) and 16 patients (14.8%) had no details provided, of these almost half were males and more likely to be the income providers. Occupational exposures to hard metals, inorganic dusts (asbestos and other fibrous silicates, mixed dust, kaolin, rare earths, cobalt, aluminium) are associated with an increased risk of IPF, and the radiological and pathological appearance of UIP[151]. Hence

a detailed occupational history is essential to ensure that pneumoconiosis is not misdiagnosed as IPF. Recognition of an occupational cause for the interstitial lung disease is important as it helps to predict prognosis, guides treatment choice, and identifies potential industrial compensation. Occupational ILD accounted for a greater proportion of parenchymal lung disease in the European disease registries compared to connective tissue disease, drugs/radiation and vasculitis combined[151]. Individual susceptibility for pneumoconiosis is determined by both exposure-related (dose and duration) and host factors. For instance, host factors are key to the development of bioaerosol induced hypersensitivity pneumonitis, cobalt-related ILD and chronic beryllium disease, while dose and duration of exposure to asbestos, coal and silica play an important role in pneumoconiosis [151]. Accurate assessment of previous inhalational exposures should include a chronological list of all jobs, the names of substances exposed to and dose (if applicable), the duration of exposure including hours during the day and total number of years, any protective equipment used and a record of any respiratory symptoms associated with the exposure. As well as occupational contact, exposures can occur in the domestic environment through hobbies or living conditions. Contact with some of the substances, such as asbestos, metal and wood dust, textile dust, stone and sand, livestock, may occur through both occupational and non-occupational routes; others predominantly arise through hobbies and non-occupational routes; i.e. caged birds, smoking, mould, wood fire. Although these exposures may lead to occupational lung disease or hypersensitivity pneumonitis, they also increase the risk of IPF. This was confirmed by a meta-analysis of 6 case control studies, which identified that cigarette smoking (odds ratio 1.58), and exposures to agriculture and farming, livestock, wood and metal dust (odds ratio 2.44), stone and silica are associated with an increased risk for IPF[31]. A minority of patients in this audit were asked about exposures to these substances associated with IPF through either a non-occupational route or spouse's employment.

The presence of pleural thickening is not sufficiently sensitive to discriminate between asbestos related lung disease and IPF, as the risk of non-asbestos related fibrotic lung disease is the same in the general population as in a patient previously exposed to asbestos [175]. In a comparative study of thin-section CT in 74 patients with asbestosis and 212 patients with IPF, 2% of those with IPF had evidence of diffuse pleural thickening but no pleural plaques, whereas the majority of patients with

asbestosis had evidence of either pleural thickening or pleural plaques and only 5% had no evidence of pleural disease[176]. Thus rarely asbestosis presents in the absence of pleural disease. In this audit, only 44% of patients were asked about potential asbestos exposure.

Chronic hypersensitivity pneumonitis (HP) is another ILD that may present with UIP radiological pattern similar to IPF. Establishing if a patient has had an exposure to potential allergens including caged birds, which is the commonest cause of HP in the UK and USA, and domestic mould. This audit identified that only 41% of patients were directly asked about exposure to birds and only 1 patient was asked about damp or mould in the home.

Furthermore, the differential of UIP pattern radiology also includes drug induced interstitial lung disease. A number of medications are potential pneumotoxins, however UIP histopathology is an uncommon manifestation of drug toxicity[177]. Medications recognised to cause a UIP radiological pattern include chemotherapeutic agents (bleomycin, busulphan, chlorambucil, cyclophosphamide and nitrosureas), amiodarone, nitrofurantoin and less frequently gold, methotrexate and sulphasalazine[178]. There have been case reports of resolution of the fibrotic radiological changes after cessation of nitrofurantoin treatment[179]. In contrast to IPF, drug induced ILD may be reversible upon cessation of the causative agent and is more likely to respond to immunosuppressive therapies. As the clinical and radiological findings of drug induced ILD may be difficult to distinguish from IPF, it is imperative that a careful history of previous medication use is obtained. The audit identified that less than a fifth of the patients were asked about the previous medications including radiotherapy, chemotherapy, cardiovascular conditions and treatments, use of Nitrofurantoin, and disease modifying anti-rheumatic agents.

Up to 20% of patients with IPF have a family history of pulmonary fibrosis[41]. Familial pulmonary fibrosis presents in a similar manner to IPF, except it has an earlier age of onset[42]. A number of studies support an autosomal dominant inheritance with variable penetrance[43] . At present, no genetic testing is available in the UK to identify familial forms of PF. Clinical screening is crucial as there is evidence to support an

independent association between cigarette smoking and phenotypic expression as the risk of developing pulmonary fibrosis is increased in a genetically susceptible individual who smokes[43]. In addition, the study by Steele et al. suggests that nearly 8% of self-reported unaffected family members have a preclinical form of PF as assessed by HRCT or histopathological findings[43], which justifyies the need for surveillance of family members of affected individuals. Our data show that a family history of pulmonary fibrosis was obtained in 12 cases (11%) only and 3 of these patients had a first degree relative with PF.

By definition IPF is not a systemic disorder, but a disease confined to the lungs. Nevertheless the lung may be the first manifestation of a systemic disease such as the connective tissue disorders (CTD). NSIP is the most frequently occurring pattern of interstitial lung involvement that occurs with CTD, except for rheumatoid arthritis which is associated with UIP. Less commonly, UIP has been reported with systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjogren's syndrome and polymyositis/dermatomyositis. There is evidence that a large proportion of cases of idiopathic NSIP have or may develop features of undifferentiated connective tissue disease[180, 181]. Identifying an underlying CTD has important consequences for disease prognosis, treatment choice and likely response to treatment. In keeping with this, patients with UIP associated with CTD have a better outcome compared to those with IPF (mean survival 177 months versus 66.9 months respectively) [40]. Quite often patients may not be aware of systemic symptoms if they are not causing significant functional impairment or if the respiratory symptoms are more prominent. Systemic sclerosis is typically associated with skin thickening, the extent of which leads to classification into limited or diffuse forms. There is a rare variant, characterised by visceral involvement in the absence of skin thickening, called systemic sclerosis sine scleroderma (ssSSc). A recent study of 6 patients with ssSSc, who were originally diagnosed with an idiopathic interstitial pneumonia, identified the criteria of telangiectasia, Raynaud's phenomenon with abnormal capillaroscopy, gastro-esophageal reflux, pericardial disease (often asymptomatic) and the presence of a nucleolar-staining ANA, that may be of help to differentiate these patients from those with IIP[182].

Antinuclear antibodies (ANA) directed against a variety of nuclear antigens are detected in the serum of patients with rheumatic conditions as well as a number of healthy controls, who were reported to have low titres of this antibody that increased with age especially in females:- 25-30% at 1:40, 10-15% at 1:80 and 5% at 1:160 or greater[183]. ANA testing is performed either by enzyme-linked immunosorbent assay (ELISA) or indirect immunofluorescent staining of fresh frozen sections of rat liver or kidney, or using the human epithelial cell tumour line (HEp-2 cell); the latter of which is most commonly used. ANA performed on HEp-2 cells are more frequently abnormal in patients with any ANA-associated disease, demonstrating increased sensitivity, but this is offset by a lower specificity[183]. ANA staining demonstrates variable patterns including speckled (i.e. extractable nuclear antigen (ENA) antibodies such as antiRo (SS-A) antibodies characteristic for SLE and Sjogren's syndrome, antiLa (SS-B) antibodies characteristic for Sjogren's syndrome, antiSmith antibodies characteristic for SLE, antiU1-RNP characteristic for undifferentiated CTD, and antiScl70 an antitopoisomerase antibody characteristic for SScl), nucleolar (ANoA) (i.e. antiTh/To, antiAFA, antiPM-Scl and antiRNPI antibodies), anticentromere (ACA) and homogeneous antibodies. These antibodies are rarely found in healthy volunteers and are usually specific for a particular type of CTD. Moreover the pattern of the ANA in SSc can predict not only the extent of the disease but also organ involvement: antiScl70 antibodies are predictive of diffuse scleroderma associated with pulmonary fibrosis whereas anticentromere antibodies are predictive of limited cutaneous scleroderma associated with pulmonary hypertension[184]. Low titres of Rheumatoid factor and antinuclear antibodies can occur in 10-20% of patients with IPF, which may be a false positive result as a consequence of the ageing population. Nevertheless in the setting of an ILD, higher titres may be of relevance and instigate a thorough evaluation for a CTD. The current BTS ILD guidelines[14] recommend that all patients with suspected interstitial pneumonia should have rheumatoid factor as well as ANA and ENA tested, and lupus anticoagulant and anticardiolipin antibodies measured in those with a raised ANA titre.

Our audit identified that a record of enquiry of CTD associated symptoms was present in less than a fifth of patients, whilst serological screening for Rheumatoid factor and ANA antibodies was performed in 61% of cases.

These results are much lower than two published studies, which found that these serological markers were utilised in the diagnostic evaluation of IPF by physicians in up to 90-95% of patients[172, 173].

HRCT is an essential part of the assessment of a patient with IIP as it can differentiate UIP from other forms of IIP. A survey of 272 academic physicians (33% response rate) by Collard et al.[172] reported that 90% of physicians accept that HRCT should be obtained in all patients suspected of having IPF. Our results are in agreement as all but one patient had HRCT scan. A histological confirmation of the diagnosis was achieved in 6.5% of our cases, which is compatible with earlier studies by Johnston et al[169] and is similar with the survey of Fellows of the American College of Chest Physician where ≤30% of clinicians utilised surgical lung biopsy in the diagnosis of IPF[173].

Our audit has a number of limitations. We did not ensure the confidence of the HRCT diagnosis by performing an additional independent radiological review, but relied upon the reporting by the local hospital radiologists who have varying expertise in ILD. Although we reviewed data on the patients who underwent a surgical lung biopsy, we did not collect the total number of patients referred for a diagnostic surgical lung biopsy who were deemed unsuitable for the procedure or who declined the investigation. None of the hospitals that participated in this audit had a dedicated ILD MDT, but all the physicians had an opportunity to discuss the cases with a respiratory radiologist within a general respiratory MDT; the number of cases when this discussion occurred was not documented.

In ILD the epidemiological studies are divided into the following three categories: the quantification of the disease (assessing incidence, prevalence and mortality), the identification of aetiological factors (by surveying outbreaks of the disease and identifying environmental and genetic associations using cohort or case-control studies), and clinical epidemiological studies (characterising disease behaviour including patterns of clinical presentation, natural history, treated course, responsiveness to therapy and definition of prognosis)[185]. Sources of data for these epidemiological studies include routine national statistics (national mortality statistics, hospital episode data), population based data (screening of “at risk” professions of occupational lung diseases and

primary care data), and specific disease registries [185]. Registries of lung diseases such as the European database for cystic fibrosis, the rare lung diseases including lymphangioleiomyomatosis, and the international registry for organ transplantation, have been essential in developing standards of care, improving survival and understanding the disease pathogenesis. Although there are ILD registries in the United States (Bernalillo County, New Mexico) and Europe (Belgium, Germany and Italy), there is no international registry for IPF[186]. The use of the ATS/ERS IPF guidelines would aid setting up such a registry, which would be invaluable for future epidemiological studies, especially for assessing incidence, prevalence, mortality, disease behaviour and response to treatment, and for recruiting to clinical trials by identifying potentially suitable candidates based upon the inclusion and exclusion criteria (age group, disease severity, previous treatment regimens). Electronic registries offer the possibility of being able to update the information on a patient's progress and treatment.

None of the three respiratory departments had a dedicated register or database of patients with interstitial lung diseases, nor used a proforma to collect the relevant clinical information that is recommended by the ATS/ERS consensus statement for the assessment of interstitial lung disease[5, 6]We are aware that most of the patients in this audit had incomplete clinical details to exclude other causes for their ILD, thus would not be suitable for epidemiological studies.

3.5 Conclusions

This audit has identified that a confident diagnosis of IPF could only be made in 9.3% (10) patients. It is possible that the remaining 90.7% (98) patients may have had an underlying cause for their ILD either as a result of occupational exposures, drug induced or associated connective tissue disease. The accurate diagnosis of IPF is important for patient care, as this determines treatment choice and predicts prognosis. Since this audit was undertaken, the ATS/ERS/JRS/ALAT have issued new guidance for the diagnosis and management of IPF[16]. Using these new criteria, we propose that a proforma (appendix 4) should be used in the evaluation of all patients with ILD to improve diagnostic certainty.

Chapter 4
Study 2
Treating Interstitial Pneumonia with the Addition of Co-Trimoxazole (TIPAC) Study

4.1 Introduction

Idiopathic pulmonary fibrosis (IPF) is the most frequently occurring form of fibrotic idiopathic interstitial pneumonia (IIP), which has a poor prognosis resulting in progressive breathlessness, impaired quality of life and a marked reduction in life expectancy[25]. The annual incidence is reported to be 7.44/100000 in the UK and 6.8/100000 in the USA with an 11% increase between 1991 and 2003[24]. The disease has a variable course in individual patients[70], however several studies performed using the current classification of IIP[6] have reported a median survival between 2 and 4 years from the time of diagnosis and a 5 year survival between 20 and 40%[63]. Furthermore, in a recent review of a US Multiple Cause-of-Death mortality database, Olson et al[28] reported that age-adjusted mortality for pulmonary fibrosis increased by 27% in males and 40% in females between 1992 and 2003.

Given the poor survival and lack of effective therapy for patients with IPF, there has been a renewed search for novel treatment options. A number of medications with anti-fibrotic, anti-oxidant, anti-proliferative, and anti-inflammatory properties have been recently evaluated[96, 98, 100-102, 105] but only a few of these studies achieved their primary endpoint. Though some had demonstrated statistically significant results and trends in secondary end-points[99, 187] this was not subsequently supported by larger studies[98, 100]. This suggests that current treatment options broadly lack efficacy though some result in a low average effect or, alternatively, are very selective and achieve important efficacy in selected patient subgroups[89].

A clinical observation that oral co-trimoxazole could result in clinical improvements in patients with advanced fibrotic lung disease prompted a previous small double-blind randomised placebo-controlled pilot study of 20 patients with IIP. Patients, were prescribed co-trimoxazole at a dose of 960 mg twice daily (1440 mg twice daily for patients over 70 kg) for 3 months which was added to the patients' existing treatment. Active

treatment produced significant improvements in outcomes including shuttle walk distance, forced vital capacity (FVC), Medical Research Council (MRC) dyspnoea score and St George's Respiratory Questionnaire (SGRQ) symptoms score[188].

Based on these observations we conducted a randomised placebo-controlled double-blind clinical trial to compare the efficacy and safety of 12 months therapy with oral co-trimoxazole when added to standard treatment in patients with fibrotic idiopathic interstitial pneumonia. The secondary objective was to estimate the incremental cost effectiveness of co-trimoxazole plus standard care compared with standard care alone.

4.2 Methods

Patients

Patients with clinical diagnosis of IPF or fibrotic NSIP were identified from the respiratory outpatient departments of 27 district general hospitals and one tertiary centre in England and Wales after being approached by their attending physician or a study coordinator (Dr Shulgina).

Patients with clinical diagnosis of non-specific interstitial pneumonia were entered if fibrotic features were predominant on HRCT. Histology was not required as an entry criterion. No patients had exacerbation of their disease or respiratory tract infection or changes in their immunosuppression treatment within 6 weeks of recruitment. Patients were greater than 40 years old and were permitted to receive oral prednisolone, azathioprine or mycophenolate mofetil at a stable dose and anti-oxidants. Patients had an MRC dyspnoea score of two or more and those who had not received immunosuppressive therapy had progressive disease with deteriorating lung function (>10% decline in FVC or >15% decline in diffusing capacity of carbon monoxide (DLCO) in the preceding 6-12 months); female subjects were of non-childbearing potential, defined as follows: postmenopausal females who have had at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhoea with serum FSH>40mIU/ml; females who have had a hysterectomy or bilateral oophorectomy within 6 weeks.

Patients were excluded from the study if a secondary cause for pulmonary fibrosis was identified, if they had a respiratory tract infection within two months prior to recruitment, a recognised significant co-existing respiratory disorder or if they had a significant medical, surgical or psychiatric disease that would affect subject safety or influence the study

outcome, if they were receiving immunosuppressant medication other than prednisolone, azathioprine or mycophenolate mofetil (including cyclophosphamide, methotrexate, d-penicillamine, colchicines, gamma-interferon), had co-trimoxazole allergy or intolerance and untreated folate or B12 deficiency.

The following concurrent therapy required caution or increased monitoring: digoxin, warfarin, phenytoin, sulphonylureas, procainamide hydrochloride.

Study design

Patients underwent 5 visits within 12 months period of the study (Table 4.1). At screening, all patients were given an opportunity to ask questions and were asked to sign informed consent form, which was followed by collection of demographical data, history of past and current medical illnesses, current treatment including immunosuppression, physical examination. Spirometry or full pulmonary function test were performed in all patients within 1 months of recruitment. In co-trimoxazole study 6 minute walk test was performed where this service provision was available, screening for glucose-6-phosphate deficiency was performed in male subjects and an ECG was taken unless performed within the previous 6 months, a questionnaire was administered to assess baseline health and social care resource utilisation and costs, an additional questionnaire assessed baseline socioeconomic status.

The following was performed at screening and 6 weeks, 6 months 9 months and 12 months after randomisation:

- Spirometry
- MRC Breathlessness score
- Full blood count, Urea and Electrolytes and Liver function tests (this is unlikely to be additional to standard care)
- The EuroQol EQ-5D
- A health and social care resource utilisation and costs questionnaire

The following was performed at screening and 6 months and 12 months after randomisation:

- Six minute walking test as described previously with assessment of desaturation during the test and distance walked – in a subgroup of patients only
- St George's Respiratory Questionnaire
- Total lung diffusing capacity of carbon monoxide
- Static lung volumes including total lung capacity (TLC)

- Blood was stored for vascular endothelial growth and KL-6 in a subgroup of patients only

For the duration of the study an assessment was made of:

- all cause mortality and mortality due to IPF
- the requirement for escalation of therapy. This included an increase or decrease in the dose of prednisolone or azathioprine, addition of other treatments including acetylcystine and the commencement of oxygen therapy
- adverse events
- hospitalisations

The 6 week assessment was undertaken between 4 and 8 weeks and the 6 month assessment was conducted between 5 and 7 months, the 9 month assessment was between 8 and 10 months and the 12 month assessment between 11-13 months to permit study visits to coincide with routine medical follow-up.

Patients on azathioprine or mycophenolate mofetil required additional monitoring of full blood count on two weekly basis due to potential risk of neutropenia. Patients on mycophenolate mofetil had their Urea and Electrolytes and Liver function tests checked two weeks after recruitment.

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	0	6 weeks	6 months	9 months	1 year
Consent	**X**				
History & Examination	**X**	**X**	**X**	**X**	**X**
Drug dispensed	**X**	**X**	**X**	**X**	
Adverse events	**X**	**X**	**X**	**X**	**X**
Concomitant medication	**X**	**X**	**X**	**X**	**X**
Spirometry	**X**	**X**	**X**	**X**	**X**
MRC score	**X**	**X**	**X**	**X**	**X**
FBC, U&E, LFT	**X**	**X**	**X**	**X**	**X**
6 Min Walk	X		X		X
SGRQ	**X**		**X**		**X**
DLCO	X		X		X
TLC	**X**		**X**		**X**
EQ-5D	**X**	**X**	**X**	**X**	**X**
Socioeconomic status questionnaire	**X**				
Cost questionnaire - baseline	**X**				
Cost questionnaire – follow-up		**X**	**X**	**X**	**X**

Table 4.1 Time and events. Bold indicates measurements that are performed in all subjects. Other measurements are performed in a subgroup of patients.

Statistical analysis

The primary endpoint was a change in FVC expressed in millilitres (ml) after 12 months of study drug. Patients were included in the intention to treat (ITT) analysis irrespective of whether they remained in or withdrew from the study at any point and the vital status of all patients was determined at 12 months. A per-protocol (PP) analysis was also completed with patients being excluded if they did not adhere to study medication or withdrew from the trial prior to death. Assuming a residual SD of 400ml (from data from ISOLDE and TRISTAN study courtesy of J. Anderson, GSK, Greenford), then with 63 patients in each group the study had an 80% power to detect a mean difference of 200ml at a significance level of $p = 0.05$. Our sample size was higher in order to allow for drop-outs. The value of 200ml for the mean difference in FVC from baseline was used to power the study since this represents the minimum change required for a favourable or unfavourable response to treatment as proposed in the ATS/ERS International Consensus statement[5].

Quality Adjusted Life Years (QALYs) were calculated by converting the EQ-5D results at each time point into utilities using UK health state valuations[189], then measuring the resulting area under the curve. We analyzed the primary outcome by a linear mixed model with site as a random effect and the use of azathioprine as a fixed effect. Site was included as a random effect due to the inclusion of a number of hospitals entering with a small number of patients. We term this the “unadjusted” analysis. In addition an “adjusted” analysis was performed by including the baseline value of the outcome as a fixed effect. A corresponding analysis was undertaken for each outcome, but for the binary outcome measures a logistic mixed model was used and for time until death a Cox proportional hazards model was used with robust variance by site.

Data from patients were analyzed according to allocated group, with all patients with data available included in the ITT analysis. Additionally, a sensitivity analysis was conducted by multiple imputation from an imputation model which contained randomisation group and all outcome measures; however if 40% or more of the data were missing the variable was not imputed or used in the imputation model. The imputation model chosen was a multivariate normal distribution[190]; which has been shown to be robust against departures from multivariate normal distribution. A total of 5 imputed datasets were created and then combined using Rubin’s equations. No safety or per-protocol data was imputed.

Two subgroup analyses were prespecified, by disease severity (classified as severe if baseline FVC was 60% of predicted or less) and by whether the patient was taking medication or not at baseline. Subgroup analysis was undertaken by testing for an interaction between subgroup and treatment group in the mixed model specified above but also including the subgroup as a fixed effect. Subgroup analyses were only completed on absolute FVC and death.

The safety analysis consisted of all patients who took at least one dose of study medication. The rate of adverse events was compared using either Poisson or Negative binomial regression as required with results presented as incidence rate ratios (IRR).

A cost-effectiveness and cost-utility analysis estimated the incremental costs and outcomes (mls improvement in FVC and QALYs gained) of treating a patient with or without co-trimoxazole, measured from the viewpoints of both the UK National Health Service and society. Health service costs were defined as drug costs, hospital costs and GP practice costs. The societal analysis included NHS costs plus costs arising from social care providers, patient out of pocket costs and informal carer time. The price year of the analysis was 2009. Quantities of resource use were multiplied by unit costs extracted from relevant UK[158, 159, 191].

Results are presented as point estimate incremental cost and outcomes and incremental cost-effectiveness ratios (ICERs) for both ITT and PP populations. A complete case analysis and imputed, adjusted (for baseline cost, FVC and QALY) analysis are reported. 95% confidence intervals around increments were calculated using a non-parametric bootstrap approach. Uncertainty in the ICER is shown as the cost-effectiveness acceptability curve (CEAC)[192].

A subgroup analysis was performed for FVC and deaths to determine the effect of patients receiving concomitant immunosuppressive therapy at recruitment and two sensitivity analyses were undertaken for those patients with a definite/probable diagnosis of IPF (UIP biopsy or definite/probable UIP on HRCT[164] and UIP biopsy, honeycombing on HRCT or a score of more than 0.6 according to the algorithm described by Fell et all[165]).

The reason for admission to hospital and the cause of death was obtained from death certificates and adverse event reporting forms. These were reviewed by two blinded physicians.

Analyses were performed in a blinded fashion by Allan Clark (statistician) and Edward Wilson (health economist).

Objective

The primary objective is to compare the efficacy and safety of 12 months therapy with co-trimoxazole 960 mg twice daily to placebo in a double-blind placebo-controlled study of patients with fibrotic idiopathic interstitial pneumonia. The secondary objective is to estimate the incremental cost effectiveness of co-trimoxazole plus standard care compared with standard care alone.

Endpoints

The primary endpoint of the study was change in forced vital capacity after 12 months of study drug.

Secondary outcomes were

- change in MRC breathlessness score
- change in total lung capacity
- change in total lung diffusing capacity of carbon monoxide
- change in St Georges Respiratory Questionnaire
- change in 6 minute walking distance and desaturation
- change in EuroQol (EQ-5D) score

Other endpoints were:

- all cause mortality and mortality due to IPF
- the requirement for escalation of therapy. This includes commencement of prednisolone or azathioprine (in patients who had not been on immunossupression prior to recruitment) or increase or decrease in the dose of prednisolone or azathioprine (in those who had been on immunosuppression prior to recruitment), addition of other treatments including acetylcystein and the commencement of oxygen therapy
- the number of hospitalisations

Safety endpoints were:

- Blood haematology and biochemistry
- Drug related adverse event

4.3 Results

4.3.1 Interim Analysis

The interim analysis of safety performed in a blinded fashion in October 2009 when 50% of patients completed six months of treatment. The baseline characteristics showed no evidence of imbalance, in particular, FVC was well balanced with a mean of 2.23 in Group A and 2.25 in Group B (Table 4.2).

Characteristic	Group A (n=35)	Group B (n=32)
Female	10/35 (28.6%)	9/32 (28.1%)
MRC dyspnoea grade		
1	0/35 (0.0%)	0/32 (0.0%)
2	2/35 (5.8%)	5/32 (15.6%)
3	14/35 (40.0%)	8/32 (25.0%)
4	14/35 (40.0%)	14/32 (43.8%)
5	5/35 (14.3%)	5/32 (15.6%)
Smoking History		
Ex-smoker	27/35 (77.1%)	23/32 (71.9%)
Never-smoker	8/35 (22.9%)	9/32 (28.1%)
UIP	29/34 (85.3%)	26/32 (81.3%)
NSIP	0/32 (0.0%)	3/25 (12.0%)
Steriods (Prednisilone)	23/35 (65.7%)	27/32 (84.4%)
Biopsy*		
Any	5 /35	10 /32
Open Lung	2 / 35	3 /32
TransBronchial	0 / 35	3 /32
VATS	3 /35	4 /32
Age (years)	73.9 (8.6)	70.6 (9.2)
FEV1		
Absolute	1.83 (0.68)	1.86 (0.56)
%	70.25 (21.56)	73.94 (24.57)
FVC		
Absolute	2.23 (0.87)	2.25 (0.71)
%	66.96 (23.02)	69.49 (23.53)
TLC		
Absolute	3.79 (1.28)	4.07 (1.00)
%	60.64 (17.38)	64.86 (15.87)
DLCO		
Absolute	3.04 (0.88)	3.20 (1.22)
%	37.03 (9.11)	38.92 (12.99)
KCO		
Absolute	0.91 (0.23)	0.97 (0.33)
%	71.30 (17.36)	72.45 (25.71)
Site		
Addenbrookes	2	1
Basildon and Thurrock	1	1
Bedford	3	3
Colchester	3	1
Ipswich	5	5
JPH	2	1
Luton	1	1
NNUH	9	9
Papworth	4	3
QEH	3	6
Southend	0	1
Whipps Cross	1	0
Wythenshaw	1	0

Table 4.2 Summary of baseline characteristics (Interim analysis).There was no imbalance in baseline characteristics between the two groups.

There was no difference in safety measures between the two treatment arms showing no significant difference in terms of the percentage dying (5.7% vs 15.6%, p=0.202), the average number of adverse events (p=0.656), and severe adverse events (p=0.681). However, in terms of the average number of adverse reactions there was borderline evidence of a difference (p=0.045) with an average of 0.34 adverse reactions per person in Group A compared with 0.09 in group B. No difference was observed in the rate of withdrawal (p=0.328), although this was high in both groups (Table 4.3).

Measure	Number Group A	Number Group B	Group A	Group B	IRR (95% CI)[+]	p-value
Adverse reaction	12	3	0.34 (0.77)	0.09 (0.30)	0.27 (0.08,0.97)	0.045
ENT	0	2	0.00 (0.00)	0.06 (0.25)	-	0.992
GI	2	0	0.06 (0.34)	0.00 (0.00)	-	0.993
Renal	1	0	0.03 (0.17)	0.00 (0.00)	-	0.993
Anorexia	2	0	0.06 (0.24)	0.00 (0.00)	-	0.993
Nausea	6	1	0.17 (0.38)	0.03 (0.18)	0.18 (0.02,1.51)	0.115
Rash	1	0	0.03 (0.17)	0.00 (0.00)	-	0.993
AR (not nausea)	6	2	0.17 (0.57)	0.06 (0.25)	0.36 (0.07,1.81)	0.217
Adverse event (inc. Adverse reactions)	55	46	1.57 (1.69)	1.44 (1.44)	0.91 (0.62,1.35)	0.656
Serious Adverse event	13	10	0.37 (1.03)	0.31 (0.54)	0.84 (0.37,1.92)	0.681
SAE related	1	0	1/35 (2.9%)	0/32 (0.0%)	NA	0.335
Deaths	2	5	2/35 (5.7%)	5/32 (15.6%)	3.06 (0.55,17.01)[*]	0.202
Withdrawn	15	10	15/35 (42.8%)	10/32 (31.3%)	0.61 (0.22,1.65)	0.328

Table 4.3 Comparison safety measures between treatment arms (interim analysis).+ is the ratio of the mean in group A divided by the mean in group B.* Odds ratio (95% CI). There was no difference in safety measures between the two groups.

4.3.2 Final analysis

4.3.2.1 Baseline characteristics

582 patients with fibrotic idiopathic interstitial pneumonia were screened between January 2008 and December 2009. The main reasons for not being included into the study were patient's refusal to participate, ongoing change in immunosuppression, a stable course of the disease and not meeting inclusion criteria due to a significant co-existing illness (for example recent myocardial infarction or significant renal impairment) or

frailty. Of these patients 192 were enrolled, 10 of which were not randomized due to death (3 patients) or not meeting inclusion criteria (for example identifiable cause of pulmonary fibrosis), and one was a postrandomisation withdrawal due to an ineligibility of the diagnosis (Figure 4.1).

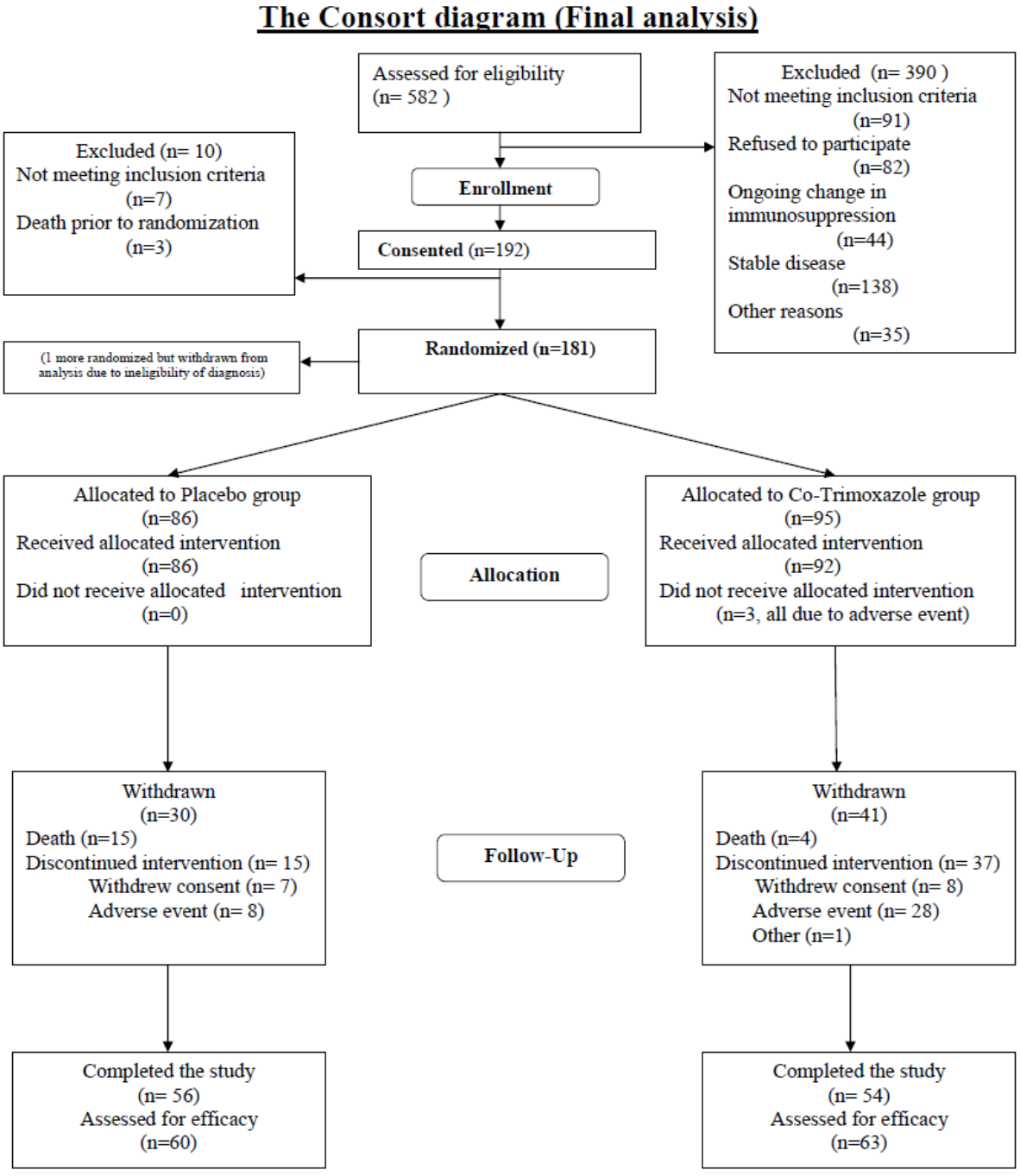


Figure 4.1 Patient disposition. n= number of patients. Lung function data required for the primary endpoint was obtained from four patients in the placebo group and nine patients in the co-trimoxazole group from routine clinical data following withdrawal from the study

The intention to treat analysis included 181 randomised patients (Figure 4.1). The mean age of the patients was 71.6 ± 8.5 years, 28% were women and 75% were ex-smokers. The majority of patients had MRC dyspnoea score of 3 or 4. The mean FVC% predicted was 70.7 ± 21.2% and DLCO% predicted was 37.5 ± 11.5% consistent with moderate/severe disease. Seventy-five patients had definite diagnosis of IPF (biopsy or diagnostic radiological features) and 86 had probable IPF radiologically[15] and 87 would be likely to have UIP on biopsy according to Fell et al[16]. Sixty percent of patients were taking immunosuppressive treatment either with prednisolone alone or in combination with azathioprine or mycophenolate mofetil, 28% were receiving antioxidants (Table 4.4). Patients who were not receiving immunosuppressive therapy showed evidence of functional decline in preceding 6-12 months (>10% decline in FVC or >15% decline in diffusing capacity of carbon monoxide (DLCO); those who were already on immunosuppression at the time of recruitment were not expected to demonstrate similar change in lung function over the preceding 6-12 months as it was assumed that they had already developed progressive disease at an earlier stage which led to prescribing of immunosuppression. The treatment groups were generally well matched (with the possible exception of MRC score), and hence no adjustment to the analysis was required to account for baseline imbalance.

	Placebo (n=86)		Co-trimoxazole (n=95)	
Characteristic	Mean / number	Sd / %	Mean/ number	Sd / %
Female	21	24.4%	29	30.5%
Age (years)	70.65	8.56	72.38	8.45
Body Mass Index (kg/m^2)	28.61	5.54	28.86	8.03
Smoking history				
Current	1	1.2%	1	1.1%
Ex-smoker	65	75.6%	71	74.7%
Never	20	23.3%	23	24.2%
Clinical diagnosis				
Usual Interstitial Pneumonia	81	94.2%	89	93.7%
Non-Specific Interstitial Pneumonia	5	5.8%	6	6.3%
Biopsy				
Open lung	5 / 15	5.8%	3 / 14	3.2%
Video-assisted thoracic surgery	10 / 15	11.6%	11 / 14	11.6%
Pathological/radiological diagnosis				
Definite UIP (histologically confirmed UIP, honeycombing on HRCT or in report on destroyed HRCT)	38		37	
Probable UIP (all features consistent with UIP except honeycombing on HRCT or in report on destroyed HRCT)	40		46	

Table 4.4 Summary of baseline characteristics for all ITT individuals.

NSIP (histologically confirmed NSIP and HRCT features consistent with NSIP)	7		11	
HRCT report destroyed	1		1	
Fell Criteria				
Definite UIP (histologically confirmed UIP, honeycombing on HRCT or in report on destroyed HRCT)	38		37	
Probable UIP (Fell score ≥ 0.6)	41		46	
Intermediate UIP/NSIP (Fell score < 0.6)	1		3	
Absent honeycombing in report on destroyed HRCT	4		6	
Histological diagnosis of NSIP	1		2	
Table 4.4				
HRCT report destroyed	1		1	
Time from diagnosis to randomisation (months)*	31.1	56.8	25.5	37.1
Diagnosis within 12 months	21	24.4%	25	26.3%
Co-existing emphysema	9	10.5%	6	6.3%
Medical Research Council (MRC) dyspnoea score				
2	17	19.8%	12	12.6%
3	28	32.6%	42	44.2%
4	31	36.1%	31	32.6%
5	10	11.6%	10	10.5%
FVC (ml)	2.4	0.8	2.3	0.9
FVC percent predicted (%)	71.5	21.0	70.0	21.5
TLC (ml)	4.2	1.6	3.8	1.1
TLC percent predicted (%)	66.3	22.5	61.8	15.8
DLCO (mmol/min/KPa)	3.5	1.9	3.2	1.6
DLCO percent predicted (%)	39.1	12.8	36.0	10.0
6 minute walk (6MW) distance (m)	331.2	117.6	285.6	96.1
6MW desaturation of 4% or more	32 / 43	74.4%	31 / 38	81.6%
St George Respiratory Questionnaire total (units)	59.3	17.5	55.7	17.9
Treatment				
Prednisolone	52	60.5%	54	56.8%
Azathioprine	26	30.2%	28	29.5%
Mycophenolate mofetil	3	3.5%	4	4.2%
Carbocysteine	2	2.3%	2	2.1%
Mecysteine	0	0.0%	1	1. 1%
N-acetylcysteine	20	23.3%	25	26.3%
Oxygen	10	11.6%	12	12.6%
FVC% <= 60	26	30.2%	34	35.8%

Table 4.4 Summary of baseline characteristics for all ITT individuals. Kg: kilogram, m: meters, MRC: Medical Research Council, FVC: forced vital capacity, ml: millilitres, TLC: total lung capacity, DLCO: diffusing capacity of carbon monoxide, 6MW: 6 minute walk. The number of patients undergoing the following measurements were: TLC: Placebo-67, co-trimoxazole-74; DLCO: Placebo-72, co-trimoxazole-77; 6 minute walk: Placebo-43, co-trimoxazole-38; SGRQ: Placebo-81, co-trimoxazole-87. Units are number of patients unless indicated. *median and interquartile range

A total of 71 patients did not complete 12 months treatment: 17 due to death and 52 (29%) discontinued the study medication prematurely, of these 17 due to withdrawal of consent and 35 due to adverse events (7 in placebo and 28 in co-trimoxazole group). 56 patients in placebo group and 54 in co-trimoxazole group completed 12 months treatment. The results of FVC at 12 months after randomization were obtained in 60 patients in

placebo group and 63 in co-trimoxazole group irrespective of whether they completed 12 months treatment or withdrew prematurely.
Overall adherence to the study medication was good with 96% of patients in the co-trimoxazole group and 90% in the placebo group receiving more than 80% of the scheduled study drug doses.

4.3.2.2 Efficacy

Intention-to-treat population

There was no significant difference between treatment groups for change in pulmonary function parameters in either the unadjusted or adjusted analyses (Table 4.5). Analysis of the other endpoints found significant differences in the symptom domain of the SGRQ (-5.73, 95% CI -11.86 to 0.40, p=0.009, above the threshold of 4 for a minimally important clinical difference) and the percentage of patients requiring an increase in oxygen therapy (OR=0.15, 95% CI 0.03 to 0.80, p=0.027) in favour of co-trimoxazole treatment.

	Placebo			Co-trimoxazole			Unadjusted		Adjusted for baseline	
Outcome	N	Mean	Sd	N	Mean	Sd	p-value	95 CI%	p-value	95% CI
FVC abs	60	-195.67	288.82	63	-182.22	330.15	0.781	15.50 (-93.6,124.63)	0.988	0.81 (-107.44,109.07)
FVC %	60	-4.79	8.70	63	-4.65	9.96	0.938	0.13 (-3.14,3.40)	0.978	0.05 (-3.22,3.32)
FEV abs	60	-140.50	252.68	63	-126.19	245.89	0.686	18.04 (-69.28,105.36)	0.942	3.15 (-82.34,88.64)
FEV %	60	-3.65	9.89	63	-3.71	9.47	0.956	0.10 (-3.26,3.45)	0.992	0.02 (-3.32,3.35)
TLC abs	45	-410.00	1328.39	44	-201.36	582.69	0.127	307.98 (-87.42,703.38)	0.943	11.29 (-298.59,321.16)
TLC %	45	-5.70	19.54	44	-3.58	9.87	0.212	3.74 (-2.14,9.62)	0.972	-0.08 (-4.73,4.57)
DLCO abs	50	-0.22	0.81	45	-0.30	0.68	0.429	-0.12 (-0.41,0.17)	0.480	-0.11 (-0.40,0.19)
DLCO %	50	-3.88	10.75	45	-3.67	8.10	0.812	-0.44 (-4.02,3.15)	0.459	-1.34 (-4.88,2.21)
SGRQ symptoms	53	0.76	15.83	53	-4.82	16.37	0.067	-5.73 (-11.86,0.40)	0.009	-6.88 (-12.06,-1.70)
SGRQ activity	55	3.09	13.27	52	0.43	15.10	0.339	-2.64 (-8.05,2.77)	0.484	-1.82 (-6.91,3.27)
SGRQ impact	54	0.99	13.88	50	2.50	18.68	0.643	1.50 (-4.83,7.83)	0.690	1.24 (-4.86,7.34)
SGRQ total	52	1.78	11.59	49	0.71	13.96	0.658	-1.13 (-6.16,3.89)	0.599	-1.30 (-6.13,3.54)
6MW distance	31	-19.48	86.49	20	-18.70	75.39	0.983	0.50 (-45.98,46.97)	0.835	-5.16 (-53.55,43.24)
EQ5D	73	-0.18	0.31	71	-0.17	0.35	0.801	0.01 (-0.09,0.12)	0.920	0.01 (-0.10,0.11)
MRC score	56	0.21	0.82	54	0.07	0.72	0.319	-0.15 (-0.43,0.14)	0.533	-0.09 (-0.37,0.19)
Hospital days	59	0.81	1.92	54	3.06	12.48	0.329	0.64 (0.26,1.56)	0.329	0.64 (0.26,1.56)
Any death		19/86	22.1		18/95	19.0	0.580	0.81 (0.39,1.68)		
IPF death		4/82	4.9		3/80	3.8	0.703	0.74 (0.16,3.44)		
Medicine increase		22/65	33.9		12/57	21.1	0.122	0.48 (0.19,1.21)		
Medicine decrease		5/57	8.8		7/54	13.0	0.541	1.47 (0.43,5.04)		
Oxygen increase		11/61	18.0		2/55	3.6	0.027	0.15 (0.03,0.80)		
Oxygen decrease		0 / 56	0.0		0 /54	0.0	-	-		
6 minute walk desaturation		31 / 35	88.6		16 / 20	80.0	0.396	0.52 (0.11,2.36)	0.634	0.64 (0.10,4.07)

Table 4.5 Change-from-baseline results of primary and secondary outcomes, ITT complete case analysis#. # The change from baseline (outcome – baseline) is presented with a negative value indicating a decrease from baseline and a positive value indicating an increase. The unadjusted and unadjusted results refer to the effect of group 2 over group 1, i.e. a positive value indicates that group 2 is higher than group 1 and a negative value indicates that group 2 is lower than group 1. * median (iqr) and IRR rather than mean difference

For the number of hospital nights a negative binomial regression model was used as opposed to a Poisson regression model due to overdispersion in the data. There was no significant difference in the number of hospital nights. There was no change in the risk of death one year after starting the drug (OR 0.84, 0.39-1.68,p=0.580) or in the time until death with a hazard ratio of 0.63 (95% CI 0.31-1.29, p=0.207). The Kaplan-Meier plot is presented in Figure 4.2.

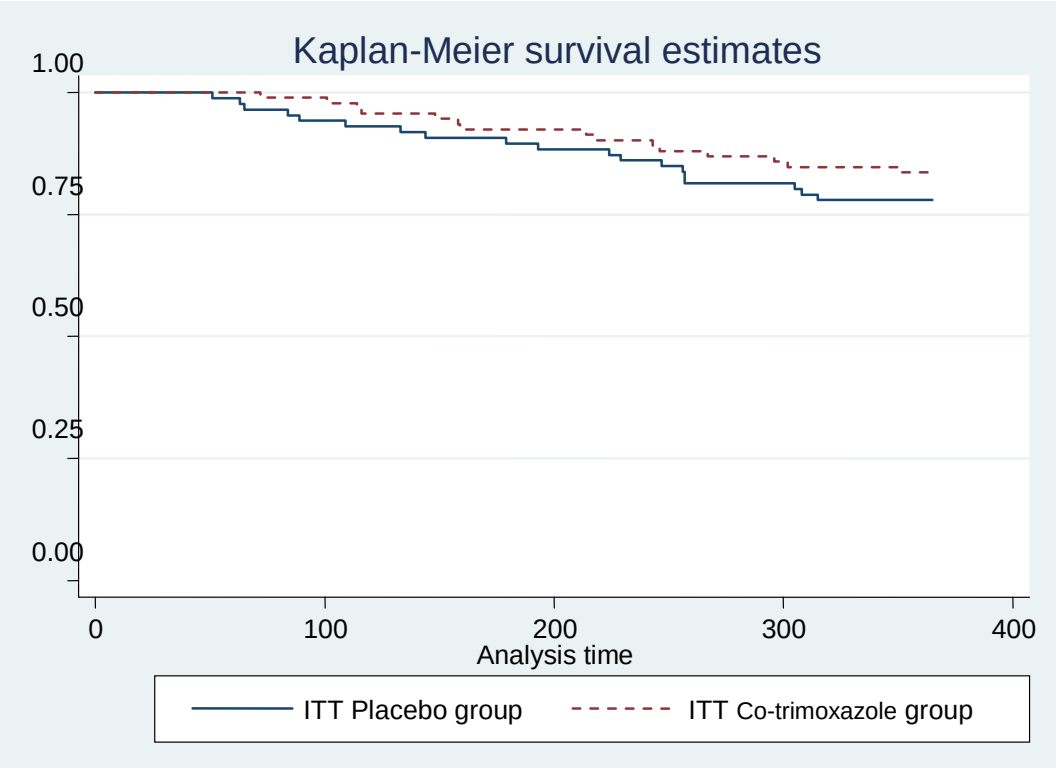


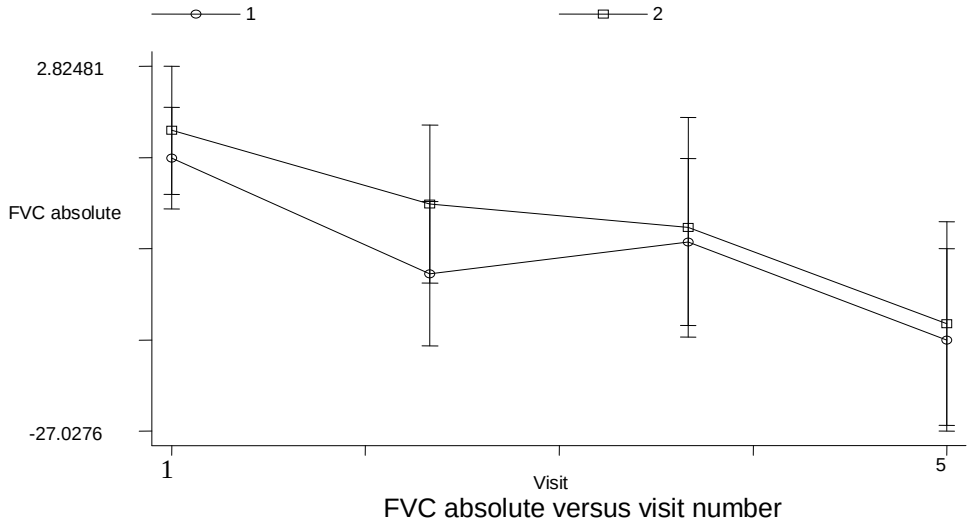
Figure 4.2 Kaplan-Meier plot of time until death based on intention to treat population.

Change over time analysis

The results of the change over time analysis are given in Table 4.6. The change over time in the primary outcome is given in Figure 4.3, in SGRQ symptoms score, EQ5D and number of hospital nights is given in Figures 4.4-4.6.

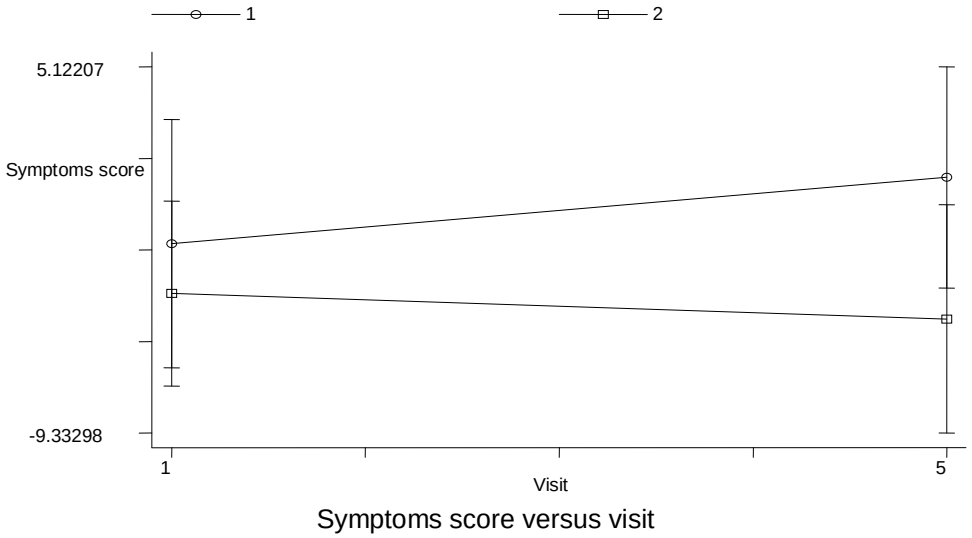
		Unadjusted			Adjusted	
Outcome	Overall mean		Treatment x time point interaction	Overall mean		Treatment x time point interaction
	95% CI	p-value	p-value	95% CI	p-value	p-value
FVC abs	25.60 (-51.04,102.23)	0.513	0.587	20.80 (-55.42,97.02)	0.593	0.595
FVC %	1.37 (-0.92,3.67)	0.241	0.403	1.33 (-0.96,.62)	0.255	0.405
FEV abs	21.49 (-42.73,85.71)	0.512	0.631	16.93 (-46.13,79.99)	0.599	0.631
FEV %	0.11 (-2.30,2.52)	0.931	0.468	0.12 (-2.27,2.50)	0.922	0.478
TLC abs	186.86 (-152.32,526.03)	0.280	0.311	-5.72 (-258.52,247.09)	0.956	0.403
TLC %	2.36 (-2.66,7.38)	0.357	0.485	0.59 (-3.34,4.52)	0.769	0.640
DLCO abs	0.20 (-0.06,0.45)	0.127	0.052	0.21 (-0.04,0.47)	0.106	0.054
DLCO %	1.93 (-1.13,4.98)	0.217	0.273	1.46 (-1.56,4.48)	0.344	0.251
SGRQ symptoms	-2.68 (-8.27,2.91)	0.348	0.302	-4.02 (-8.86,0.82)	0.103	0.274
SGRQ activity	-1.89 (-6.56,2.77)	0.427	0.989	-1.64 (-6.06,2.78)	0.467	0.920
SGRQ impact	1.35 (-4.14,6.84)	0.630	0.661	0.52 (-4.79,5.83)	0.847	0.637
SGRQ total	-0.29 (-4.65,4.07)	0.895	0.976	-0.68 (-4.91,3.54)	0.752	0.994
6MW distance	-0.43 (-43.26,42.4)	0.984	0.723	-1.96 (-45.31,41.40)	0.930	0.703
EQ5D	0.04 (-0.05,0.13)	0.363	0.647	0.04 (-0.05,0.12)	0.420	0.645
MRC score	0.03 (-0.17,0.22)	0.803	0.323	0.03 (-0.16,0.22)	0.758	0.355

Table 4.6 Results of change-over-time analysis



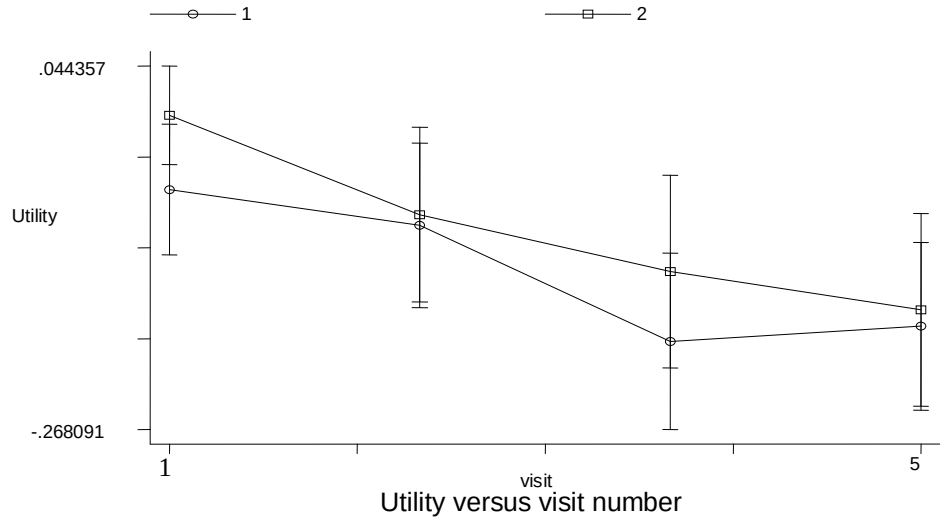
Group 1 – Placebo, Group 2 - Co-trimoxazole

Figure 4.3 Change over the period of 12 months (visit 1 to visit 5) in FVC (absolute) since baseline visit



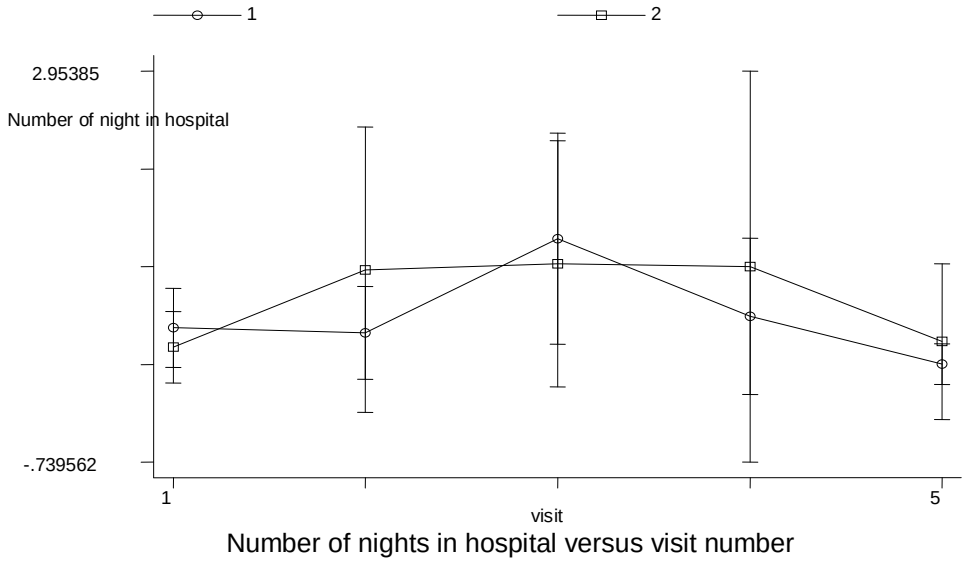
Group 1 – Placebo, Group 2 - Co-trimoxazole

Figure 4.4 Change over the period of 12 months (visit 1 to visit 5) in SGRQ symptoms since baseline visit



Group 1 – Placebo, Group 2 - Co-trimoxazole

Figure 4.5 Change over the period of 12 months (visit 1 to visit 5) in EQ5D score since baseline visit



Group 1 – Placebo, Group 2 - Co-trimoxazole

Figure 4.6 Cumulative number of nights in hospital over the period of 12 months (visit 1 to visit 5)

Subgroup analysis

No evidence of a subgroup effect for disease severity was observed on FVC (adjusted p=0.809) or deaths (p=0.816). Similarly, no evidence of a subgroup effect for medication was observed on FVC (adjusted p=0.816) or deaths (p=0.059) the OR for those not on medication was 3.50 (95% CI: 0.62-19.96) compared to 0.54 (95% CI: 0.23 – 1.31) for those on medication.

ITT imputed results

Due to convergence problems with ICE it was decided to switch to multiple imputations assuming a multivariate normal distribution. The Markov chain Monte Carlo algorithm was ran for 1,000 burn-in iterations subsequently imputing the data every 500 iterations to construct 5 imputed datasets. The results of the imputation sensitivity analysis revealed that the results were robust to missing data with the results not changing significantly (Table 4.7).

	Unadjusted		Adjusted for baseline	
Outcome	p-value	95 CI%	p-value	95% CI
FVC abs	0.998	-0.19 (-141.18,140.80)	0.931	-5.99 (-146.78,134.79)
FVC %	0.807	-0.22 (-2.00,1.56)	0.745	-0.30 (-2.08,1.48)
FEV abs	0.808	-5.64 (-51.29,40.00)	0.586	-12.44 (-57.15,32.27)
FEV %	0.629	-0.44 (-2.24,1.35)	0.582	-0.50 (-2.29,1.29)
EQ5D	0.557	0.02 (-0.04,0.08)	0.976	0.00 (-0.05,0.05)
Hospital days	0.295	0.47 (0.66,3.82)	0.098	0.69 (0.88,4.53)

Table 4.7 Change-from-baseline results of primary and secondary outcomes, ITT imputed analysis

Per-protocol analysis

The per-protocol sample consisted of 118 individuals, 65 in placebo group and 53 in co-trimoxazole group. The results were in keeping with the ITT analysis with the exception of deaths. Co-trimoxazole resulted in a significant improvement in the symptom domain of SGRQ (mean difference -5.30 (-11.99, 1.40) units) and QALYs gained (mean difference 0.12 (0.01,0.22) QALYs), and a reduction in the percentage of patients requiring an increase in oxygen therapy (OR=0.05 (0.00,0.61)) compared to placebo (Table 4.8).

	Placebo			Co-trimoxazole			Unadjusted		Adjusted for baseline	
Outcome	N	Mean	Sd	N	Mean	Sd	p-value	95 CI%	p-value	95% CI
FVC abs	51	-183.73	279.90	48	-175.21	359.30	0.864	11.09 (-115.47,137.64	0.985	1.23 (-125.9,128.37)
FVC %	51	-4.35	8.88	48	-4.80	10.88	0.851	-0.37 (-4.23,3.49)	0.819	-0.45 (-4.33,3.42)
FEV abs	51	-128.43	241.18	48	-124.79	273.11	0.820	11.73 (-89.48,112.94)	0.987	0.81 (-99.12,100.75)
FEV %	51	-3.19	10.06	48	-3.84	10.32	0.866	-0.34 (-4.32,3.64)	0.822	-0.45 (-4.41,3.50)
TLC abs	42	-427.14	1371.9	34	-167.35	635.41	0.104	381.28 (-78.36,840.92)	0.811	44.10 (-317.16,405.37)
TLC %	42	-5.92	20.19	34	-3.11	10.49	0.169	4.77 (-2.03,11.57)	0.881	0.41 (-4.98,5.80)
DLCO abs	43	-0.21	0.84	33	-0.39	0.70	0.222	-0.22 (-0.56,0.13)	0.247	-0.20 (-0.55,0.14)
DLCO %	43	-4.03	11.11	33	-4.66	7.91	0.456	-1.63 (-5.91,2.65)	0.368	-1.94 (-6.18,2.29)
SGRQ symptoms	47	0.36	16.44	49	-4.63	16.75	0.121	-5.30 (-11.99,1.40)	0.046	-5.73 (-11.38,-0.10)
SGRQ activity	49	2.99	13.97	48	1.56	14.91	0.879	-0.52 (-7.25,6.21)	0.660	-1.23 (-6.73,4.27)
SGRQ impact	48	0.49	14.05	47	1.26	17.97	0.811	-0.92 (-8.48,6.64)	0.839	0.66 (-5.68,6.99)
SGRQ total	46	1.40	11.93	46	0.36	14.07	0.694	-1.08 (-6.49,4.32)	0.602	-1.38 (-6.59,3.82)
6MW distance	29	-13.34	85.10	19	-20.74	76.89	0.768	-7.21 (-55.15,40.72)	0.546	-15.31 (-64.97,34.36)
EQ5D	64	-0.16	0.30	53	-0.05	0.28	0.025	0.12 (0.01,0.22)	0.024	0.11 (0.01,0.21)
MRC score	51	0.16	0.83	50	0.08	0.72	0.643	-0.07 (-0.38,0.23)	0.841	-0.03 (-0.33,0.27)
Hospital days*	54	0.89	1.99	50	3.28	12.95	0.181	0.53 (0.21,1.34)	0.182	0.53 (0.21,1.35)
Any death		14/65	21.5		3/53	5.7	0.018	0.20 (0.05,0.76)		
IPF death		4 / 65	6.2		3 / 53	3.8	0.551	0.59 (0.10,3.37)		
Medicine increase		18/58	31.0		9 /51	17.7	0.08	0.39 (0.14,1.12)		
Medicine decrease		4 / 51	7.8		6 /50	12.0	0.610	1.42 (0.37,5.56)		
Oxygen increase		10 / 55	18.2		1 / 50	2.0	0.019	0.05 (0.00,0.61)		
Oxygen decrease		0 /51			0 /50		-	-	-	-
6 minute walk desaturation		27 / 31	87.1		15 / 19	79.0	0.446	0.55 (0.12,2.54)	0.644	0.64 (0.10,4.15)

Table 4.8 Results of per-protocol analysis

Also there was a significant (p=0.02) reduction in deaths with co-trimoxazole treatment (3/53) compared to placebo (14/65) with a hazard ratio of 0.21 (0.06,0.78) (P=0.02). A Kaplan-Meier plot of the time until death is given in Figure 4.7.

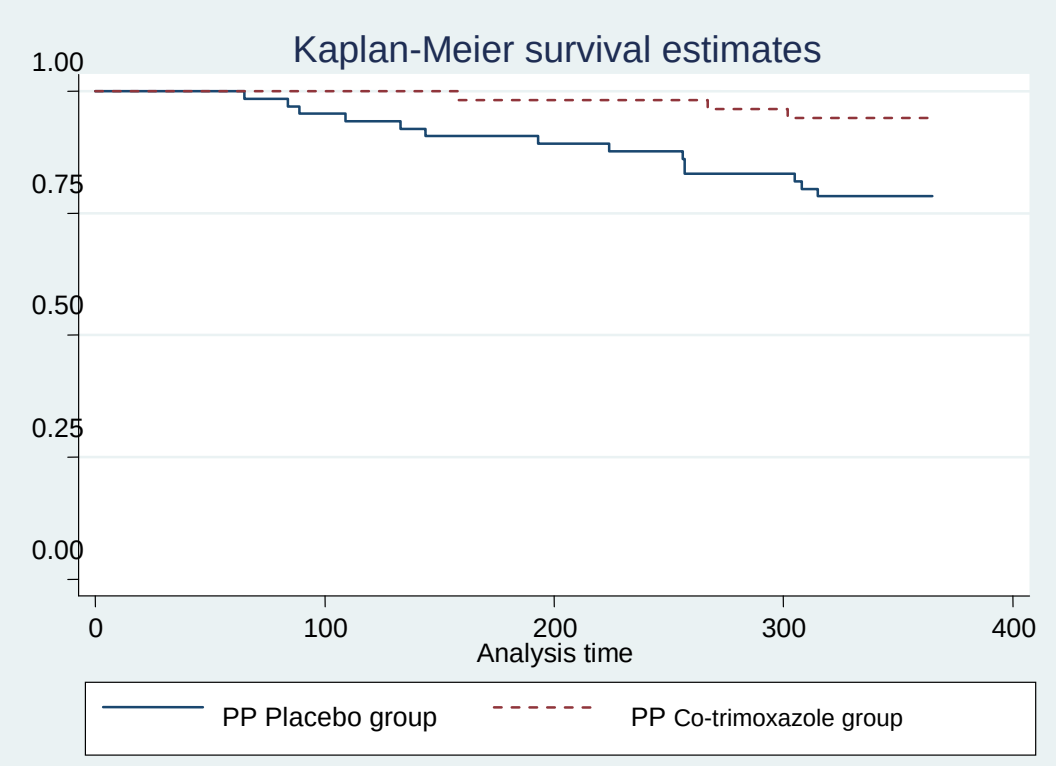


Figure 4.7 Kaplan-Meier estimate of survival function for the per-protocol population.

In the placebo group 13% (2/15) of those who withdrew died within 1 month of withdrawing, in the intervention group 6% (2/36) of those who withdrew died within 1 month.

Sensitivity analyses

The findings were the same as in the full analysis. For patients with honeycombing, UIP or likely to have UIP on biopsy using Fell's algorithm there was a significant (p=0.024) reduction in deaths with co-trimoxazole (2/46) compared to placebo (12/62) with a hazard ratio of 0.17 (0.04,0.79)). The results of analysis using radiological review data remained significant too (p=0.032) with a reduction in deaths with co-trimoxazole (2/42) compared to placebo (11/58) with a hazard ratio of 0.18 (0.04,0.86) (Table 4.9).

	Placebo			Co-trimoxazole			Unadjusted		Adjusted for baseline	
Outcome	N	Mean	Sd	N	Mean	Sd	p-value	95 CI%	p-value	95% CI
FVC (millilitres) [primary analysis]	51	-183.73	279.90	48	-175.21	359.30	0.864	11.09 (-115.47,137.64)	0.985	1.23 (-125.92,128.37)
FVC (millilitres) [Fell criteria]	50	-184.80	282.64	42	-185.24	365.68	0.992	-0.65 (-132.18,130.87)	0.865	-11.47 (-144.15,121.21)
FVC (millilitres) [radiology review]	47	-173.19	279.65	38	-218.16	351.31	0.552	-39.69 (-170.48,91.09)	0.329	-65.72 (-197.62,66.17)
Deaths [primary analysis]		14/65	21.54		3/53	5.66	0.02	0.21 (0.06,0.78)		
Deaths [Fell criteria]		12/62	19.35		2/46	4.35	0.024	0.17 (0.04,0.79)		
Deaths [radiology review]		11/58	18.97		2/42	4.76	0.032	0.18 (0.04,0.86)		

Table 4.9 Sensitivity analysis of FVC (change from baseline) between the original sample and the subsamples in the PP analysis.

Subgroup analysis

Patients receiving immunosuppressive treatment at entry into the study were more likely to die if they were in the control group in both the ITT (immunosuppression 17/53 no immunosuppression 2/33) and PP (immunosuppression 12/35 no immunosuppression 2/30) analyses. However baseline immunosuppressive therapy did not have an effect on mortality over 12 months in the intervention group: ITT (immunosuppression 11/54 no immunosuppression 7/40) and PP (immunosuppression 3/28 no immunosuppression 0/25).

Comparison of baseline characteristics of intention to treat and per protocol population

Comparing the baseline data for those who have valid FVC measurements at visit 5 with those who do not (Table 4.10) reveals significant differences in terms of FEV1, FVC and DLCO.

Outcome	Valid visit 5 results		No valid visit 5 results		95% CI	p-value
	Mean	Sd	Mean	Sd		
FEV1 absolute	2.00	0.65	1.68	0.49	0.32 (0.13,0.51)	0.0010
FEV1 percent	75.38	20.62	68.44	18.51	6.94 (0.66,13.22)	0.0304
FVC absolute	2.47	0.84	2.09	0.67	0.38 (0.13,0.62)	0.0032
FVC percent	72.92	21.20	66.07	20.71	6.85 (0.24,13.47)	0.0424
TLC absolute	4.08	1.49	3.76	1.10	0.32 (-0.18,0.82)	0.2025
TLC percent	65.30	20.85	60.96	15.21	4.34 (-2.59,11.27)	0.2180
DLCO absolute	3.52	1.78	2.79	1.54	0.73 (0.10,1.36)	0.0225
DLCO percent	39.00	11.33	33.54	11.29	5.46 (1.33,9.60)	0.0100

Table 4.10 Differences in baseline lung measurements between those with valid visit 5 data and those without

Change in FVC and DLCO over 12 months

22 (40%) patients in placebo arm had equal to or greater than 10% annual decline in absolute FVC; 29 (54%) patients demonstrated an annual change in FVC within 10% decline and 10% improvement (Table 4.11).

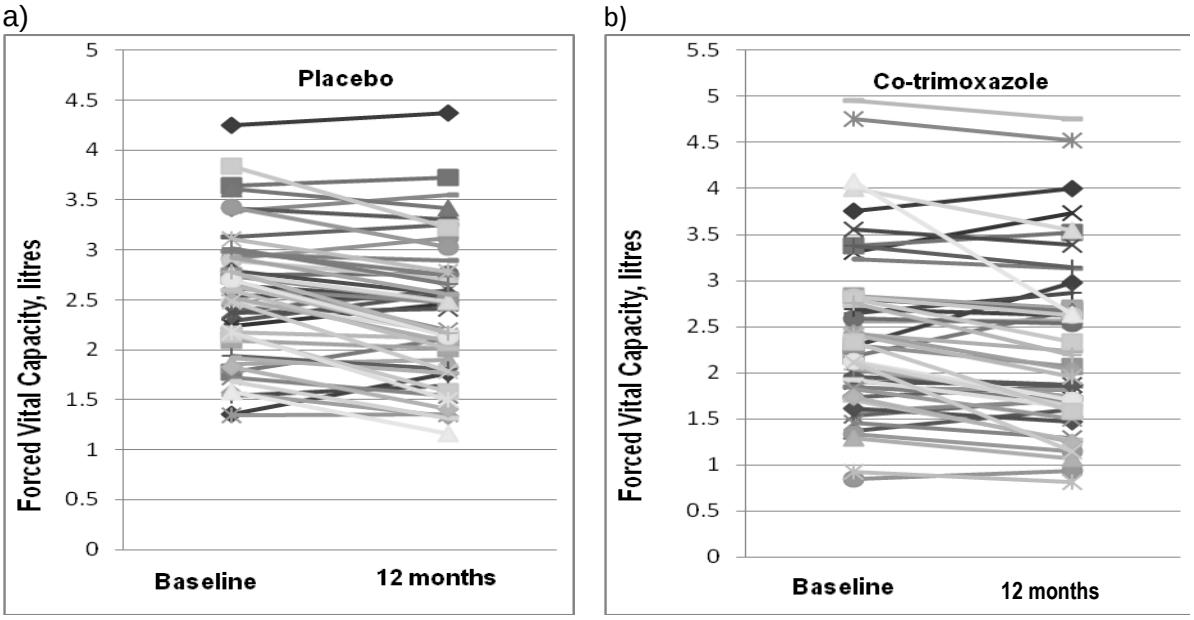


Figure 4.8 Change in Forced Vital capacity over 12 months in per protocol population in a) placebo arm and b) co-trimoxazole arm. Each symbol represents a different subject

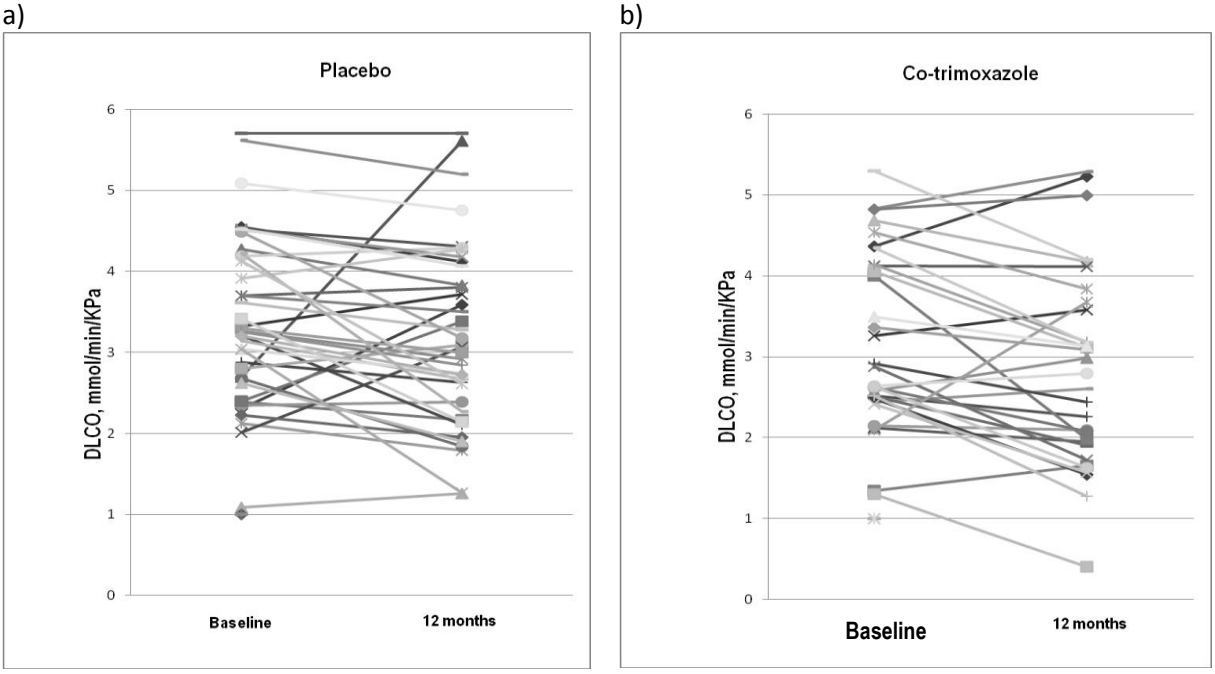


Figure 4.9 Change in Diffusion Capacity of carbon monoxide over 12 months in per protocol population in a) placebo arm and b) co-trimoxazole arm. Each symbol represents a different subject

% change in absolute FVC	Placebo and co-trimoxazole arms (n=112) n (%)	Placebo arm (n=54) n (%)
≥ 10% decline	45 (40)	22 (40)
10% decline/10% increase	58 (52)	29 (54)
≥10 % increase	9 (8)	3 (6)

Table 4.11 12 months change in FVC in TIPAC study patients

4.3.2.3 Safety analysis

Adverse events

The safety results are based on every individual who took at least one dose of the study drug. One patient receiving co-trimoxazole and azathoprine, developed severe transient neutropenia which required hospitalisation. Following this event, all patients receiving azathioprine or mycophenolate mofetil had 2 weekly monitoring of their full blood count and two other patients (both receiving azathioprine and co-trimoxazole) were withdrawn because of neutropenia. There was a significant reduction in number of patients with one or more infection (41.3% versus 68.9%) with co-trimoxazole treatment compared to placebo (Table 4.12). Whereas no patient receiving co-trimoxazole developed clinician diagnosed pneumonia, eight patients (9.3%) in the placebo group had one or more episodes of pneumonia. There were also significant differences between placebo and active treatment in terms of lower (38 (44.2%) versus 27 (29.4%) patients) and upper (14 (16.3%) versus 6 (6.5%) patients) respiratory tract infections (Table 4.13). An increase in the reporting of nausea (18.5% versus 7.0%) was seen in the co-trimoxazole group (Table 4.15). In the placebo group 12.5% (7/56) had an increase in creatinine from their baseline by 10 mmol/l, compared to 59.3% (32/54) in the treatment group.

	Placebo	Co-trimoxazole	Total	Placebo	Co-trimoxazole	
Group	Number of events	Number of events		Number of individuals with 1 or more	Number of individuals with 1 or more	p-value
Blood disorder	5	7	12	3 (3.5)	6 (6.5)	0.356
Cardiac disorder	10	3	13	9 (10.5)	3 (3.3)	0.055
Dental condition	1	2	3	1 (1.2)	2 (2.2)	1
Ear disorder	1	0	1	1 (1.2)	0 (0.0)	0.483
Eye disorder	3	7	10	3 (3.5)	5 (5.4)	0.722
General disorders	16	22	38	14 (16.3)	17 (18.5)	0.699
Gastrointestinal	37	78	115	21 (24.4)	41 (44.6)	0.005
Immune system disorders	2	0	2	1 (1.2)	0 (0.0)	0.483
Infection	125	68	193	59 (68.6)	38 (41.3)	<0.001
Injury	0	4	4	0 (0.0)	3 (3.3)	0.247
Investigations	7	12	19	7 (8.1)	11 (12.0)	0.399
Metabolic disorder	11	15	26	8 (9.3)	13 (14.1)	0.318
Muscle and tissue disorder	15	13	28	11 (12.8)	12 (13.0)	0.96
Neoplasia	4	1	5	4 (4.7)	1 (1.1)	0.199
Nervous system	16	17	33	11 (12.8)	11 (12.0)	0.866
None	21	24	45	21 (24.4)	16 (17.4)	0.248
Phsychiatric	4	5	9	4 (4.7)	5 (5.4)	1
Renal and urinary disorder	3	3	6	3 (3.5)	3 (3.3)	1
Respiratory	55	48	103	39 (45.4)	35 (38.0)	0.323
Reproductive and breast	2	0	2	2 (2.3)	0 (0.0)	0.232
Skin disorder	5	16	21	4 (4.7)	14 (15.2)	0.019
Surgical and medical	6	1	7	5 (5.8)	1 (1.1)	0.318
Vascular disorders	7	9	16	7 (8.1)	9 (9.8)	0.702

Table 4.12 Tabulation of adverse event by category. There was a significant reduction in number of patients with one or more infection, pneumonia, lower and upper respiratory tract infections in the co-trimoxazole group. There was an increase in the reporting of nausea and an increase in creatinine from their baseline by 10 mmol/l in the co-trimoxazole group.

	Placebo	Co-trimoxazole	Total	Placebo	Co-trimoxazole	
Group	Number of events	Number of events		Number of individuals with 1 or more	Number of individuals with 1 or more	p-value
Candida infection	1	0	1	1 (1.2)	0 (0.0)	0.483
Cellulitis	1	2	3	1 (1.2)	2 (2.2)	1
Fungal infection	1	3	4	1 (1.2)	3 (3.3)	0.622
Gastritis	0	1	1	0 (0.0)	1 (1.1)	1
Gastroenteritis	3	3	6	3 (3.5)	3 (3.3)	1
Infectious enteritis	0	1	1	0 (0.0)	1 (1.1)	1
Infectious gastritis	2	1	3	1 (1.2)	1 (1.1)	1
Respiratory						
Upper respiratory tract infection	17	6	23	14 (16.3)	6 (6.5)	0.039
Low respiratory tract infection	76	45	121	38 (44.2)	27 (29.4)	0.04
Pneumonia	8	0	8	8 (9.3)	0 (0.0)	0.002
Oral candidiasis	1	0	1	1 (1.2)	0 (0.0)	0.483
Rhinitis	0	1	1	0 (0.0)	1 (1.1)	1
Sepsis	1	0	1	1 (1.2)	0 (0.0)	0.483
Sinusitis	1	0	1	1 (1.2)	0 (0.0)	0.483
Skin varicella zoster	2	1	3	2 (2.3)	1 (1.1)	0.61
Urinary tract infection	7	4	11	7 (8.1)	4 (4.4)	0.294
Verruca	1	0	1	1 (1.2)	0 (0.0)	0.483
Vulvovaginal candidia	3	0	3	2 (2.3)	0 (0.0)	0.232

Table 4.13 Preferred term for all infections

	Placebo	Co-trimoxazole	Total	Placebo	Co-trimoxazole	
Group	Number of events	Number of events		Number of individuals with 1 or more	Number of individuals with 1 or more	p-value
Aspiration pneumonia	1	0	1	1 (1.2)	0 (0.0)	0.483
Bronchospasm	0	1	1	0 (0.0)	1 (1.1)	1
Copd	0	3	3	0 (0.0)	1 (1.1)	1
Cough	14	14	28	13 (15.1)	13 (14.1)	0.852
Dyspnoea	14	17	31	12 (14.0)	15 (16.3)	0.662
Epistaxis	2	2	4	2 (2.3)	2 (2.2)	1
Increased expectoration	1	0	1	1 (1.2)	0 (0.0)	0.483
IPF	2	0	2	2 (2.3)	0 (0.0)	0.232
IPF exacerbation	3	2	4	2 (2.3)	2 (2.2)	1
IPF progression	5	2	7	5 (5.8)	2 (2.2)	0.265
Nasal congestion	1	0	1	1 (1.2)	0 (0.0)	0.483
Pleural effusion	1	0	1	1 (1.2)	0 (0.0)	0.483
Respiratory failure	7	5	12	7 (8.1)	4 (4.4)	0.359
Respiratory failure on exercise	4	2	6	4 (4.7)	2 (2.2)	0.431

Table 4.14 Preferred terms for respiratory adverse events

	Placebo	Co-trimoxazole	Total	Placebo	Co-trimoxazole	
Group	Number of events	Number of events		Number of individuals with 1 or more	Number of individuals with 1 or more	p-value
Abdominal discomfort	3	3	6	3 (3.5)	3 (3.3)	1
Abdominal pain	1	8	9	1 (1.2)	5 (5.4)	0.212
Anorectal disorder	1	0	1	1 (1.2)	0 (0.0)	0.483
Bloating	0	1	1	0 (0.0)	1 (1.1)	1
Constipation	5	7	12	5 (5.8)	7 (7.6)	0.633
Diarrhoea	6	12	18	4 (4.7)	10 (10.9)	0.124
Dry mouth	0	2	2	0 (0.0)	2 (2.2)	0.498
Dyspepsia	5	2	7	4 (4.7)	2 (2.2)	0.431
Epigastric discomfort	1	0	1	1 (1.2)	0 (0.0	0.483
Flatulence	0	2	2	0 (0.0)	2 (2.2)	0.498
Gastrointestinal upset	2	1	3	2 (2.3)	1 (1.1)	0.61
Glossitis	0	4	4	0 (0.0)	4 (4.4)	0.122
Mouth ulceration	1	0	1	1 (1.2)	0 (0.0)	0.483
Nausea	6	21	27	6 (7.0)	17 (18.5)	0.022
Soft bowel motions	1	0	1	1 (1.2)	0 (0.0)	0.483
Stomatitis	2	2	4	2 (2.3)	2 (2.2)	1
Strangulated inguinal	0	1	1	0 (0.0)	1 (1.1)	1
Tongue coating	0	1	1	0 (0.0)	1 (1.1)	1
Tongue discoloration	0	2	2	0 (0.0)	2 (2.2)	0.498
Vomiting	3	9	12	2 (2.3)	6 (6.5)	0.28

Table 4.15 Preferred term for all gastrointestinal adverse events

Serious adverse events

There was a total number of 93 serious adverse events (SAE) defined as deaths, events requiring hospitalisation, life-threatening or medically significant; 61% (57) were respiratory in origin with gastrointestinal and general medical (6.5% each) as well as cardiac (5.4%) being next most frequent organ localisation (Table 4.16).

Organ System Classification	Freq.	Percent	Cum.
Cardiac	5	5.38	5.38
Cardiac and Respiratory	1	1.08	6.45
Dermatology	1	1.08	7.53
Dermatology and Respiratory	1	1.08	8.60
ENT	2	2.15	10.75
Gastrointestinal	6	6.45	17.20
General medical	6	6.45	23.66
Haematology	3	3.23	26.88
Infection of unknown source	1	1.08	27.96
Neoplasia	2	2.15	30.11
Neurology	1	1.08	31.18
Ophthalmology	1	1.08	32.26
Orthopaedic	3	3.23	35.48
Respiratory	57	61.29	96.77
Respiratory AND GASTROINTESTINAL	1	1.08	97.85
Urological	1	1.08	98.92
infection	1	1.08	100.00
Total	93	100.00	

Table 4.16 SAE including deaths by organ (Intention to treat analysis)

Two analyses of SAE were performed – analysis of all SAE and analysis of those due to a respiratory cause for both intention to treat and per protocol population.

Intention to treat population

All SAE

The number of individuals with all SAE including death is given in Table 4.17. After adjusting for medication status at baseline (a stratifying factor) the odds ratio was 0.64 (0.34,0.1.18) in favour of the intervention group. There was a total of 51 SAE events in the control group, an average of 0.59 events per individual compared with 42 in the intervention group an average of 0.44 event per individual. From a Poisson regression model this was not significant (p=0.145).

	Intention to treat analysis		
	Placebo	Co-trimoxazole	Total
Patients without SAE, n	52	70	122
Patients with any SAE, n	34	25	59
Total	86	95	181

Table 4.17 All SAE including death by group (Intention to treat analysis)

Respiratory SAE

The number of individuals with any respiratory SAE including death is given in Table 4.18. After adjusting for medication status at baseline (a stratifying factor) the odds ratio was 0.49 (0.24,1.04) in favour of the intervention group. There was a total of 32 SAE events in the control group, an average of 0.37 events per individual compared with 25 in the intervention group an average of 0.26 event per individual. From a Poisson regression model this was not significant (p=0.171).

	Intention to treat analysis		
	Placebo	Co-trimoxazole	Total
Patients without respiratory SAE, n	63	80	143
Patients with respiratory SAE, n	23	15	38
Total	86	95	181

Table 4.18 Any respiratory SAE including death by group (Intention to treat analysis)

Per protocol population

All SAE

The number of individuals with all SAE including death is given in Table 4.19. After adjusting for medication status at baseline (a stratifying factor) the odds ratio was 0.29 (0.12,0.71) in favour of the intervention group. There was a total of 41 SAE events in the control group, an average of 0.63 events per individual compared with 19 in the intervention group an average of 0.36 event per individual. From a Poisson regression model this was significant (p=0.035).

	Per protocol analysis		
	Placebo	Co-trimoxazole	Total
Patients without SAE, n	39	44	83
Patients with any SAE, n	26	9	35
Total	65	53	118

Table 4.19 Any SAE including death by group (per protocol analysis)

Respiratory SAE

The number of individuals with any respiratory SAE or death is given in Table 4.20. After adjusting for medication status at baseline (a stratifying factor) the odds ratio was 0.25 (0.09,0.75) in favour of the intervention group. There was a total of 26 SAE events in the control group, an average of 0.40 events per individual compared with 9 in the intervention group an average of 0.17 event per individual. From a Poisson regression model this was significant (p=0.021).

	Per protocol analysis		
	Placebo	Co-trimoxazole	Total
Patients without respiratory SAE, n	47	48	95
Patients with respiratory SAE, n	18	5	23
Total	65	53	118

Table 4.20 Any respiratory SAE or death by group (per protocol analysis)

Cause of death

Cause of death of patients in per protocol population is shown in table 4.21. All 17 deaths were due to a respiratory cause with 7 (40%) resulting from gradual progression of IPF itself and 5 following pneumonia (all in placebo arm), with 80% of non-IPF related deaths exhibiting signs of gradual rather than acute progression of underlying IPF.

	Placebo (n=14)	Co-trimoxazole (n=3)
Mean age, years	72.8	74
Respiratory related[#]	14 (100%)	3 (100%)
IPF related	5 (36%)	2 (67%)
Non-IPF related	9 (64%)	1 (33%)
Pneumonia	5 (36%)	0
LRTI	1 (7%)	0
Aspiration pneumonia	1 (7%)	0
Cardiorespiratory failure*	1 (7%)	0
Multiorgan failure∞	1 (7%)	0
Metastatic lung cancer	0	1 (33%)

[#] Death was defined as respiratory related if resulted from respiratory failure, acute exacerbation or progression of IPF, pneumonia or respiratory tract infection, pulmonary embolism, lung cancer, pneumothorax or pulmonary embolism

*Due to IPF and ischaemic heart disease. ∞ Due to IPF, LRTI and perforated Meckel's diverticulum

Table 4.21 Cause of death in per protocol population

4.3.2.4 Cost-effectiveness and cost-utility analysis

The results of resource use quantities and summary costs by sector are displayed in Table 4.23 and Table 4.24 respectively. The results of cost effectiveness and cost utility analyses are in Table 4.26 and Table 4.27 respectively.

In all analyses, 95% confidence intervals did not exclude zero. Point estimate results, adjusted for baseline and with missing data imputed showed a higher cost and worse change in FVC for the treatment group compared with placebo. However, overall health gain was higher in the treatment group: the incremental cost per QALY gained was estimated at between £2,530 in favour of co-trimoxazole and £16,636 in favour of placebo, depending on perspective and ITT/PP population: given a typical threshold of £30,000 per QALY, co-trimoxazole is cost-effective in the ITT analyses and PP analysis from the perspective of the NHS, the incremental

cost-effectiveness ratios (ICER) is higher (is less cost effective) when societal costs are included rather than just NHS costs There is between 46.9% and 89.8% probability that the ICER is below £30,000 (Figure 4.10).

Economic evaluation additional details

NHS costs	Social services costs	Out of pocket expenditure	Lost productivity
Prescribed medications (including study medication) Primary care Secondary care Tertiary care & allied health professionals	Social care	Travel Other OOP	Patient time off work Carer time off work Informal caring time

Table 4.21 Cost categories and subcategories within each

Cost item	Unit cost	Source
Cost OP appt for PF	£132.00	Ref Costs 2008-09,[193] Respiratory medicine consultant led FU attendance, non-admitted f2f. Appendix NSRC4, worksheet TPCTCLFUSFF code 340
Cost OP appt for other	£126.00	PSSRU 2009,[194] P93, weighted average of all adult OP attendances (follow-up face-to-face attendance)
Cost Daycase appt for PF	£669.00	Ref Costs 2008-09,[193] daycase HRG data. HRG DZ19B: Other respiratory diagnoses with CC. Appendix NSRC4, worksheet TPCTDC code DZ19B
Cost Daycase appt for other	£638.00	PSSRU 2009,[194] P93, weighted average of all stays
Cost IP admission for PF	£1,425.00	Ref Costs 2008-09,[193] elective IP data. HRG DZ19B: Other respiratory diagnoses with CC. Appendix NSRC4, worksheet TPCTEI code DZ19B
Cost IP admission for Other	£2,626.00	PSSRU 2009,[194] P93, weighted average of all elective IP stays
Cost per day, IP Admission	£335.00	Ref Costs 2008-09,[193] elective IP excess bed day data. HRG DZ19B: Other respiratory diagnoses with CC. Appendix NSRC4, worksheet TPCTEIXS code DZ19B
Cost of A&E attendance	£93.00	PSSRU 2009,[194] A&E services not leading to admitted. P93.
Hourly wage	£11.03	ONS,[195] Annual Survey of Hours and Earnings (ASHE) 2009, Table 1.5a: Hourly pay Gross.
Cost GP surgery consultation	£35.00	PSSRU 2009,[194] P121, per surgery consultation 11.7mins with qual costs and direct care staff costs
Cost GP home visit	£117.00	PSSRU 2009,[194] P121, per home visit 23.4mins in qualification and direct care staff costs
Cost GP phone consultation	£21.00	PSSRU 2009,[194] P121, per telecon 7.1mins inc qualification and direct care staff costs
Cost nurse surgery consultation	£11.00	PSSRU 2009,[194] P118, per consultation inc qualifications
Cost nurse home visit	£20.00	PSSRU 2009,[194] P118, per home visit inc qualifications
Cost nurse phone consultation	£11.00	Assumed same as surgery consultation
Cost health visitor surgery consultation	£27.33	PSSRU 2009,[194] P115, per hr clinic contact inc qualifications * 20/60 (length of contact - assumed same as for home visit)
Cost health visitor home visit	£41.00	PSSRU 2009,[194] P115, per home visit inc qualifications
Cost health visitor phone consultation	£27.33	Assumed same as surgery consultation
Cost physio surgery	£17.00	PSSRU 2009,[194] P105, per clinic visit inc qualifications

consultation		
Cost physio home visit	£48.00	PSSRU 2009,[194] P105, per home visit inc qualifications
Cost physio phone consultation	£17.00	Assumed same as surgery consultation
Cost OT surgery consultation	£41.33	PSSRU 2009,[194] P130, per hour client contact * 40mins (length of visit - assumed same for clinic visit)
Cost OT home visit	£43.00	PSSRU 2009,[194] P130, per home visit inc qualifications
Cost OT phone consultation	£41.33	Assumed same as surgery consultation
Cost Other AHP surgery consultation	£17.00	Assumed same as physiotherapist
Cost Other AHP home visit	£48.00	Assumed same as physiotherapist
Cost Other AHP phone consultation	£17.00	Assumed same as physiotherapist
Cost carer home visit	£18.00	PSSRU 2009,[194] P129, per hour face to face weekday contact
Cost social worker office visit	£39.00	PSSRU 2009,[194] P126, per hour of client related work.
Cost social worker home visit	£130.00	Assumed same proportionate increase as GP home/surgery visit (= £39 * 117/35)
Cost social worker phone call	£23.40	Assumed same proportionate decrease as GP phone/surgery visit (= £39 * 21/35)
Cost cleaner home visit	£18.00	Assumed same as carer home visit
Cost car transport to hospital	£2.40	assumed 6 miles x 40p per mile
Cost car transport to GP surgery	£1.20	assumes half distance to hospital
Cost child care per hour	£5.00	child or other dependent care cost per hour during hospital or GP visit

Table 4.22 Cost and the source of the cost information for each unit of inpatient and outpatient medical activity as well as social worker and occupational therapist activity due to pulmonary fibrosis (PF) and non-pulmonary fibrosis (other) related issues

Variable	N (intervention, control)	Intervention mean (SD)	Control mean (SD)	Increment
Primary care				
GP Surgery visits due to PF	(64, 72)	1.13 (1.65)	1.44 (2.23)	
due to other	(64, 72)	2.16 (2.58)	2.44 (3.24)	
Total	(64, 72)	3.28 (3.08)	3.89 (3.83)	-0.608
GP home visits due to PF	(64, 72)	0.13 (0.55)	0.18 (0.66)	
due to other	(64, 72)	0.23 (1.09)	0.1 (0.38)	
Total	(64, 72)	0.36 (1.2)	0.28 (0.83)	0.082
GP phone calls due to PF	(64, 72)	0.19 (0.56)	0.24 (0.66)	
due to other	(64, 72)	0.13 (0.63)	0.1 (0.34)	
Total	(64, 72)	0.31 (0.89)	0.33 (0.87)	-0.021
Nurse surgery visits due to PF	(64, 72)	0.14 (0.5)	0.24 (0.66)	
due to other	(64, 72)	3.36 (4.77)	2.99 (3.71)	
Total	(64, 72)	3.5 (4.71)	3.22 (3.7)	0.278
Nurse home visits due to PF	(64, 72)	0.83 (3.78)	0.08 (0.6)	

due to other	(64, 72)	0.86 (4.78)	0.43 (2.19)	
Total	(64, 72)	1.69 (5.98)	0.51 (2.62)	1.174
Nurse phone calls due to PF	(64, 72)	0.02 (0.13)	0.04 (0.26)	
due to other	(64, 72)	0.03 (0.25)	0.13 (0.95)	
Total	(64, 72)	0.05 (0.28)	0.17 (1.09)	-0.12
Secondary care				
OP appts due to PF	(64, 72)	2 (4.49)	1 (1.36)	
due to other	(64, 72)	0.89 (1.45)	0.99 (1.63)	
Total	(64, 72)	2.89 (4.91)	1.99 (2.13)	0.905
Daycase appts due to PF	(64, 72)	0.09 (0.34)	0.03 (0.17)	
due to other	(64, 72)	0.11 (0.44)	0.17 (0.41)	
Total	(64, 72)	0.2 (0.54)	0.19 (0.46)	0.009
IP admissions due to PF	(64, 72)	0.19 (0.75)	0.19 (0.46)	
due to other	(64, 72)	0.08 (0.32)	0.1 (0.3)	
Total	(64, 72)	0.27 (0.84)	0.29 (0.59)	-0.026
A&E attendances due to PF	(64, 72)	0.13 (0.58)	0.14 (0.42)	
due to other	(64, 72)	0.02 (0.13)	0.03 (0.17)	
Total	(64, 72)	0.14 (0.61)	0.17 (0.47)	-0.026
Other health professional				
Health visitor office visits due to PF	(64, 72)	0.05 (0.28)	0.01 (0.12)	
due to other	(64, 72)	0.03 (0.18)	0 (0)	
Total	(64, 72)	0.08 (0.37)	0.01 (0.12)	0.064
Health visitor home visits due to PF	(64, 72)	0.25 (1.39)	0.06 (0.23)	
due to other	(64, 72)	0.02 (0.13)	0 (0)	
Total	(64, 72)	0.27 (1.39)	0.06 (0.23)	0.21
Health visitor phone calls due to PF	(64, 72)	0.03 (0.25)	0.03 (0.24)	
due to other	(64, 72)	0 (0)	0 (0)	
Total	(64, 72)	0.03 (0.25)	0.03 (0.24)	0.003
Physiotherapist office visits due to PF	(64, 72)	0.06 (0.3)	0.13 (0.5)	
due to other	(64, 72)	0.02 (0.13)	0.18 (1.42)	
Total	(64, 72)	0.08 (0.32)	0.31 (1.49)	-0.227
Physiotherapist home visits due to PF	(64, 72)	0.06 (0.39)	0.06 (0.37)	
due to other	(64, 72)	0 (0)	0.04 (0.35)	
Total	(64, 72)	0.06 (0.39)	0.1 (0.51)	-0.035
Physiotherapist phone calls due to PF	(64, 72)	0.02 (0.13)	0 (0)	
due to other	(64, 72)	0 (0)	0 (0)	
Total	(64, 72)	0.02 (0.13)	0 (0)	0.016
OT office visits due to PF	(64, 72)	0.16 (1.01)	0 (0)	
due to other	(64, 72)	0 (0)	0.03 (0.17)	
Total	(64, 72)	0.16 (1.01)	0.03 (0.17)	0.128
OT home visits due to PF	(64, 72)	0.03 (0.18)	0.06 (0.37)	
due to other	(64, 72)	0.16 (0.91)	0.28 (1.4)	

Total	(64, 72)	0.19 (0.92)	0.33 (1.43)	-0.146
OT phone calls due to PF	(64, 72)	0 (0)	0 (0)	
due to other	(64, 72)	0.02 (0.13)	0.01 (0.12)	
Total	(64, 72)	0.02 (0.13)	0.01 (0.12)	0.002
Other health prof. office visits due to PF	(64, 72)	0.25 (0.87)	0.18 (0.81)	
due to other	(64, 72)	0.2 (0.82)	0.19 (0.68)	
Total	(64, 72)	0.45 (1.19)	0.38 (1.23)	0.078
Other health prof. home visits due to PF	(64, 72)	0.25 (0.99)	0.14 (0.45)	
due to other	(64, 72)	0.02 (0.13)	0.01 (0.12)	
Total	(64, 72)	0.27 (1)	0.15 (0.46)	0.113
Other health prof. phone calls due to PF	(64, 72)	0.11 (0.51)	0 (0)	
due to other	(64, 72)	0 (0)	0.06 (0.47)	
Total	(64, 72)	0.11 (0.51)	0.06 (0.47)	0.054
Pulmonary rehabilitation sessions	(64, 72)	0.92 (3.14)	0.47 (1.8)	0.45
Social Services				
Social services office visit due to PF	(64, 72)	0 (0)	0.03 (0.17)	
due to other	(64, 72)	0 (0)	0 (0)	
Total	(64, 72)	0 (0)	0.03 (0.17)	-0.028
Social services home visit due to PF	(64, 72)	0.34 (2.51)	0 (0)	
due to other	(64, 72)	0 (0)	0 (0)	
Total	(64, 72)	0.34 (2.51)	0 (0)	0.344
Social services phone call due to PF	(64, 72)	0 (0)	0.03 (0.24)	
due to other	(64, 72)	0 (0)	0.01 (0.12)	
Total	(64, 72)	0 (0)	0.04 (0.26)	-0.042
Carer home visit due to PF	(64, 72)	1.22 (7.23)	0 (0)	
due to other	(64, 72)	0.52 (4)	0 (0)	
Total	(64, 72)	1.73 (9.56)	0 (0)	1.734
Cleaner home visit due to PF	(64, 72)	0 (0)	0 (0)	
due to other	(64, 72)	0.03 (0.25)	0.01 (0.12)	
Total	(64, 72)	0.03 (0.25)	0.01 (0.12)	0.017

Table 4.23 Resource use quantities

	N (intervention, control)	Intervention	Control	Increment	SE
Study drug	(64, 72)	186.58 (68.83)	0 (0)	186.581	
Prescription medicines (excl. study drug)	(63, 71)	1469.59 (1737.04)	1642.99 (1964.97)	-173.402	
Primary care	(64, 72)	236.22 (256.2)	223.17 (183.73)	13.052	
Secondary care	(64, 72)	1004.31 (1793.56)	961.51 (1195.68)	42.799	
Other health professionals	(64, 72)	71.62 (155.55)	52.01 (96.85)	19.61	
Social services	(64, 72)	285.47 (1002.14)	85.07 (415.58)	200.397	
Patient Out of Pocket Costs	(57, 68)	274.86 (826.66)	226.22 (711.77)	48.64	
Indirect Costs	(54, 62)	12531.47 (19061.81)	10472.06 (18008.26)	2059.41	
NHS	(63, 71)	2988.3 (2760.56)	2896.3 (2495.15)	92	454
Societal (NHS + social services + patient OOP + indirect)	(51, 57)	14321.36 (17462.04)	14724.29 (20183.74)	-403	3652

Table 4.24 Summary costs by sector
Results are mean (SD)

							Unadjusted			Imputed, adjusted for baseline FVC		
	N		Cost		dFVC		Inc £	Inc dFVC	ICER	Inc £	Inc dFVC	ICER
Analysis	Co-Trim	Placebo	Co-Trim	Placebo	Co-Trim	Placebo	(95%CI)	(95%CI)		(95%CI)	(95%CI)	
ITT NHS	51	55	£3,400	£3,121	-0.170	-0.199	£279 (-£763, £1328)	0.029 (-0.091, 0.150)	£9,634	£295 (-£483, £1067)	0.001 (-0.095, 0.094)	£239,047
ITT Societal	41	45	£16,321	£15,872	-0.207	-0.199	£449 (-£8094, £8928)	-0.008 (-0.147, 0.127)	[Placebo dominant]	£1,145 (-£4854, £6849)	0.001 (-0.094, 0.099)	£928,564
PP NHS	48	50	£3,421	£3,194	-0.175	-0.174	£226 (-£892, £1346)	-0.001 (-0.130, 0.126)	[Placebo dominant]	£256 (-£481, £1039)	-0.022 (-0.138, 0.089)	[Placebo dominant]
PP Societal	39	41	£16,620	£17,003	-0.212	-0.170	-£383 (-£9390, £8576)	-0.042 (-0.185, 0.093)	£9,156	£366 (-£5618, £6135)	0.005 (-0.095, 0.106)	£76,966

Table 4.25 Cost effectiveness

Co-Trim: Co-trimoxazole; ITT: Intention to treat; PP: Per Protocol; NHS: NHS cost perspective; Societal: Societal cost perspective; FVC: change in FVC; Inc: Incremental; ICER: Incremental Cost Effectiveness Ratio

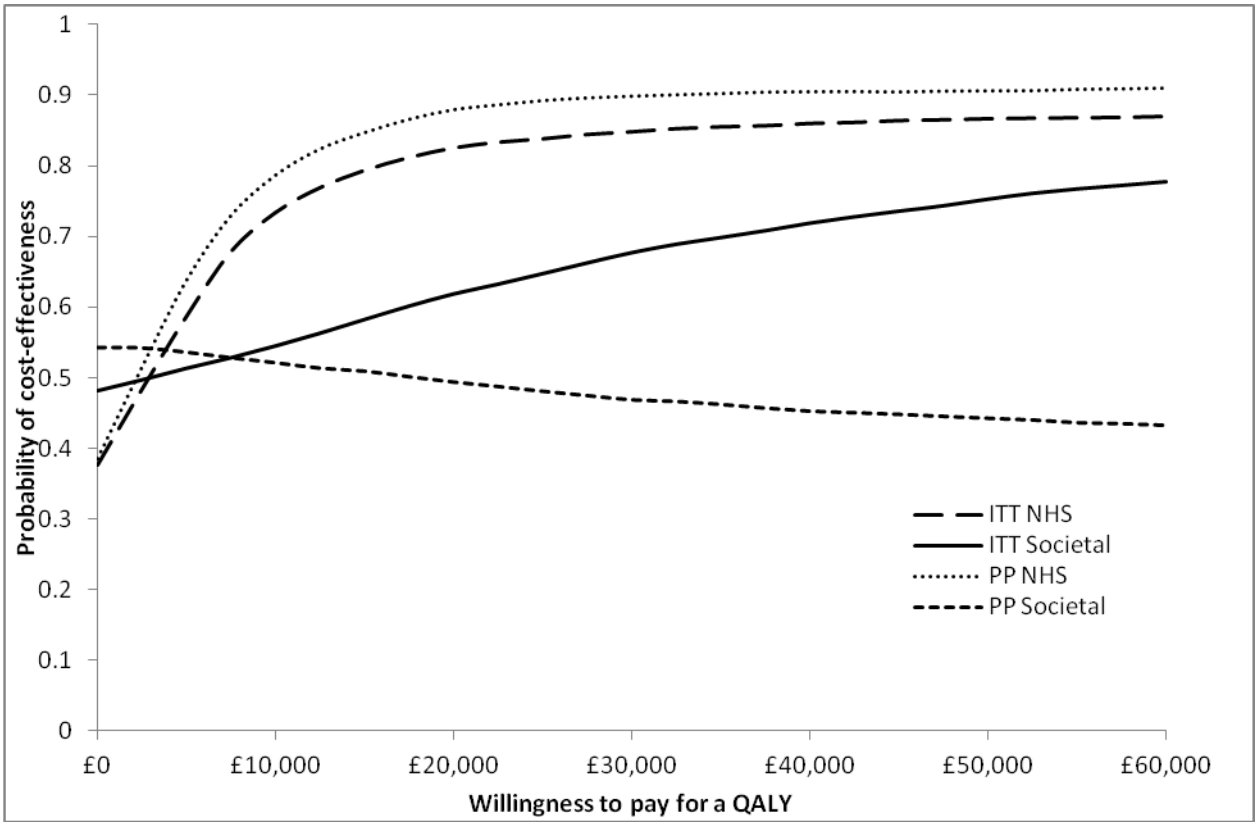


Figure 4.10 Cost-effectiveness acceptability curves
ITT=intention to treat analysis. PP=per protocol analysis. The cost-effectiveness acceptability curve is the probability that the incremental cost-effectiveness ratios (ICERs) is below a given willingness to pay for a quality adjusted life year (i.e. the probability that co-trimoxazole is cost-effective given a threshold of X). There is between 46.9% and 89.8%probability that the ICER is below £30,000.

	N		Cost		QALYs		Unadjusted Inc £	Inc QALYS	ICER	P(CE|£30k)	Imputed, adjusted for baseline utility and cost Inc £	Inc QALYS	ICER	P(CE|£30k)
Analysis	Co-Trim	Placebo	Co-Trim	Placebo	Co-Trim	Placebo	(95%CI)	(95%CI)			(95%CI)	(95%CI)		
ITT NHS	61	64	£2,989	£2,918	0.571	0.539	£71 (-£848, £991)	0.032 (-0.062, 0.127)	£2,244	70.52%	£136 (-£628, £915)	0.045 (-0.028, 0.116)	£3,002	84.78%
ITT Societal	51	53	£14,321	£15,131	0.590	0.539	-£810 (-£8412, £6491)	0.051 (-0.055, 0.157)	[Active dominant]	69.68%	£115 (-£5024 £4726)	0.045 (-0.029, 0.115)	£2,530	67.76%
PP NHS	58	61	£2,999	£2,922	0.571	0.527	-£77 (-£895, £1051)	0.045 (-0.053, 0.140)	£1,724	77.80%	£149 (-£674, £884)	0.054 (-0.024, 0.121)	£2,743	89.80%
PP Societal	41	38	£14477	£16,307	0.584	0.527	-£1830 (-£9797, £5741)	0.057 (-0.052, 0.167)	[Active dominant]	78.08%	-£246 (-£5326, £4511)	-0.015 (-0.103, 0.063)	£16,636 [favour placebo]	46.92%

Table 4.26 Cost utility

Co-Trim: Co-trimoxazole; ITT: Intention to treat; PP: Per Protocol; NHS: NHS cost perspective; Societal: Societal cost perspective; Inc: Incremental; ICER: Incremental Cost Effectiveness Ratio; P(CE|£30k): Probability that the ICER is below £30,000 per QALY gained.

4.4 Discussion

TIPAC is a large randomised, double-blind placebo-controlled clinical trial that assessed the efficacy and safety of co-trimoxazole in a dose of 960 mg twice a day prescribed for 12 months in patients with fibrotic idiopathic interstitial pneumonia. Similar to a number of recent interventional trials using novel or existing drugs with anti-fibrotic, anti-oxidant, anti-proliferative, and anti-inflammatory properties [97-99, 104, 105, 109] this study did not demonstrate an effect on a primary endpoint but led to a reduction in mortality over 12 months associated with a reduction in a rate of infections.

4.4.1 The effect on lung function

A range of trials assessed the efficacy of treatment by measuring changes in physiological parameters [96, 99, 101-104, 109]. Three other trials used change in vital capacity and forced vital capacity absolute value as a primary end-point [96, 102, 109] while two other used change in FVC % predicted as a primary end-point [103, 104]. Overall of all the recent trials using physiological measures as primary endpoint significant differences were demonstrated for two drugs only – n-acetylcysteine and pirfenidone [96, 102, 103].

Assessment of changes of FVC over the study period demonstrated that both patient groups experienced decline in this parameter (196 ml decline in placebo group and 182 ml decline in co-trimoxazole group). This rate of decline is consistent with a slowly progressive course of the disease and is comparable with mean annual rate of decline in FVC shown in other clinical trials ranging from 130 ml to 200 ml (Figure 4.10). [196].

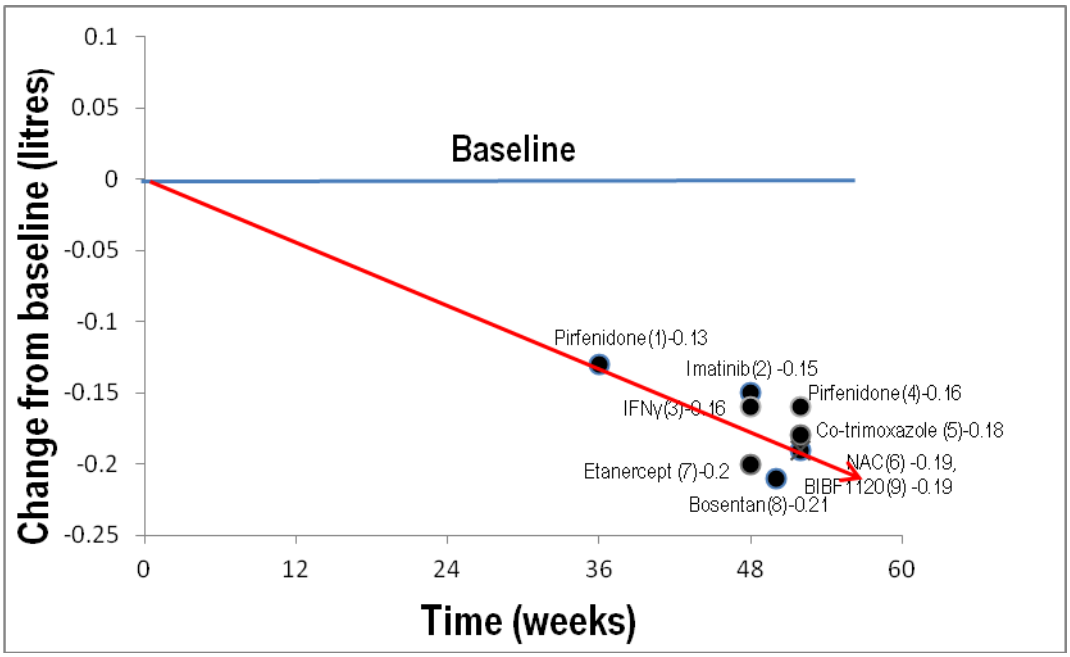


Figure 4.10 Decline in FVC in idiopathic pulmonary fibrosis (IPF). Shown are the mean rates of decline in FVC observed in the placebo arms of clinical trials of patients with IPF. The FVC declines approximately 150-200 ml/year in patients with IPF. Data are from the placebo arms of the following clinical trials: 1 Pirfenidone[101], 2 Imatinib[105],3 Interferon-γ-1b[97], 4 Pirfenidone[102], 5 Co-trimoxazole (current thesis), 6 N-acetylcysteine (NAC)[96], 7 Etanercept[104], 8 Bosentan[99], 9 BIBF 1120[109]. Adapted from Ley et al[196].

In this study, there were no significant differences in other physiological measures including DLCO, TLC and 6 minute walk distance and desaturation of >4% in both ITT and PP analyses.

Why was there no difference in FVC?

Potential reasons for a study not to have an effect on the FVC include: inappropriate choice of the primary endpoint, inadequate duration of treatment, inadequate sample size to detect significant difference, the drug not being effective, the drug being effective but only in a subgroup of patients.

I considered the first three reasons not to be a case in this study. It has been suggested that FVC may be the most appropriate single prognostic parameter, given its ease of measurement, reproducibility, and ability to predict prognosis at baseline and over time with even marginal changes (5-10% decline over 6 months) being associated with a higher risk of mortality[196, 197]. It has also been demonstrated that of all physiological parameters change in FVC over 6-12 months is not only associated with survival [23, 62, 63] but is more predictive of prognosis and outcome than

the majority of baseline characteristics including histopathologic diagnosis[23]. FVC has been used and estimated to be an appropriate outcome measure in clinical trials [198]. Also, taking into account the results of the pilot study which showed significant improvement in FVC as its secondary endpoint, it was relevant to use change in FVC as the primary endpoint in this larger study.

The value of 200ml for the mean difference in FVC from baseline was used to power the study since this represented the minimum change required for a favourable or unfavourable response to treatment as proposed in the ATS/ERS International Consensus statement from 1999 which was the most up to date document at the time of the study protocol approval (2007). Assuming a residual Standard Deviation of 400ml (from data from ISOLDE and TRISTAN study courtesy of J. Anderson, GSK, Greenford), then with 63 patients in each group this study had an 80% power to detect a mean difference of 200ml at a significance level of $p = 0.05$. The total patient sample was higher (181) to allow for drop outs and 111 patients completed 12 months of treatment nearing the required number; with this number of patients completing the study the power was 74%.

For a drug to have an effect on lung function tests in IPF it should be able to affect the underlying pathogenic process. Changes in lung function should not be a result of other concomitant conditions for example infection and emphysema. Since changes in FVC reflect either progression or stability of the disease and co-trimoxazole did not show any preservation in this parameter (or any other lung function parameters) it is more likely that it does not have a disease modifying action.

The reasons for a discrepancy in the results of this study and the pilot study regarding changes in FVC are not clear. Baseline characteristics in both studies were similar in terms of the mean age, gender distribution and the number of patients on prednisolone at recruitment. Seven patients out of 20 in the pilot study had a sibling with IIP which makes it possible that the spectrum of the disease was somewhat different to definite/probable UIP or fibrotic NSIP. These patients also had milder disease as evidenced by DLCO of 59% predicted in placebo and 51% predicted in active group as opposed to 39 and 36% in the TIPAC study respectively. The authors of the pilot study admit difficulty in interpreting of the lung function results in the blinded part of the study (the first 3 months) due to the change in lung function equipment and a wide time range of baseline PFT measurement from 0 to 8 months (due to demand on the service from three other

hospitals). Nevertheless the out of study measurements in the following 9 months (when patients continued taking co-trimoxazole as an open label treatment) demonstrated a sustained effect on FVC in the active group. At the same time there was no effect on FVC for the placebo arm patients during this open labelled phase.

Our patient population had a slower progression of disease - <5% decline in FVC over 1 year versus 11% seen by Varney el al [188], indicative of slowly progressive disease and this may account for the lack of effect with co-trimoxazole treatment,.

Subgroup analysis in patients with mild/moderate disease showed no significant difference in the rate of decline of FVC over 12 months (p=0.816 in the ITT analysis and 0.378 in the PP analysis). Though DLCO % predicted at a given time point is more reflective of the severity of the disease and more predictive of outcome a FVC % predicted with a cut off of 60% was used to discriminate severe (≤60% predicted) from mild/moderate (≥60% predicted) as this was the measure assessed in all patients unlike DLCO (measured in 150 out of 181).

4.4.2 Survival

This study has shown that although co-trimoxazole treatment has no effect on pulmonary function in patients with fibrotic idiopathic interstitial pneumonia, this treatment, when subject to a per protocol analysis had a significant reduction in all-cause mortality over 12 months. The difference between the findings of the intention-to-treat and per-protocol analyses may be due to improved survival in those adhering to treatment as we would not expect any effects of co-trimoxazole to be exhibited following cessation of this treatment. Alternatively, it could be due to an increased mortality in those withdrawing from the drug because of side effects or the higher withdrawal rate in the active group could be a marker of the disease severity. However, the reduction in mortality was not due to disproportionate withdrawal of patients in the treatment arm immediately prior to death as only 4 patients (2 from each group) withdrew from the study within 1 month of death.

IPF has a variable course in individual patients[70], however several studies performed using the current classification of IIP[6] have reported a median survival between 2 and 4 years from the time of diagnosis and a 5 year survival between 20 and 40%[10, 12, 17, 63].

Few studies have reported the effects of a pharmacological intervention on survival in IPF. Raghu et al[97] showed no difference in death or disease progression with interferon gamma, though a post-hoc exploratory analysis suggested a survival benefit in patients with milder disease with FVC of greater than 62% (12% died in placebo arm vs. 4% in treatment arm). Nevertheless in a meta-analysis with a larger study[98] of patients with mild to moderate disease, no effect on mortality was observed (hazard ratio 0.88)[199]. Kubo et al[106] demonstrated a significant increase in survival with anticoagulation (hazard ratio 0.34) in 56 prednisolone-treated patients with IPF. However, the open labelled nature of this study resulted in greater healthcare contact with active treatment due to coagulation monitoring and 20% of the active treatment group withdrew consent at the start of the study because of concerns about the treatment or monitoring. In our study, we have shown a reduction in all-cause mortality over 12 months (hazard ratio 0.21) from 18 in the placebo group to 3 in the co-trimoxazole group. Of note, the death rate returns to that of the placebo group when co-trimoxazole is discontinued.

The mortality rate in recently performed high quality interventional studies varied from under 10% in studies using pirfenidone[101], bosentan (BUILD-1)[99], etanercept[104] and acetylcysteine[96] (in the latter deaths were reported for PP population only) to around 13-16% in studies using imatinib[105] and interferon-gamma[97, 98] and up to as high as 45% in a study using warfarin[106]. The total number of deaths by the end of this study was higher than in the majority of trials - thirty-seven (20%) patients died (19 (22%) in placebo group and 18 (19%) in co-trimoxazole group (p=0.379)). Possible explanations for this could be that patients were older with mean age of 71 years and had moderate to severe disease as opposed to a mean age of 62-65 years and mild to moderate disease in the majority of recent trials. Recent commercially sponsored clinical trials recruited predominantly incident cases while a high number of TIPAC study patients were prevalent cases with only 25% patients being diagnosed in 12 months prior to recruitment.

4.4.3 Anti-infective role

Our study demonstrated a significant reduction in the rate of upper and lower respiratory tract infections in the treatment group and the occurrence of pneumonia in the placebo group only.

It has been postulated that infectious agents may perpetuate the pathogenesis of IPF and may increase the risk of an acute exacerbation. It is possible that chronic inflammatory stimulus in a genetically susceptible host disrupts the normal healing response thus making the lung highly susceptible to a separate injurious trigger [200]. Much more is known about the role of viruses than bacteria, but the information on both remains limited.

Some viruses exist as an antigenic stimulant in the epithelial cells of the lung in an actively replicating and potentially injurious phase for an entire lifetime. Viruses such as Epstein-Barr virus, infect most people at some point in their life and that's where the differential host responses may modify the pathogenesis [200], as only a small proportion of exposed people will develop the disease. A number of viruses have been associated with IPF including hepatitis C, adenovirus, cytomegalovirus but the strongest association was found with the gammaherpesvirus Epstein-Barr virus. Given that hepatitis C virus (HCV) is not known to replicate in the lung, it is not clear if the association with HCV is pathogenic in IPF or if it indicates that IPF patients develop HCV cross-reactive antibodies. Kuwano et al did not find correlation between adenovirus infection and IPF but showed that the incidence of the adenovirus gene product E1A was considerably higher in patients treated with corticosteroids (67%) compared to the untreated group(10%)[201]. E1A has been shown to upregulate the production of the profibrotic mediator TGF-ß and to induce lung epithelial cells to express mesenchymal markers [202]. Human cytomegalovirus DNA (HCMV), a widespread opportunistic pathogen, was found in higher levels in IPF tissue compared to control samples [203] and HCMV IgG and complement fixation titres were found to be elevated in the serum of IPF patients compared to controls[204]. The mechanism of the association between HCMV and IPF is not clear. An association between Epstein-Barr virus infection and IPF was first established in 1984 by Vergnon et al [205] who identified raised levels of immunoglobulins A and G against EBV antigens in 13 patients with IPF in contrast to normal levels in 12 patients with ILD of known cause. Stewart et al [206] confirmed by immunohistochemistry and polymerase chain reaction that EBV is present

in the lung tissue of patients with IPF in significantly higher number of cases (48%) than in control subjects (14%). Tang et al extended the hypothesis to see if there is an association between IPF and herpesviruses and confirmed the presence of one or more of four herpesviruses (EBV, HCMV, HHV-7 and HHV-8) in 32 of 33 patients with IPF against 9 [207]of 25 control subjects. Viral infection is often complicated by a secondary bacterial infection which might be responsible for the initiating or maintaining inflammatory and/or fibrotic process in IPF.

There is a very limited data on the role of fungal and bacterial infection in IPF. Shimizu et al. demonstrated a high prevalence of Pneumocystis jirovecii colonisation (23.3%) among a group of 25 patients with IPF and 19 patients with collagen vascular disease, treated with oral corticosteroids which is a significant risk factor for colonisation ($p<0.05$) (P. jirovecii DNA was detected in sputum samples)[207]. Chlamidophila pneumoniae (C. pneumoniae) is a frequent causative agent for exacerbations of asthma and COPD, Tomioka et al. [208] conducted a prospective observational study over 5 years to evaluate its role in the pathogenesis of exacerbations of IPF. Though the evidence of previous exposure to C. pneumonia is high with 18 out of 27 patients having positive C. pneumonia IgG index, there was no evidence of acute infection at the time of the exacerbation as evidenced by the change in IgA and IgG index in paired sera.

The only study evaluating bacterial colonisation in IPF, which was undertaken as a disease control group for comparison with patients with Wegener granulomatosis, demonstrated that a significant number of IPF patients cultured pathogenic bacteria from their broncho-alveolar lavage fluid - 36% (8/22) compared to none (0/8%) of the controls. None of these patients were immunosuppressed or had evidence of infection in the preceding 4 weeks. These included Haemophilus influenza and parainfluenzae (2 cases each), Streptococcus pneumonia, Moraxella catarrhalis, Pseudomonas Aeruginosa and Proteus mirabilis (1 case each). There were no cases of Staphylococcus aureus which was a dominating agent (40%) in patients with Wegener granulomatosis. The authors postulated that unrecognised airway colonisation may contribute to the presence of cellular neutrophilic inflammation in the vasculitis group[209].

Whilst acute exacerbation (defined as an acute worsening for which an identifiable cause eg pneumothorax, pulmonary embolism, pneumonia and heart failure cannot be identified) is reported to be the leading cause of

acute deterioration in IPF[210], infections were reported to be often present in a number of studies with an acute exacerbations [56, 210, 211]. Huie et al in their study of 27 patients with acute deterioration of fibrotic lung disease (13 IPF patients) identified an infective agent in a third of cases[211]. So did Kim in a study of acute exacerbations in 147 patients with biopsy proven IPF, among 23 patients with an acute worsening 7 had to be excluded as infection could not be completely excluded[56]. Unrecognised infection may be the cause of exacerbation in many more cases particularly as the clinical and radiological features of both infection and non-infectious exacerbations may be indistinguishable[212]. Infection is the most important differential diagnosis in patients with an acute exacerbation especially those immunocompromised, as shown by Song et al. Opportunistic infections comprised 57.1% of the documented organisms and usually developed in those patients treated with steroids regardless of other cytotoxic agent ued. Opportunistic infections included PCP (17%), CMV (single organism in 42% and as a co-infection in further 17%), candida, influenza virus, aspergillosis and M. tuberculosis in 8% each[210].

Another study of an Egyptian IPF population assessed the spectrum of bacteria involved in previously untreated infective exacerbations of IPF. Although the study did not have a control arm)[213], it showed that 80% of 25 patients with an infective exacerbation of IPF had positive sputum culture, with the majority of cases showing growth of Pneumococci and Staphylococci (16/20 patients). The remaining patients grew gram negative bacteria, 28% of cases had co-infection with fungi and one case was positive for acid fast bacilli (the data is in abstract form only).

With mortality rates from IPF increasing progressive pulmonary fibrosis itself is reported to be an underlying cause of death in approximately 60% of cases in epidemiological and autopsy studies [28, 214] and up to 71% of cases of the placebo group from the Interferon gamma clinical study [97]. An analysis of cause of death in a number of recent clinical trials showed that 77% of patients died from respiratory causes, including progression of IPF, acute exacerbation, acute lung injury, pneumonia, and cor pulmonale[98, 104, 105, 196, 215]. Respiratory infections were found to lead to death in 6.5-14% cases in a number of observational studies[124, 216, 217], and pneumonia was specified as a cause of death in 2.4 ± 0.5% in an epidemiological study [28], and in 5-23.3% of cases in autopsy studies [214, 218].

Respiratory tract infections including pneumonia were reported to be the cause of death in a large proportion of patients from four clinical trials (Table 4.27) and though the results are difficult to compare, due to different analyses being and small number of patients, the average number of patients with respiratory tract infections appears to be higher than that reported in the epidemiological study[28].

	Interferon-gamma (ITT)		IFIGENIA (NAC) (PP)		Etanercept (ITT)		INSPIRE (Interferon-gamma) (ITT)		TIPAC (Co-trimoxazole) (ITT)	
Duration of treatment	58 weeks		12 months		48 weeks		96 weeks		12 months	
	Active	Placebo	active	placebo	active	placebo	active	placebo	active	placebo
Total number of deaths	16 (10%)	28 (17%) p=0.08	7 (9%)	8 (11%) p<0.69	4 (9%)	2 (5%) p=0.41)	93 (17%)	39 (14%) p=0.346	18 (19%)	19 (22%) p=0.379
Respiratory deaths	81%	82%	6 (86%)	6 (75%)	3 (75%)	2 (100%)	75 (81%)	32 (81%)	16 (89%)	19 (100%)
RTI	3 (19%)	3 (11%)	3 (43%)	1 (13%)						
Pneumonia					1 (25%)	1 (50%)			4 (22%)	7 (37%)

Table 4.27 Respiratory system infections reported as the cause of death in 4 clinical trials and this trial. ITT – intention to treat analysis, PP – per protocol analysis, RTI – respiratory tract infection.

Respiratory tract infections are also reported as adverse events in a large proportion of patients in clinical trials (Table 4.28). Although the results cannot be compared directly due to difference in definitions of respiratory tract infections with some studies including pneumonia and some not, it is clear that a large proportion of patients (from 33 to 68%) experience a respiratory system related infective event within 48 weeks minimum to 96 weeks maximum observation period and in one study pneumonia was reported to be the most commonly occurring form of serious adverse event[98]. None of the study drugs have previously been reported to have an effect on respiratory tract infections.

	Interferon-gamma		IFIGENIA (NAC)		Etanercept		INSPIRE (Interferon-gamma)		TIPAC (Co-trimoxazole)	
Duration of treatment	58 weeks		12 months		48 weeks		96 weeks		12 months	
Active/placebo	Active	Placebo	active	placebo	active	placebo	active	placebo	active	placebo
RTI	68%	56%	20* (25%)	24* (32%)	15 (33%)	13 (32%)			27∞ (29%)	38∞ (44%)
Bronchitis					10 (22%)	11 (27%)				
Pneumonia	15%	8%							0	8 (9%)
Admission with RTI	16%	10%								
SAE							32 (6%)	13 (5%)		

Table 4.28 Respiratory tract infections reported as adverse events in safety analysis in 4 clinical trials and current trial. *including LRTI, pneumonia, bronchitis; ∞ LRTI

The data from this study suggests that the survival benefit of co-trimoxazole is more likely due to its anti-infective activity despite a lack of data on pneumocystis jirovecii and bacterial colonisation. This is probably not unexpected considering co-trimoxazole is a sulphonamide with

bacteriostatic activity. Co-trimoxazole exerts its antimicrobial effect by inhibiting synthesis of tetrahydrofolic acid, the metabolically active form of folic acid with the resulting inhibition of thymidine synthesis; sulphamethoxazole acts primarily through inhibiting synthesis of dihydrofolic acid, while trimethoprim acts as a competitive inhibitor of dihydrofolate reductase, the final enzyme in the pathway to tetrahydrofolic acid[219]. Co-trimoxazole is a broad spectrum antimicrobial agent, *in vitro* it is active against a wide range of organisms including gram-positive (Staphylococcus species (including invasive methicillin-resistant Staphylococcus aureus infections), Streptococcus species (including Streptococcus pneumoniae), Corynebacterium diphther) and gram-negative aerobic (Neisseria gonorrhoeae, Escherichia coli, Shigella species, Salmonella, Proteus, Enterobacter, Klebsiella, Yersinia, Vibrio cholerae, Haemophilus influenza) bacteria, Chlamydia, Nocardia (actinomycetes), some mycobacteria and protozoa and many anaerobic bacteria[220]. Pseudomonas aeruginosa, Treponema species., Mycoplasma pneumonia, Mycobacterium tuberculosis are resistant to co-trimoxazole. Taking into account a spectrum of colonising bacteria in non-immunocompromised patients with IPF[209] and of bacteria associated with exacerbation of IPF[210, 213] it is possible that co-trimoxazole treats bacterial colonisation and prevents or provides early treatment of acute infection for some types of microorganisms. Since over half of patients were on immunosuppressive treatment at recruitment it is possible that co-trimoxazole acts by preventing steroid-induced infections.

4.4.4 Other antibiotics in pulmonary fibrosis

The effects of two other antibiotics were assessed in murine models of bleomycine induced pulmonary fibrosis and of one of them in a small clinical study. Azithromycin significantly reduced fibrotic lesions (spindle cell proliferation and collagen I deposition) as well as restrictive lung function pattern after 35 days of treatment with changes found in neutrophils and macrophages (innate immunity) and TH2, TH17 and Treg cytokines (adaptive immunity)[221]. Doxycycline was also shown to have an inhibitory effect in mice with bleomycine induced pulmonary fibrosis in two studies. Its use led to a reduction in secretion and activity of collagenase type IV and in hydroxyproline level associated with a decrease in the extensiveness of the fibrotic lesions, thickness of the alveolar septa and accumulation of nucleated cells on image analysis[222] as well as to a

reduction of production of collagen type I, connective tissue growth factor (CTGF), TGF-beta 1 and to inhibition of mRNA expression of matrix metalloproteinases 2 and 9, CTGF, collagen type I in alveolar epithelial cells but not in normal lung fibroblasts[223]. The latter effects were assessed in a prospective open label study which showed that in 6 patients taking doxycycline for 24 weeks the BALF levels of MMP3 and 9 as well as of tissue inhibitor of metalloproteinase-1 and VEGF were reduced nearer to the normal level shown in 6 healthy control subjects; these changes were associated with significant improvement in total score of SGRQ and such clinical parameters as 6MWD, FVC which was not significant[224].

On the grounds of animal studies it was proposed that doxycycline through the inhibition of alveolar epithelial cells production of MMP and growth factors which are involved in remodelling and degradation of extracellular matrix, and azithromycin through the modulation of both innate and adaptive immunity might play an antifibrotic role in IPF. At present there is no sufficient evidence to suggest that these effects would translate into clinical practice with the effect on markers of disease activity and/or mortality.

As far as we are aware there is no literature on use of other antibiotics in experimental models of PF or in clinical settings.

4.4.5 Serious adverse events

In our study, respiratory events were the most frequent cause (61%) of SAE (Chapter 4, Table 4.16) which is similar to previously reported interventional studies.[98, 100] studies previously. In total 33% of study patients, including 26% of patients receiving co-trimoxazole experienced at least one SAE (Chapter 4, Table 4.17). The latter is similar to the number of SAEs reported in the active arms of clinical trials using etanercept[104] and BIBF[109] (26-27%) but is lower than the trials evaluating bosentan[100] and interferon-gamma[98] (32-39%) as well as in the observational study of rapid deteriorations where 35% of patients sustained admissions[210]. In the intention to treat analysis the total number of patients experiencing at least one SAE (Chapter 4, Table 4.17) and the average number of events per person were lower in the active group but this was not statistically significant. Similarly amongst patients adhering to treatment both of these outcomes as well as the number of patients with respiratory SAE and an average number of respiratory events

per person were significantly lower in the co-trimoxazole arm compared to the placebo arm (Chapter 4, Table 4.19 and Table 4.20). None of the previous interventional trials have reported a significant difference in the total number of SAEs or in a number of respiratory related SAEs in favour of the treatment arm.

4.4.6 Acute exacerbations

The natural history of IPF is variable with a 5-year survival of only 20-30%[11, 20] is unpredictable at the time of diagnosis[16]. The majority of patients show slow progression over a number of years, some remain stable and other have an accelerated decline[16]. Recent observations have also suggested that acute respiratory worsening can occur in a small minority of patients with IPF annually ranging from 5-10%[16, 99, 101, 225], to 19%[210] with some patients experiencing multiple episodes of acute exacerbations[210]. Episodes of acute worsening can occur at any point in the course of IPF in patients with both stable and slowly progressive disease which may explain the fact that patients with more stable disease (i.e. those showing a < 10% change in FVC over 6-12 months after diagnosis) in spite of having a better survival still continue to die albeit at a lower rate[23, 63]. In one study the onset of acute exacerbations was not related to the degree of pre-existing lung function impairment[56] whilst in another study the risk was higher in patients with more severe disease[210]. Mortality associated with an acute exacerbation of IPF is up to 75%[226] and in patients requiring mechanical ventilation it is as high as 90%[210]. As has been prospectively recorded in published clinical trials, 30% of all deaths is the result of an acute exacerbation[196]. The aetiology of acute exacerbation is unknown but many patients present with fever, flu-like symptoms and neutrophilic bronchoalveolar lavage (BAL) suggesting an unrecognised infective aetiology[227].

The effect of co-trimoxazole on acute exacerbations is not known. In this study 7 deaths in per protocol population were attributable to IPF in the absence of identifiable cause (infection, heart failure, pulmonary embolism or pulmonary hypertension). All of these were preceded by a gradual (over months) decline in lung function associated with a gradual deterioration of symptoms rather than had features consistent with an acute exacerbation.

4.4.7 Immuno-modulatory and disease modifying action

Oxidative stress, from the release of reactive oxygen species, is thought to be a mechanism of epithelial injury in IPF[228]. Repetitive injury to the alveolar epithelium and endothelial injury causes chemokines and growth factors release which in turn drives recruitment of fibroblasts and endothelial cells which leads to collagen-matrix remodelling with little evidence of inflammation. There is evidence of inflammatory cell recruitment with infiltration of lymphocytes, plasma cells and histiocytes associated with type II pneumocyte hyperplasia[6]. It is thought that free radicals are involved in fibrogenesis and the activation of inflammatory cells, which leads to the production of reactive oxygen species. A strong expression of nitrotyrosine (a byproduct of protein nitration caused by a potent oxidant peroxinitrate) and nitric oxide synthase is found in macrophages, neutrophils and the alveolar epithelium in the lungs of patients with early to moderate stage of IPF compared to normal control subjects[229].

Potential immunomodulatory properties of co-trimoxazole have been poorly studied. Roberts et al[230] have demonstrated that sulfamethoxazole interferes with the production of oxygen derived free radicals by activated neutrophils. Co-trimoxazole has been shown to suppress tumour necrosis factor (TNF)α secretion from stimulated peripheral blood mononuclear cells[231]. Other researchers suggest that the hydroxylamine metabolite of sulfamethoxazole causes a shift towards a TH1 response from a TH2 response with inhibition of the production of TNFα, interleukin (IL)-2 and IL4 without inhibiting interferon (IFN) secretion[232]. Co-trimoxazole may therefore reverse the shift from TH1 to pro-fibrotic TH2 cytokine seen in patients with IPF[233].

Co-trimoxazole has been shown to reduce the rate of relapse in patients with granulomatosis with polyarteritis (formerly Wegner's granulomatosis)[234, 235], relapsing polychondritis[236] and to have beneficial effects in rheumatoid arthritis[237]. The response to co-trimoxazole granulmatosis polyarteritis is greater if treatment is started in the initial phase of the disease[238] and is not related to nasal disease or infection[235].

Though the trigger initiating the development of fibrosis in IPF is not known it has been suggested that the disease has a multiple pathway mechanism of pathogenesis (Figure below 4.11, [239] and that the balance of abnormalities in each of the key pathways may vary between affected

individuals which would explain the range of clinical, radiological and pathological phenotypes observed in IPF[239]. As a result taking into account pathogenic complexity of the process the need for multimodality therapy to target multiple fibrosis pathways simultaneously has been proposed[239, 240] and supported by the committee of the joint IPF guidelines group[16], this has been echoed by the approach used in the treatment of many cancers. If the multiple pathways hypothesis suggested is correct it is possible that co-trimoxazole may play a role in one of these pathways as an adjunct to other therapies as an antibiotic treating subtle subclinical infection or colonisation or having a prophylactic effect against infective exacerbations or even possible antioxidant effect.

From the data presented here suggests that co-trimoxazole is unlikely to have a relevant effect on the progression of IPF, but may have a considerable effect on survival, probably due to anti-infective properties.

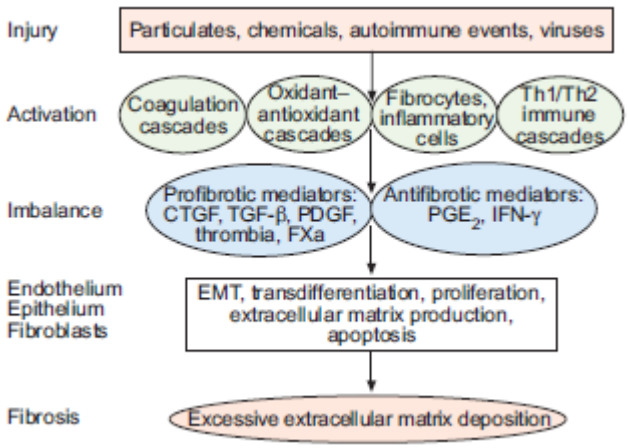


Figure 4.11 A model for pathogenesis of IPF[239]

4.4.8 Quality of life

Taking into account that the majority of existing therapies do not improve survival in IPF, improvement in symptoms and quality of life is important from a patient's perspective.

The TIPAC study showed that patients had significant deterioration in their SGRQ total score at recruitment (59 in placebo and 57 in active group) and that the use of co-trimoxazole led to a significant improvement in the symptom domain of SGRQ in both ITT and per protocol analyses.

The degree of impairment of the total SGRQ score at baseline was compatible with a moderate degree of impairment demonstrated in other clinical trials ranging from 41-46 in trials using interferon-gamma,

etanercept and bosentan[97, 99, 104] to 50-55 demonstrated in trial using NAC, sildenafil and a pilot study using co-trimoxazole[96, 109, 188]. Of studies using SGRQ as a tool of HRQL assessment only two other studies demonstrated a statistically significant difference between the two groups in favour of active drug: a study using a new tyrosine kinase inhibitor BIBF 1120 in a group taking a dose of 100mg twice a day and a group taking a dose of 150mg twice a day in patients with mild to moderate IPF[109], and in a study using sildenafil in patients with advanced IPF[132]. It is not unexpected that the majority of trials did not demonstrate significant changes in quality of life scores as the instrument has to be sensitive to detect a treatment effect and there has to be a treatment effect which has not been the case with most of recently examined drugs.

In our study the magnitude of change in SGRQ symptoms score was what has been considered to be significant by the majority of investigators (4 and above). Since there was no difference in any PFT parameters it is unlikely that it was a disease modifying activity of co-trimoxazole that led to the improvement in symptoms and thus scores. An anti-infective activity is a possible mechanism of action of co-trimoxazole but it is not clear at this stage if an improvement in cough, sputum and breathlessness was due to treatment of subtle infections, treatment of lower airway colonisation or prevention of infections.

It has been debated whether SGRQ is a reliable and valid instrument in the assessment of HRQL in IPF. An instrument is reliable if it measures something in a reproducible way; validity refers to whether an instrument truly measures what it intends to measure and whether its scores convey important information about particular attributes of the people who produce them [74]. There is no reference standard for the psychological construct HRQL therefore clinical parameters are used as a point of reference; it is not expected that that there would be a high correlation as this would suggest that the instrument is unable to provide unique information and is therefore not required; it is nevertheless expected that the correlations would be in direction and of magnitude that make sense in terms of a concept of HRQL[74]. Validity is population-specific (instrument is valid for performing a role in a particular type of population) and use-specific (instrument is valid for performing a particular purpose in population)[74].

While SGRQ was designed and validated for the use in patients with COPD[241], it has subsequently been validated for the use in IPF[81, 83, 242]. At the same time use of non-disease specific measures for

assessment of HRQL may not capture some effects of IPF on patients' lives or can cover areas that are not relevant to IPF. Due to physiological differences between COPD and IPF some symptoms do not usually occur in IPF patients (unless there is co-existing obstructive airways disease) therefore questions about wheezing, attacks of disease and productive cough become irrelevant.

On the other hand patients in both previous studies that assessed IPF patients' perspectives felt that SGRQ did not adequately capture their disease experience. Compared with twelve primary conceptual categories (the domains of IPF-related quality of life) identified by Swigris et al (symptoms, IPF therapy, sleep, exhaustion, forethought, employment and finances, dependence, family, sexual relationship, social participation and leisure activities, mental and spiritual well-being, mortality) 5 areas were not covered by the questionnaire: sleep, dependence, family, sexual relations, and mortality[76]. Exclusion of these items means that the questionnaire is not able to reflect changes in all aspects of QOL.

To address these issues Yorke et al went through the stages of reducing and refining the original questionnaire, developing a new scoring scheme, assessing cross-sectional and longitudinal validity arrived to create SGRQ-I followed by examining internal consistency reliability for each domain of the SGRQ-I and for comparison purposes for each domain of the original SGRQ[243]. Rasch analysis and psychometric testing confirmed that the SGRQ-I has acceptable measurement properties; the construct validity was supported by multiple significant correlations between component scores and FVC% predicted, DLCO% predicted, 6MWD, BDI, SF-36. Prospective studies are required to assess the responsiveness of the new instrument and to determine the minimum important difference[243].

A change in SGRQ score of four units was shown to be consistent with clinically significant change in patients with COPD based upon expert opinion and anchor based approach[244]. One recent study determined that grand means of minimum important difference (MID) estimates for SGRQ domains were 5 for the activity domain, 7 for the impact domain and 8 for the symptoms domain. Possible explanations for this difference are firstly the difference in physiology of the diseases (COPD and IPF) and irrelevance of some of the questions when applied to the IPF population (wheeze, chest attacks); secondly a small number of study patients who had significant change in their physiological parameters over 6 months (47% had a change in FVC of >7% and only 35% had a change in DLCO of

>15%), thirdly only patients with mild to moderate disease were included into the study therefore not the full spectrum of disease severity was represented. These MID estimates will need to be reassessed in future studies before they are recommended for regular application.

On the grounds of the results of the first assessment of the longitudinal performance of SGRQ its use has been recommended in studies until IPF-specific instrument is developed and tested[83]. The first two versions of such instrument have been developed. ATAQ-IPF (A Tool to Assess Quality of life in IPF) is based on patients' perspectives and is composed of 74 items comprising 13 domains[245]. The questionnaire validity is supported by the pattern of correlation with psychologic variables known to be important in IPF as well as significant differences in its scores between patients using and not using supplemental oxygen. Simple summation scoring is used to derive individual domain scores as well as a total score. King's Brief ILD questionnaire (K-BILD) was generated from patient interviews, literature review and multi-disciplinary team meeting and comprises 15 items that generate an overall and three health domain QOL scores (physiological, breathlessness and activities, and physical symptoms)[246]. Rasch analysis was used for construction of both questionnaires, Future studies will build on the validity of both questionnaires.

4.4.9 Cost effectiveness

There are very few data on the costs of interstitial lung disease or the cost-effectiveness of treatments. Researchers have investigated the economics of diagnostic assessments. When comparing VATS biopsy with limited thoracotomy (LT) in homogeneous patient populations with IPF operating time, number of specimens obtained, chest tube output, day of chest tube removal, and amount of analgesics did not differ; at the same time operating room cost and anesthesia-related costs for VATS was significantly greater than that for LT[247]. Only procedure-related costs were assessed in that study and it is not clear if the results of biopsy were equally conclusive for both procedures. Another study compared the use of CA 15-3 as a viable alternative to KL-6 for ILDs with and without fibrosis; the use and costs of CA 15-3 and KL-6 were found to be equally sensitive and specific in terms of differentiating between ILDs with and without fibrosis; at the same time the wide availability, ease of use, and cost effectiveness, made CA 15-3 a suitable alternative for KL-6 as a possible

marker for pulmonary fibrosis[248]. A pharmacogenetic cost-effectiveness analysis of Thiopurine methyltransferase (TPMT) testing before commencement of azathioprine, NAC, and steroids found that TPMT testing (a genotypic assay developed to help to identify those at risk of leucopenia with azathioprine and therefore to limit the toxicity) was the most costly but the most effective strategy compared to commencement of triple therapy without prior TPMT testing, and conservative therapy, consisting of only supportive measures. This study is an example of decision modelling and does not involve real patients. The therapeutic choices and treatment outcomes were modelled based on clinical practice and TPMT activity (normal, intermediate and low) after a survey of expert panel of pulmonologists specialising in treatment of ILD to provide estimates of therapies and complications. Available (at the time) data on the prevalence of types of TPMT activity from population based studies was used as base case values. Costs are expressed in dollars and cost of medications as well as in and outpatient events and disease progression similarly to our study was obtained from the relevant US online group codes sources. The marginal cost-effectiveness of the TPMT testing strategy was $49,156 per QALY gained versus conservative treatment which is below the societal $50,000 willingness to pay threshold; compared with triple therapy without prior testing, the TPMT testing strategy cost only $29,662 per QALY gained[249]. Both the co-trimoxazole study and the study of Hagaman et al[249] demonstrate the value of the low cost intervention and as shown in the TPMT model though as many as 313 patients would need to undergo TPMT testing to prevent one admission due to leucopenia the relatively low cost of the test allows cost recovery by admission prevention. The health-economics part of the co-trimoxazole study and the study of Hagaman et al[249] can not be compared directly due to different design and outcome measures used. At the same time as opposed to large dataset modelling used in Hagaman's study, the co-trimoxazole study used prospective data collection over 12 months based on the use of a detailed questionnaire amid an element of recall bias.

The only data relating to IPF treatment are in abstract form and show rising healthcare costs using database of medical and pharmacy claims from private health plans in the USA and that 70% of mean annual total health-care costs were due to hospitalisation, were increasing with age and were significantly higher in those who died at the end of the annual follow up[250]. Ours is the first study to examine the cost-effectiveness of

a treatment for IPF from a healthcare provider and from a societal prospective. We have shown that co-trimoxazole may increase mean costs, but may also increase QALYs. The point estimate extra cost per QALY gained is of borderline cost-effectiveness compared with the threshold commonly adopted in the UK NHS (£21,391 vs. £20,000 - £30,000 per QALY gained[251]). The lower ICER in the per protocol analyses is consistent with a dose-response effect. However this is not the case when considering cost per ml change in the primary outcome. The explanation for this is that the primary outcome (change in FVC) does not take mortality into account, whilst QALYs do by definition. Two studies in patients with COPD of similar age group (mean age 64 years) assessed cost-effectiveness of treatment with new agents. Analytic modelling study using Markov model in patients with moderate to severe COPD evaluated cost-effectiveness of indacaterol, a novel inhaled once-daily long-acting beta2agonist, compared to existing inhaled monotherapies (tiotropium and salmeterol)[252]; it showed that indacaterol was dominant (lower total costs and better outcomes) against other two therapies and had an ICER of 28,300 per QALY. In patients with severe COPD (mean FEV1 41% predicted) a cost-effectiveness analysis was performed alongside randomised double-blind placebo-controlled study of the effect of one-year treatment with roflumilast, an oral once daily phosphodiesterase IV inhibitor[253]; incremental costs were related to the differences in the number of moderate to severe exacerbations and the net proportion of patients with at least 4 unit improvement in total SGRQ score. The result of this multinational study showed that annual COPD-related costs were high in roflumilast group compared to placebo from both societal and HNS prospective; treatment with roflumilast was cost saving in patients with very severe COPD due to a statistically significant reduction in a number of exacerbations; in a subgroup of patients with high health-care utilisation a 19% reduction in exacerbation rate was observed which translated into an ICER of 804 per exacerbation avoided.

The example of these two COPD studies and the TIPAC confirms that that health economic analysis concerns itself not only the inputs (costs) but outcomes too and that while the treatment could be overall more costly the effect of saving due to reduction of exacerbations of the disease/infections and related hospital admissions and usage primary healthcare services could not be disregarded. Interestingly economic evaluation of different disease groups might demonstrate that different sectors attract higher

costs. For example in asthma where patients are younger with the majority being employed the costs associated with the loss of productivity are likely to be higher compared to disease of older age like COPD and IPF with the majority being retired where this aspect is more relevant to family members who would be caring after their relative during the disease exacerbation. Disease of older age also encounter higher costs in terms of social care including care attendant service and meals-on-wheels, occupational therapy including home and walking adaptations like walking sticks and wheel chairs, travel to hospital.

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4.4.10 Limitations

HRCT review

This study was conducted prior to publication of the recent guidelines for diagnosis and management of IPF[113]. Patients were entered into the study based on clinical and HRCT findings and few patients (16%) had histological confirmation of their disease, which reflects current clinical practice (with many patients being elderly and having contraindications for a surgical lung biopsy), and is similar to other clinical trials[101, 106]. A radiological review was undertaken in a blinded fashion by two respiratory radiologists in patients who did not undergo lung biopsy (132 of 153 (86%) of HRCT scans were available). 10% were felt by radiologist to have NSIP. Amongst patients with IPF 43 patients (28%) had a confident diagnosis (scans showed all features of IPF including honeycombing) and 74 patients (48%) had a probable diagnosis (in the absence of honeycombing). For the latter group an algorithm described by Fell et al. was used to predict a histological diagnosis of IPF. The algorithm showed that when using age at a cut-off of 70 years as a sole predictor in patients with even modest amount of fibrosis a positive predictive value of the diagnosis of IPF is 95%[165]. A probability of IPF score combining age with the HRCT interstitial score was calculated for 89 patients without honeycomb change on HRCT and showed that it was equal or greater than 0.6 in 83 (93%) patients. This cut-off of 0.6 is associated with a positive predictive value and specificity for the diagnosis of IPF of 100%. Both our sensitivity analyses of patients with a confident diagnosis of IPF (biopsy, characteristic radiological features or clinic-radiological features using Fell

criteria) showed the same degree of mortality benefit with co-trimoxazole. The weakness of the radiological review is that it was retrospective.

Treatment with corticosteroids

BTS ILD guidelines from 2008[14] as well as the current IPF guidelines from 2011[113] recommend against the routine use of immunosuppression. 59% of study patients were treated with immunosuppressive therapy either in a form of prednisolone alone or in combination with azathioprine or mycophenolate mofetil at recruitment. This reflected current practice at the time of the study and may be also partially explained by the fact that only 25% of cases were prevalent, which means that the majority of patients were diagnosed and treated according to the IPF guidelines from 2000[5] which did recommend the use of immunosuppression. Interestingly the BTS national interstitial lung disease survey with data collected during late 2010 and early 2011 showed that around a half of responders from a total of 120 continued to use prednisolone (55%) and azathioprine (49%) for the treatment of IPF[254].

NSIP

We included a small proportion (6%) of patients with NSIP and some of these (4% of total study population) were not biopsy proven. This was a real life study where some patients were not suitable for a lung biopsy and where an overall clinical diagnosis was used rather than radiological diagnosis alone. Patients with nonbiopsy proven NSIP had a mean DLCO of 36% predicted and there is an evidence that NSIP patients with advanced disease have an outcome similar to patients with IPF[23].

Absence of microbiological analysis

It was not a part of study assessment to conduct microbiological evaluation of all cases for the presence/absence of pneumocystis or bacterial colonisation at recruitment or of all subsequent cases with respiratory tract infections therefore it is not known if co-trimoxazole had an antipneumocystis effect or acted as a broad spectrum antibiotic. It is also not known if another antibiotic (for example from a group of macrolides) would have a similar effect on the rate of infections and survival.

Absence of DLCO measurements in some patients

Provision of DLCO measurements was not an obligatory requirement for the study. There was a number of reasons for this: DLCO was not a primary endpoint and it is known that some patients with significant functional impairment are not able to produce valid DLCO measurements. Hence it was considered that the absence of DLCO should not prevent patients with otherwise suitable disease from participating in the study. Some sites did not have access to the necessary equipment. Nevertheless 83% of patients had DLCO measurement at recruitment and 84% of those who completed 12 months of treatment and were included in per protocol analyses.

Variable PFT equipment

The study participants were recruited from 28 sites. Local pulmonary function equipment was used at each site. Static lung volumes were measured with the use of body pletismography (103 patients) or helium dilution (69 patients) and two sites (12 patients) used nitrogen washout in addition to body pletismography. Vitalograph was used in a small number

of patients (9 patients). All PFT laboratories use ATS guidelines for the measurement of PFT and 6 MWT but it is possible that there were inter-site discrepancies. Nevertheless since for the duration of the study each patient had all measurements performed on the same equipment hence there should not have been inconsistency in the technique and inter-patient results.

It was ensured that all patients who had a LRTI would have PFT performed at least 4 weeks after the resolution of symptoms.

Quality of questionnaires and other missing data

Each patient visit along with clinical and functional assessment involved completing a number of questionnaires – four at recruitment (SGRQ, EQ5D, socioeconomic status questionnaire, cost questionnaire - baseline), three at 6 and 12 months visit (SGRQ, cost questionnaire–follow-up and EQ5D), and two at 6 weeks and 9 months visit (EQ5D and cost questionnaire–follow-up). Lack of regular check of adequacy of questionnaire completion led to incomplete data in some patients for all four questionnaires at recruitment. This was indentified a few months into recruitment and the attempts were made to ensure that all questionnaires were completed adequately at each visit. Some patients found it onerous to fill in four questionnaires at recruitment which was another reason for providing either no entries or incomplete entries. In a small proportion of patients information for a Background Questionnaire (which is a part of socio-economical analysis and includes education, living arrangements, employment, wellfare benefits) was obtained retrospectively. Also patients who reported adverse events during their last study visit or in whom missing data in their final visit clinical questionnaires was identified were contacted for the purpose of accurate data collection and to follow up adverse events. An approval of the Ethics committee was obtained for these out of study contacts. Some patients took a decision to withdraw from the study prematurely outside clinic visit. Ideally all these patients should have had a withdrawal visit organised within a short period of time after stopping taking the study drug with measurements taken as at exit visit. Nevertheless this did not happen on some occasions either because the study team was not informed of premature discontinuation of the study drug or because adequate arrangements for withdrawal visit were not made or because patient refused to attend.

Missing data was dealt with by performing a sensitivity analysis conducted by multiple imputations from an imputation model (by using linear interpolation, in other words replacing the missing values with the results derived from non-missing adjacent values) which contained randomization group and all outcome measures; however if 40% or more of the data were missing the variable was not imputed or used in the imputation model. The imputation model chosen was a multivariate normal distribution[190], which has been shown to be robust against departures from multivariate normal distribution. Due to the small number of deaths, deaths or changes in medication were not imputed. Additionally, due to the small number of available data it was decided it was not appropriate to impute the six minute walk data. A total of 5 imputed data sets were created and the results were averaged over these 5 datasets using Rubin's equations. No safety or per-protocol data were imputed.

Withdrawal rate

30 patients (34.9%) in placebo arm and 41 patients (43.2%) in co-trimoxazole arm withdrew prior to prespecified end of treatment at 12 months. Excluding deaths, the withdrawal rate due to adverse events/ adverse reactions or withdrawal of consent was 17.4% in placebo arm and 38.9% in co-trimoxazole arm – while the rate of withdrawal of consent was similar in both groups (8 (9.3%) and 9 (9.5%) patients respectively), patients in active arm had a higher risk of adverse event/reactions leading to withdrawal (28 patients (29.5%) as opposed to 8 (9.3%) in placebo arm). There are a number of factors that may influence the withdrawal rate in an interventional study including duration of the study, patients' characteristics (severity of the disease studied, age at recruitment, comorbidities), side effect profile of the study drug. In IPF trials disease progression, acute exacerbation and lung transplantation may lead to patient withdrawal too. When it comes to drug related adverse reactions it could be a patient decision to discontinue treatment if it affects their quality of life or an investigator decision if patient's safety is being compromised. Interestingly disease progression itself could be a reason for withdrawal of consent by a patient as one might feel it harder to continue attending time and effort consuming visits or become frustrated if the hopes of disease stabilisation while in the study are not met. Some practical aspects like travel distance and frequency of study visits, support in terms of travel means and costs could also influence a patient decision

whether to take up or continue in the study. Rate of total treatment withdrawal (excluding deaths) in the treatment arms of recent trials varies between 18-26% in trials using bosentan, NAC, etanercept and interferon gamma[96, 98, 100, 104] and 30-37% in trials using imatinib and pirfenidone (higher dose group)[102, 105]. Withdrawal rate due to adverse events was around 14-15% in the majority of these trials with an exception of the trial using imatinib where it was 22%. Possible explanations for a higher rate of withdrawals due to adverse events may be that an older population with more severe disease recruited into this study. Also a large proportion of withdrawals were early withdrawals due to drug related adverse reactions, predominantly gastrointestinal (8 patients (8.4%)), rash (3 patients (3.2%), and neutropenia (3 patients (3.2%)) which is probably not unexpected taking into account the side effects profile of co-trimoxazole. All cases of rash leading to withdrawal were mild in severity, were not associated with blister formation or mucosal involvement and were self terminating within 3-5 days after drug withdrawal. The occurrence of nausea as the most frequent cause for drug related treatment withdrawal was higher than in the study using pirfenidone (where it was 1%)[103] but lower than in the study using BIBF1120 in a dose of 150 mg twice a day (where it was 16.5%). At the same time withdrawal rate (excluding deaths) in placebo arm was lower (17.4%) than in some trials – 25% in trials using imatinib[105] and BIBF[109] though patients in those trials were younger. The majority of recent studies in patients of similar age (mean age 62-64 years) with COPD which do not included true placebo arm but rather compare treatment effects of different drugs demonstrate that the withdrawal rate is also high particularly in studies of more than six months duration and ranges between 20 and 40%[255, 256]. A recent Cochrane review concluded that due to a high withdrawal rate (35-42%) coupled with a high proportion of missing outcome data the efficacy and safety of combined treatment with inhaled corticosteroid and long acting beta-2 agonists as well as with tiotropium remained uncertain[255]. The rate of consent withdrawal in COPD studies is similar to our study while the rate of adverse events is only marginally lower (20-23%)[257]. High withdrawal rate in patients of similar age and different underlying problems might suggest that age related comorbidities and perception of disease stability might play a role.

Over the course of the study three patients receiving co-trimoxazole and azathioprine developed transient neutropenia, which resolved in all cases

following discontinuation of co-trimoxazole. In the first case neutropenia was severe (aneutrophilia) and required hospitalisation and treatment with granulocyte-macrophage colony-stimulating growth factor. The neutrophil count returned to normal with 7 days. Although co-trimoxazole is known to cause pancytopenia due to its mode of action (inhibiting synthesis of tetrahydrofolic acid, the metabolically active form of folic acid) this side effect was unexpected to see any of its forms considering it was ensured that all patients had normal blood folate level at recruitment and were receiving supplemental folic acid in a standard dose of 5 mg a day. Interestingly Medicines and Healthcare products Regulatory Agency (MHRA) which was contacted after the first case of neutropenia stated there had been no previous reports of cytopenia in patients treated with a combination of co-trimoxazole and azathioprine. Following this, all patients receiving azathioprine or mycophenolate mofetil had 2-weekly monitoring of their full blood count and two further cases were withdrawn as a result of mild rather than severe neutropenia.

Attempts were made to obtain the data on primary endpoint (FVC) on all patients who withdrew prematurely and remained alive at 12 months after recruitment; this was possible in 4 patients in placebo arm and 9 in active arm bringing up the total number of patients assessed for efficacy to 60 and 63 respectively (see consort diagram).

Difference in baseline characteristics in patients in PP and ITT analyses

The results of per protocol population are potentially biased. Comparing the baseline lung function data for those who have valid FVC measurements at 12 months visit with those who do not reveals significant differences in terms of FEV1, FVC and DLCO (Chapter 4, Table 4.10). This implies that the results of the per protocol analysis are not generalisable to the population from which the original sample was drawn.

How to improve

In an ideal study of patients with IPF along with using appropriate endpoints one would want to enrol patients with all disease severity groups, optimise recruitment, reduce withdrawal rate and compare treatment effects with a true placebo arm. In retrospect it is clear that IPF studies should be arranged on a national level as recruitment at a regional level even in as large region as large as East Anglia can be a limiting factor. Although the overall IPF population in the study sites was sizable

(582 patients), it is necessary to take into account that 14% declined participation and further 24% had stable disease. Recruitment of patients with stable disease in to a study that uses change in a functional parameter as a primary endpoint would make it difficult to detect a difference over time. It would have been ideal to include a true placebo arm to enable a definitive assessment of the effects of co-trimoxazole. It would have been ideal to have radiological review in advance of randomisation to ensure a selection of correct patient group. Optimising data collection by using a checklist for each visit and ensuring completeness of questionnaires from the start of the study are required. In a study using antibiotics it would be useful to determine the microbiological profile of patients at recruitment in terms of PCP colonisation as well as obtain evidence of infective agent causing respiratory tract infection/pneumonia during the course of the study. Prospective assessment of causes of deterioration to establish the effect on acute exacerbations would be required.

Strengths

This was a real life study among patients from district general hospitals population predominantly. It allowed patients with any severity of IPF to participate and reflects the range of disease that is seen in clinical practice. TIPAC was a relatively large study with a total of 181 patients randomised similar to studies using NAC[96], bosentan[99] (BUILD-1) and a larger scale than some other[101, 104]. It was pragmatic and is the only one in IPF that incorporated health-economics analysis. It is the only non-pharmaceutically funded study in IPF and its total budget was relatively small. An integrated database was used for data collection and analysis which could be used for other trials. Statistical analysis plan was produced in advance of recruitment and there was a good adherence to protocol without change in primary or secondary endpoints after its approval.

Chapter 5

Study 3

Are alveolar nitric oxide and plasma VEGF markers of disease severity and progression in patients with idiopathic pulmonary fibrosis?

5.1 Introduction

IPF is a progressive chronic ILD of unknown cause associated with histopathologic pattern of UIP. Although the median survival in IPF is poor, there is considerable variability in disease progression with only a proportion of patients showing evidence of decline at 6 and 12 months from diagnosis. Flaherty et al[63] showed that whilst 32% of patients with IPF had a 10% decline in FVC at 6 months and 54% had a similar decline at 12 months, 68% and 31% remained within 10% or had a 10% improvement in their FVC at 6 and 12 months respectively. Even with this enormous variability, the best method to assess disease progression and hence to predict outcome is serial pulmonary function over a 6 to 12 month period. Biomarkers, biochemical tests which predict prognosis or response to treatment, are required to help identify those patients with a good or poor outlook. Two potential biomarkers are exhaled nitric oxide or vascular endothelial growth factor (VEGF).

Current concept of pathogenesis of IPF suggests that repetitive injury to alveolar epithelium and endothelial injury causes chemokines and growth factors release which in turn drives recruitment of fibroblasts and endothelial cells which leads to collagen-matrix remodelling with little evidence of inflammation. Nevertheless there is evidence of inflammatory cell involvement with an alveolar septal infiltrate of lymphocytes, plasma cells, and histiocytes associated with type II pneumocytes hyperplasia[5]. This is in line with a multiple pathways hypothesis of pathogenesis of IPF with evidence of activation of oxidant-antioxidant cascades[239]. It is thought that free radicals are involved in the role of fibrogenesis of human lungs in ILD and the activation of inflammatory cells leads to the production of reactive oxygen species: a strong expression of nitrotyrosine (a byproduct of protein nitration caused by a potent oxidant peroxynitrate) and nitric oxide synthase is seen in macrophages, neutrophils and alveolar

epithelium of lungs of patients with early to intermediate stage of IPF compared to normal control subjects[229].

NO is a gaseous signalling molecule and can act as a bronchial and vascular smooth muscle dilator[258]. It was first detected in 1991 in the exhaled breath in rabbits, guinea pigs and humans[259]. NO is produced by constitutive NO synthases (cNOS) (endothelial NOS and neuronal NOS) in the physiological state; during inflammation inducible NO synthase (iNOS) is produced in higher quantities leading to secretion of large amounts of NO[260]. This secretion takes place in airway epithelial cells, airway and circulatory endothelial cells and trafficking inflammatory cells in both large and peripheral airways and alveoli[261]. Fraction of exhaled NO (FeNO) is easily measured, these measurements are simple and highly reproducible[262]. It is known that FeNO concentration is inversely related to the exhalation flow which is a result of a reduction of the contact time of the airstream with a surface serving as a source of NO. It is also known that the elimination rate of NO (product of FeNO and flow) is a positive function of exhalation flow which is consistent with the source of NO from a region of the lung that changes volume during exhalation. Both of these observations imply that an exhaled NO has two origins: alveolar origin and bronchial origin[261]. These principles were used as a basis for creating a two-compartment model of NO exchange consisting of airway and alveolar compartment reported by Tsoukias et al in 1998 [263], Fig 5.1

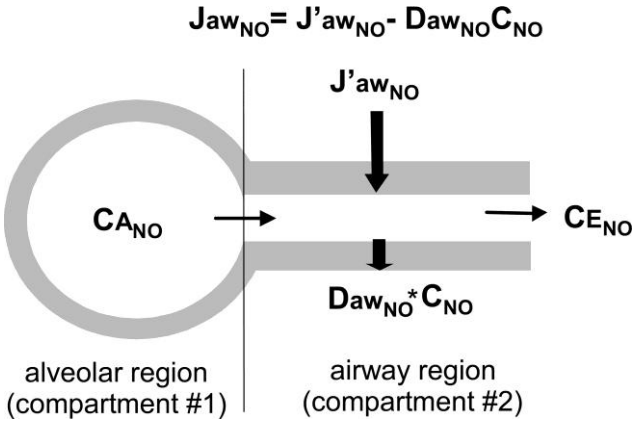

Figure 5.1 Schematic of 2-compartment model used to describe nitric oxide (NO) exchange dynamics. Exhaled NO concentration (CENO) is the sum of 2 contributions, the alveolar region and the airway region, which depends on 3 flow-independent parameters: maximum total volumetric flux of NO from the airway wall (J'awNO, pl/s), diffusing capacity of NO in the airways (DawNO, pl·s-1·ppb-1), and steady-state alveolar concentration (CaNO, ppb). JawNO, total flux (pl/s) of NO between the tissue and gas phase in the airway and is an inverse function of the exhalation flow rate (VE); CNO, concentration of NO in the gas phase within the airway compartment[167].

When FeNO is measured at two or more flow rates (VE, ml/s) there is a linear relationship between VE and the elimination rate of NO VNO (a product of FeNO and measurement flow rate). The way to determine J'awNO and CaNO is to extrapolate the a plot of VNO against the exhalation flow back to the Y-axis (where flow is zero) to determineJ'awNO and to calculate the slope of the plot to determine the CaNO("slope-intercept" method) (Fig 5.2). Clinical usefulness of differentiating between CaNO and JawNO is that its change is able to provide information about the site of inflammation (alveolar or bronchial).

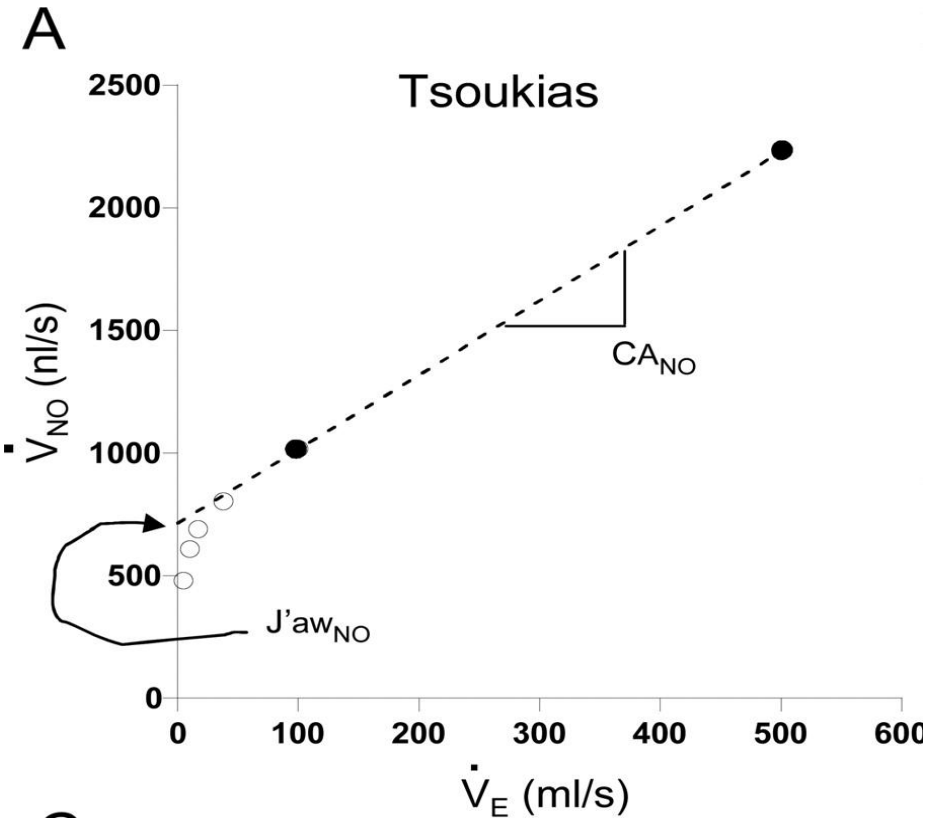

Figure 5.2 "Slope-intercept" method for estimation of alveolar concentration and bronchial flux of nitric oxide[167]

Exhaled NO in healthy subjects is independent of age and lung function and there is no evidence of diurnal variation; at the same time there is a number of factors that can affect NO levels: intravenous, inhaled or digested L-arginine, environmental factors such as NO ozone, and chlorine dioxide; smoking and alcohol consumption reduce the levels of exhaled NO[264]. There is no complete agreement on the effect of gender (some large studies with more than 500 participants reported an association between female gender and lower eNO levels) and physical exercise[265].

Reference values for CaNO have been published by a number of research groups but it is emphasized that the choice of flow rates and algorithms for calculating the alveolar NO would result in different alveolar NO values[265].

Previous studies of patients with asthma show that FeNO measurements at a single expiratory flow rate of 50 ml/l may be an important adjunct to diagnosis and management in selected cases[261], that inhaled steroids reduce the levels of exhaled NO in the asthmatic airways, that these levels correlate well with the disease activity in a form of sputum eosinophilia and that they could well be used successfully to guide titration of the dose of inhaled steroids[266]. Recent ATS guidelines on interpretation of exhaled NO levels recommend the use of FeNO in diagnosing eosinophilic inflammation, monitoring disease activity and predicting steroid responsiveness in asthma[267]. It was also shown that multiple exhalation flow FeNO differentiates between bronchial and alveolar inflammation in COPD and asthma and that CaNO is increased in COPD patients and its levels depend upon the severity of the disease as assessed by GOLD criteria. [268].

A number of studies have investigated the role of exhaled NO in patients with ILD including systemic sclerosis with and without its complications in a form of interstitial lung disease and/or pulmonary hypertension[269-273], in patients with asbestosis[274], eosinophilic pneumonia [275] and stage 1-4 sarcodosis[260, 276]. Some of these studies looked at alveolar rather than total exhaled NO. At the same time there is a paucity of research investigating the role of NO in patients with idiopathic pulmonary fibrosis. To date three studies involved measuring exhaled NO in patients with IPF: one assessed if total eNO levels could be used for monitoring of disease activity[277], one other assessed if multiple exhalation flow NO levels would help to identify the level of inflammation (alveolar or bronchial) in patients with alveolitis (including IPF) and would correlate with the severity of the disease[258], and one more used IPF patients as a control group in assessment of role of eNO in eosinophilic pneumonia[275].

Vascular endothelial growth factor (VEGF) is know for its dual action – it promotes both neoangiogenesis and increased vascular permeability as well as epithelial proliferation and repair[278]. Vascular endothelial growth factor-A is a heparin binding glycoprotein; several other members of VEGF family have been cloned recently including VEGF-B, -C and –D,

angiogenesis is mainly regulated by VEGF-A (subsequently called as VEGF in this thesis) and lymphogenesis by VEGF-C and -D. Macrophages and type II pneumocytes are two major sources of VEGF in the lung with former known to be one of the main inflammatory cells infiltrating lung tissue in IPF[279, 280]. Increased production of VEGF in both epithelial cells and fibroblasts is induced by TGF-β which is one of the main cytokines implicated in pathogenesis of IPF[138]. VEGF in turn increases the expression of connective tissue disease growth factor which promotes proliferation of fibroblasts[281] and production of matrix metalloproteinases by muscular smooth muscle cells[282]. VEGF can be measured in blood (both serum and plasma), BAL fluid, sputum, bronchial epithelial cells, alveolar type II cells, alveolar macrophages and endothelial cells. Serum VEGF levels are higher compared to those measured in plasma reflecting ex vivo platelet and leukocyte release during blood clotting thus resulting in an increase of VEGF concentration by 2-7 fold; in healthy adult epithelial lining fluid VEGF level is 500 times higher than plasma levels[148]. Plasma concentrations of VEGF correlate with HRCT thoracic scan fibrosis scores[149]. In support of its role in the development of pulmonary fibrosis, a VEFG receptor antagonist attenuated bleomycin-induced lung fibrosis in a murine model[150]. Although its concentration is higher in patients with progressive disease (defined as those with a 10% change in FVC after 6 months)[149], the usefulness of VEGF as a survival indicator has not been evaluated.

The aims of the study were:

To determine if there is an association between the disease severity (as assessed by DLco) of patients with idiopathic pulmonary fibrosis and alveolar NO or plasma VEGF.

To determine if alveolar NO and/or plasma VEGF measured at baseline might help to predict subsequent disease progression (defined as death or 10% decline in FVC and/or 15% decline in DLCO) at 18 months.

5.2 Methods

The study was conducted in accordance with Good Clinical Practice including Research Ethics Committee (09/H0310/78) and all participants gave written informed consent.

Patients

Patients were identified from the respiratory clinic of the Norfolk and Norwich Hospital and approached by the Chief Investigator (Dr Shulgina). Eligible patients had clinically labelled diagnosis of idiopathic pulmonary fibrosis with HRCT scan features compatible with Usual Interstitial Pneumonia (UIP)[5] and were able to provide informed consent. Histology was not required as an entry criterion. Patients were greater than 40 years old; none had exacerbation of their disease or respiratory tract infection or changes in their immunosuppression treatment within 6 weeks of recruitment. None of the patients were taking co-trimoxazole. Patients were excluded from the study if a secondary cause for pulmonary fibrosis was identified, if they had a recognised significant co-existing respiratory disorder or if they had a significant medical, surgical or psychiatric disease that would affect subject safety or influence the study outcome, if they had clinical evidence of right heart failure or were current smokers or females who were pregnant or were breast-feeding.

Study design

Patients attended the clinic for a screening visit and baseline measurements including history, medical examination, and assessment of alveolar nitric oxide, and a venepuncture to collect peripheral venous blood for plasma VEGF analysis, following informed consent. All other data was obtained from the medical notes. Patients attended clinic for visit 2 between four and eight months and visit 3 between sixteen and twenty months after the screening visit for repeat pulmonary function tests. Disease progression was defined as death or 10% decline in FVC and/or 15% decline in DLCO at 18 months.

Exhaled nitric oxide measurement

Exhaled nitric oxide was measured using a NIOX nitric oxide analyzer at baseline visit (Aerocrine, Chicago, Illinois USA), with an expiratory flow rate of 50ml/sec according to American Thoracic Society guidelines (18). In addition, measurements were made at expiratory flow rates (VE) of 30, 100 and 200 ml/sec. An attempt to obtain three valid FeNO measurements was undertaken at each of four flow rates for each patient. The mean of three separate measures of nitric oxide at each flow rate was used in the analysis. A model by Tsoukias and George was used to estimate CaNO and

JawNO[167, 263]. For each flow rate VE the elimination rate of NO (VNO) was calculated as a function of VE (VNO = VE x FeNO). At a flow rate of ≥ 50 ml/s this relationship is linear and could be expressed as VNO = VE x FeNO = CaNO x VE + JawNO . The analyser was calibrated two weekly using a cylinder of nitric oxide at concentration of 208ppb.

Vascular endothelial growth factor (VEGF)

Five millilitres of venous blood was drawn during venepuncture into ethylene diamine tetra acetic acid bottle, centrifuged within 1 hour of collection at 300g for 10 min. Plasma was separated and stored at -80°C freezer. All samples were analysed simultaneously after being kept in a freezer for 18-24 months. Level of VEGF in plasma was assessed using a commercially available validated Human VEGF-A Platinum Enzyme-linked immunosorbent assay (ELISA) kit (eBioscience, Bender MedSystems GmbH). The assay was performed by Dr D Sexton, a Lecture in Immunology at the University of East Anglia A manufacturer's recommendation was used as guidance and each sample, standard and control was assayed in duplicate. Seven standard dilutions ranging from 1000 to 15.6 pg/ml were used. The absorbance was measured at 450 nm. A standard curve was prepared from seven human VEGF-A standard dilutions and sample concentration determined. The limit of detection of human VEGF-A defined as the analyte concentration resulting in an absorbance significantly higher than that of the dilution medium (mean plus two standard deviations) was determined to be 7.9 pg/ml (mean of 6 independent assays). Intra-assay reproducibility was previously calculated in three experiments and the coefficient of variation was 6.2%. The calculated overall inter-assay coefficient of variation was 4.3%. There was no cross reactivity detected for the assay, notably not with human VEGF-B, C, D and PfGF. According to a manufacture's brochure an expected VEGF-A level in plasma of healthy donors was estimated as mean 45.7 pg/ml.

Statistical analysis

All statistical analysis was completed using statistical analysis using SPSS version 18 (Statistical Package for the Social Sciences). Because of non-normally distributed data of exhaled nitric oxide measurements it was transformed using natural log with subsequent back-transformation for the purpose of obtaining means and standard deviations. A T test was undertaken to compare the differences between baseline demographic data, pulmonary function tests and exhaled nitric oxide measurements in

(1) patients with severe or mild/moderate IPF defined as DLCO < 40% and ≥ 40% predicted respectively and (2) patients with or without a combined event defined as death, or a 10% decline in absolute FVC and/or 15% decline in absolute DLCO at 18 months after recruitment. Univariate correlation between alveolar NO as well as VEGF and lung function parameters at baseline was examined using Spearman's rank correlation coefficient. Multiple linear regression analysis was used to evaluate an ability of alveolar NO as well as VEGF to predict (1) a 10% decline in absolute FVC, (2) 15% decline in absolute DLCO, and (3) a combined event defined as death or a 10% decline in absolute FVC and/or 15% decline in absolute DLCO, at 18 months after recruitment. A two-sided p-value <0.05 was considered statistically significant.

5.3 Results

A total 27 patients with IPF were recruited into the study. The mean age of patients was 73.1 ± 9.4 years and 23 (85%) were men. All patients were non smokers. The majority (82%) were prevalent cases. Four (15%) patients had histopathological confirmation of diagnosis and 13 (48%) patients had severe disease as evidenced by DLCO of < 40% predicted. Six (22%) patients were receiving treatment with long term prednisolone, two of these in combination with azathioprine. All patients were able to perform the multiple flow rate manoeuvre and 89% patients were able to produce three valid measurements for each of the flow rates. Two patients died, one was withdrawn from the study (following development of lung carcinoma) and two more were lost to follow up by 18 months after recruitment.

5.3.1 Association between the disease severity and alveolar NO and plasma VEGF

Baseline characteristics

13 patients had evidence of severe disease. In two patients who did not have baseline DLCO measurements the disease severity was assessed on the grounds of FVC percent predicted as severe if less than 60% and mild/moderate if greater than 60% (both patients had mild/moderate disease based on this cut off). Patient baseline characteristics pending on disease severity are shown in Table 5.1. At baseline patients with severe disease were older, had higher MRC dyspnoea grade, longer disease duration and lower FVC.

	Severe IPF (n=13)	Mild/moderate IPF (n=14)
Male, n	10	13
Age, years	75.3 ± 9.7	71 ± 9.0
Smoking history, n Never smoker Ex-smoker	 3 10	 4 10
Clubbing, n	4	4
Histopathological confirmation, n	2	2
Emphysema	4	3
Time from diagnosis, years	3.4 ± 2.3	2.3 ± 1.9
MRC dyspnoea grade, mean	3.2	2.7
FVC, % predicted	68.7 ± 11.2	74.2 + 22.7
DLCO, % predicted	31.9 ± 5.7	56.2 +14.2
Immunosuppressive therapy, n Prednisolone Azathioprine	 4 2	 2 0
Use of oxygen, n	2	0

Table 5.1 Baseline characteristics of patients with severe (DLCO < 40% predicted) and mild/moderate (DLCO ≥ 40% predicted) idiopathic pulmonary fibrosis. MRC: Medical Research Council, FVC: forced expiratory volume, ml: millilitres, DLCO: diffusing capacity of carbon monoxide.

Exhaled NO and its correlation with clinical parameters

Patients with severe disease had lower FeNO50, JawNO and plasma VEGF but higher CaNO, the results were statistically significant for FeNO and JawNO (Table 5.2).

	Severe IPF (n=13)	Mild/moderate IPF (n=14)	p
FeNO 50, ppb	18.45 ± 2.38	27.34 ± 3.43	0.038
CaNO, ppb	4.67 ± 0.74	3.27 ± 0.64	0.171
JawNO, nl/sec	663.22± 137.36	1200.51± 166.92	0.023
Plasma VEGF, pg/ml	103.86 ± 17.00	146.10 ± 17.06	0.095

Table 5.2 Comparison of FeNO50, CaNO, JawNO and VEGF results between patients with severe and non-severe IPF. All data presented as mean and SD. FeNO: fraction of end tidal nitric oxide, CaNO: alveolar concentration of nitric oxide, JawNO: nitric oxide flux from the airway wall, VEGF: vascular endothelial growth factor.

Correlation between exhaled NO and pulmonary function parameters at baseline are shown in Table 5.3 and Figure 5.3. There was a significant negative correlation between plasma FeNO50 and TLC percent predicted (r = -0.482, p = 0.017).There was a significant positive correlation between plasma VEGF concentration and FVC percent predicted (r = 0.393, p = 0.047) and DLCO percent predicted (r = 0.575, p = 0.003). There was also a significant positive correlation between alveolar concentration of nitric oxide and Medical Research Council dyspnoea score and a negative correlation between bronchial flux JawNO and FVC percent predicted and TLC percent predicted.

		SaO2	MRC	FVC, %predicted	TLC, % predicted	DLCO, % predicted
FeNO 50	Correlation Coefficient	.221	-.028	-.361	-.482*	.162
	Sig. (2-tailed)	.269	.892	.065	.017	.440
CaNO	Correlation Coefficient	-.076	.394*	.061	.045	-.341
	Sig. (2-tailed)	.707	.042	.761	.835	.096
JawNO	Correlation Coefficient	.179	-.015	-.417*	-.555**	.220
	Sig. (2-tailed)	.371	.942	.030	.005	.291
Plasma VEGF	Correlation Coefficient	.013	.037	.393*	.291	.575**
	Sig. (2-tailed)	.950	.856	.047	.178	.003

**. Correlation is significant at the 0.01 level (2-tailed)
*. Correlation is significant at the 0.05 level (2-tailed)

Table 5.3 Correlation between exhaled NO and baseline lung function parameters

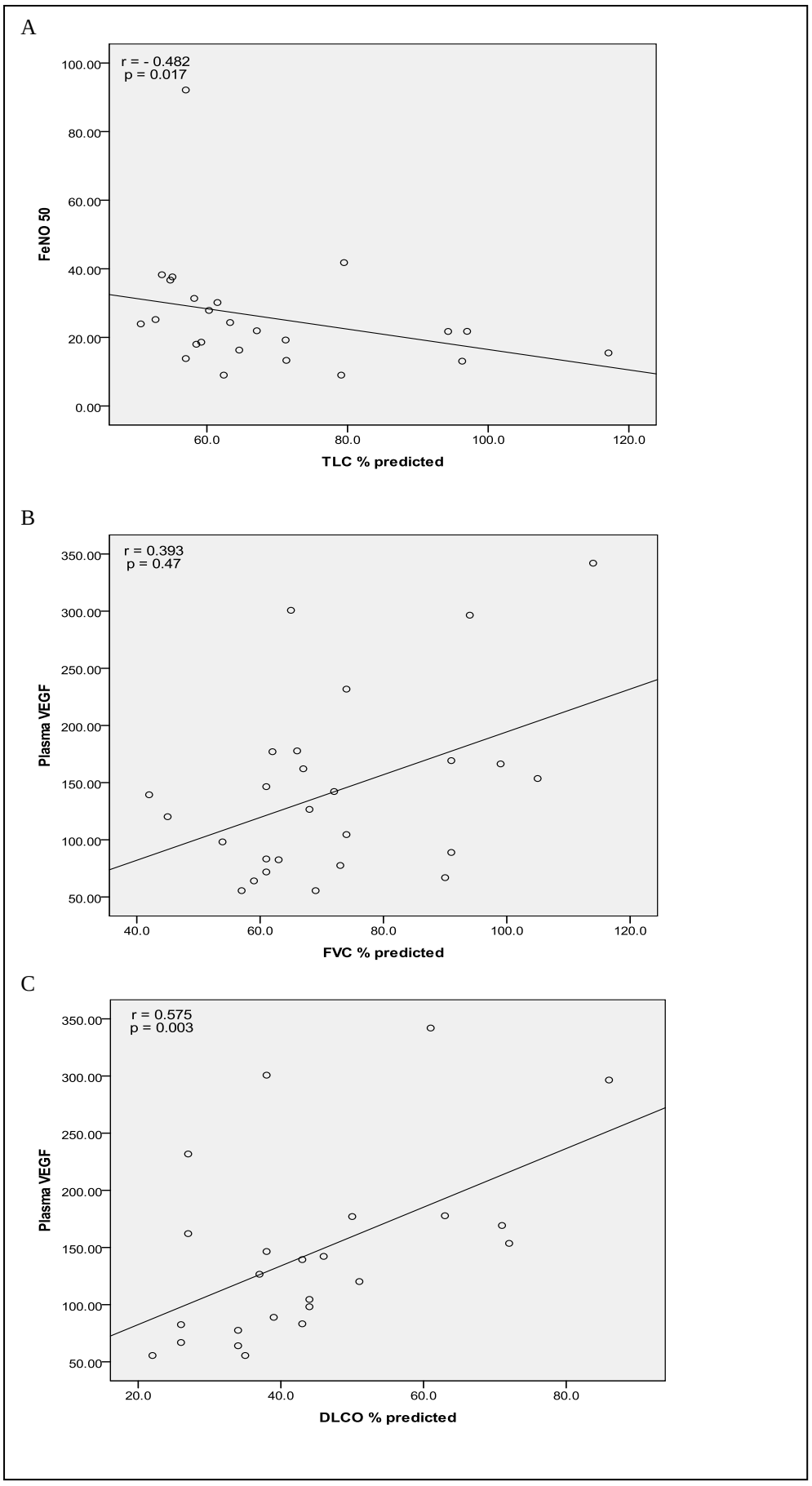

Figure 5.3 Relationship between (A) exhaled NO and TLC % predicted, (B) plasma VEGF and FVC % predicted and (C) plasma VEGF and DLCO % predicted at baseline

5.3.2 An association between alveolar NO and/or plasma VEGF and disease progression at 18 months

Disease status at 18 months after recruitment was established in 26 patients. One patient was lost to follow up, was confirmed to be alive but did not have lung function measurements after the baseline visit and is therefore not included in this analysis; in two more patients who did not have 18 months measurements (but were confirmed to be alive at that time point) the disease status was assessed on the grounds of their lung function results at a 6 months follow up visit using the same pre-defined lung function criteria. Overall two patients died and further sixteen experienced a decline in their FVC and/or DLCO during 18 months of follow up.

Baseline characteristics

Baseline characteristics of patients with progressive and stable idiopathic pulmonary fibrosis are shown in Table 5.4. Patients with progressive disease were younger, had a significantly lower baseline FVC percent predicted ($p = 0.008$), TLC percent predicted ($p = 0.025$) and DLCO percent predicted ($p = 0.005$). Only patients with progressive disease were prescribed with immunosuppression and oxygen.

	Progressive disease (n=18)	**Stable disease (n=8)**
Male, n	14	8
Age, years	71.8 ± 10.3	75.1 ± 7.3
Smoking history, n Never smoker Ex-smoker	 4 14	 3 5
Clubbing, n	5	2
Histopathological confirmation, n	4	0
Time from diagnosis, years	2.9 ± 1.9	2.7 ± 2.9
MRC dyspnoea grade, mean	2.9	3.0
FVC, % predicted	65.8 ± 14.2	85.5 + 19.9
TLC, % predicted	64.0 ± 13.7	82.0 ± 21.2
DLCO, % predicted	38.0 ± 12.1	57.9 +18.0
Immunosuppressive therapy, n Prednisolone Azathioprine	 6 2	 0 0
Use of oxygen, n	2	0

Table 5.4 Baseline characteristics of patients with progressive and stable idiopathic pulmonary fibrosis.

Exhaled nitric oxide and plasma VEGF

Comparison of exhaled nitric oxide results shows that there is no difference in any of nitric oxide parameters between patients with and without progressive disease but patients who progressed had a significantly lower VEGF levels compared to those who did not (Table 5.5, Figure 5.4).

	Disease progression (n=18)	**Stable disease (n=8)**	**p**
FeNO 50, ppb	22.72± 2.86	21.62± 3.60	0.82
CaNO, ppb	3.83± 0.64	3.53 ± 0.68	0.77
JawNO, nl/sec	934.77± 141.87	800.95± 248.81	0.62
Plasma VEGF, pg/ml	105.54± 11.21	159.68 ± 29.87	0.05

Table 5.5 Comparison of FeNO50, CaNO, JawNO and VEGF results between patients with stable and progressive IPF. All data presented as mean and SD. FeNO: fraction of end tidal nitric oxide, CaNO: alveolar concentration of nitric oxide, JawNO: nitric oxide flux from the airway wall, VEGF: vascular endothelial growth factor.

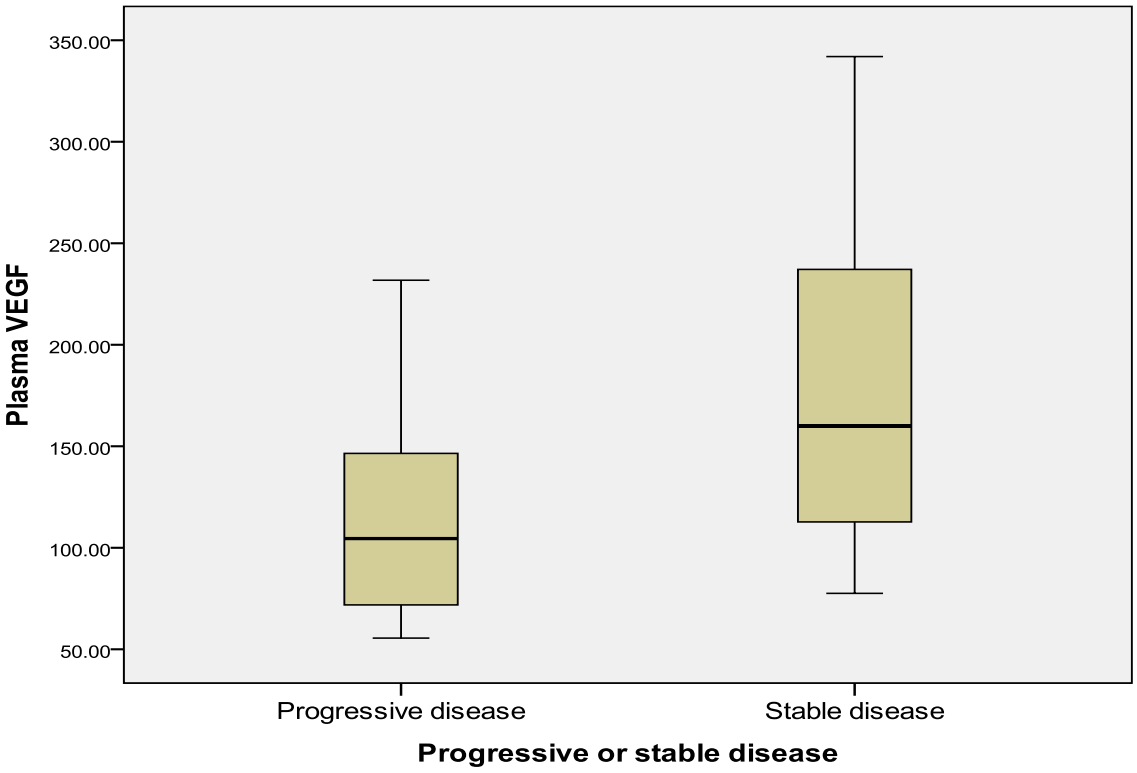

Figure 5.4 Comparison of plasma VEGF results between patients with progressive and stable IPF

Prediction power of exhaled nitric oxide and VEGF

Multiple linear regression model used to predict a risk of 10% decline in FVC or 15% decline in DLCO or a combined event (either or both of the above or death at 18 months) was set to include the following baseline parameters: MRC dyspnoea score, SaO2, FVC percent predicted, TLC percent predicted, DLCO percent predicted, FeNO, CaNO, JawNO, plasma VEGF.

The risk of 10% decline in absolute FVC at 18 months after recruitment was significantly and independently related to MRC dyspnoea score (regression coefficient = 9.11; 95% confidence interval = 2.94, 15.29; p = 0.007), DLCO percent predicted (regression coefficient = 0.91; 95% confidence interval = 0.54, 1.27; p = < 0.001), JawNO (regression coefficient = -0.02; 95% confidence interval = -0.02, -0.006; p = 0.004), and plasma concentration of VEGF (regression coefficient = -0.01; 95% confidence interval = -0.17, -0.03; p = 0.01). The R and R square values for this model were 0.83 and 0.69 respectively; the resulting model significance value was 0.002. Using the model output the resulting FVC at 18 months could be calculated using the following formula:

FVC = -47.42 + (9.11xMRC) + (0.91xDLCO%predicted) – (0.02xJawNO) – (-0.1xVEGF)

The same model set at predicting a 15% absolute decline in DLCO at 18 months after recruitment showed that MRC dyspnoea score (regression coefficient = 6.34; 95% confidence interval = 0.19, 12.5; p = 0.044) and alveolar concentration of nitric oxide (CaNO) (regression coefficient = 3.46; 95% confidence interval = 1.40, 5.51; p = 0.003) were significantly predictive of this outcome. The R and R square values for this model were 0.82 and 0.68 respectively; the resulting model significance value was < 0.001. Using the model output the resulting DLCO at 18 months could be calculated using the following formula:

DLCO = -40.49 + (0.19xMRC) + (03.CaNO)

Only baseline DLCO percent predicted (regression coefficient = 0.02; 95% confidence interval = 0.005, 0.03; p = 0.006) remained in the model predicting an occurrence of a combined events of death or 10% decline in FVC and/or 15% decline in DLCO at 18 months. The R and R square values for this model were 0.58 and 0.33 respectively; the resulting model significance value was < 0.006.

5.4 Discussion

This prospective study looking at the role of exhaled nitric oxide parameters and plasma vascular endothelial growth factor in patients with idiopathic pulmonary fibrosis showed that alveolar nitric oxide concentration which is a marker of alveolar inflammation has a strong predictive value for subsequent clinically significant decline in DLCO and that plasma VEGF level is significantly lower in patients with progressive disease, that it correlates positively with FVC and DLCO, and that it is a strong predictive factor of a clinically significant FVC decline over time.

A number of studies assessed the role of eNO in patients with interstitial lung disease (ILD) and found that its measurement might be useful in patients with systemic sclerosis both with and without ILD as well as in eosinophilic pneumonia and less useful in both active and inactive sarcoidosis. Moodley et al[269], demonstrated that alveolar NO was elevated in patients with scleroderma without ILD compared to those with ILD suggesting presence of subclinical inflammation (confirmed by higher neutrophil and eosinophil count in broncho-alveolar lavage fluid in scleroderma patients compared to healthy controls) before the clinical and radiological evidence of it becomes apparent. Girgis et al[270] demonstrated increased concentrations of alveolar NO in scleroderma patients with ILD with and without concomitant pulmonary hypertension. It had also been shown that in patients with scleroderma the levels of alveolar NO accurately identify patients with a high risk of developing lung function deterioration[273], are related to the extent of ILD as evidenced by the CT scan fibrosis score and are inversely related to the severity of ILD as evidenced by diffusing capacity for carbon monoxide[271, 283].

A recent study of patients with eosinophilic pneumonia (EP) showed that CaNO levels in these patients were significantly higher than in patients with IPF and healthy controls, this was associated with a higher number of iNOS positive cells in BAL fluid (suggesting that more ntirosative stress occurs in EP compared to IPF), that CaNO levels had a significant correlations with VC, VC % predicted and peripheral blood eosinophilia (prior to treatment with corticosteroids) and that CaNO level along with FeNO level was reduced by treatment with corticosteroids[275]. Alveolar NO has also been suggested for use as a noninvasive marker for assessment of severity of inflammation in asbestosis[274].

In a study of 42 patients with sarcoidosis no difference was found in FeNO, CaNO and JawNO compared to healthy controls; also there was no difference in these measures between patients with active and inactive sarcoidosis though there was a significant negative correlation between CaNO and FVC % predicted and DLCO % predicted[276].

The data on role of eNO in diagnosis and management of IPF is limited and does not allow drawing any firm conclusions. A study by Paredi et al[277] assessed total exhaled NO in 11 patients with fibrosing alveolitis in relation to the disease activity based on the cellular content of broncho-alveolar lavage fluid and the effect of treatment with oral corticosteroids on its levels. It showed that all patients (irrespective of disease activity) had elevated total exhaled NO levels (11.2 ppb) compared to 13 nonsmoking healthy subjects (6.9 ± 0.5 ppb, $p<0.05$) and this correlated well with disease activity (as indicated by any of the following cell count in BAL fluid: lymphocytes >14%, neutrophils >4%, eosinophils >3%); patients treated with corticosteroids had lower levels of NO than untreated patients (9.0 ± 1.0 ppb and 13.1 ± 1.0 ppb respectively, $p<0.05$). Lehtimaki et al's study[258] of patients with alveolitis suggested that there was an increased alveolar concentration of NO in these patients compared to healthy controls (4.1 ± 0.3 ppb and 1.1 ± 0.1 ppb respectively) and that bronchial NO flux was equal in both alveolitis and healthy control groups suggesting inflammatory process on alveolar rather than conducting airways level. Alveolar NO concentration correlated negatively with DLCO percentage of predicted. It has to be kept in mind that patients enrolled in the first study were relatively young (mean age 58 ± 12 years), had milder disease (DLCO 61 ± 7% predicted) and were diagnosed prior to reconsideration of IPF diagnostic criteria[5] with only 3 of 11 patients having undergone lung biopsy therefore they might have represented a more heterogeneous disease group. Also only total eNO was measured therefore it is not possible to comment on the level of inflammation in details. In the second study alveolitis group included patients with both IPF and hypersensitivity pneumonitis with no separate analysis made for each of conditions. A study of Furukawa et al assessing the role of eNO in diagnosis and management of eosinophilic pneumonia enrolled 13 patients with mild/moderate IPF (mean DLCO 66.7%) as a control group and showed that there was no significant difference between FeNO and CaNO levels between patients with IPF and healthy controls and that JawNO levels were not different between all three groups[275]. Two other studies

are presented in an abstract form; one compared CaNO and JawNO levels between 12 patients with IPF (all with clinical-radiological diagnosis), sarcoidosis and healthy controls and found that patients with IPF had a higher level of CaNO compared to two other groups and that JawNO was not different between all three groups[284]. Another study comparing combined pulmonary fibrosis and emphysema with emphysema alone recruited 14 patients with IPF as a control group but the details of the IPF patients and their NO characteristics are not available[285].

This study is the first one assessing a discriminating role of exhaled nitric oxide in disease severity and disease progression in patients with IPF. CaNO was able to strongly (R square 0.69) predict a clinically significant decline in DLCO over subsequent 18 months which is a marker of disease progression and poor outcome. Elevated levels of alveolar NO in IPF reflect presence of an inflammatory component in addition to an epithelial injury which is considered to be the main pathogenic pathway in IPF[286]. The presence of inflammation in IPF has been previously confirmed by an expression of inducible NOS in alveolar epithelium the intensity of which is related to histologic abnormalities found in biopsy specimens of the lung of patients with IPF and is more pronounced in patients with signs of active inflammation rather than with honeycombing[229].

A significant difference in FeNO and JawNO between patients with severe and non-severe IPF is unexpected and the reason for it is not clear. Raised levels of FeNO and JawNO would reflect an inflammation at the level of airways which would not be affected in IPF alone. While similar number of patients were formally diagnosed with emphysema in both groups it is possible that a higher number of patients had undiagnosed emphysema or asthma in non-severe group that would explain a difference in markers of bronchial inflammation.

There is conflicting data on the role of VEGF in pulmonary fibrosis. Most of these data come from animal models and in humans VEGF levels have been studied predominantly in BAL fluid. Data from murine model suggests that high levels of VEGF can aggravate pulmonary fibrosis but alleviate pulmonary hypertension[140]. In contrary recent work by Stockman et al showed that that deletion of VEGF in myeloid cells (which include macrophages) resulted in significantly reduced formation of blood vessels which was associated with aggravated fibrotic tissue damage with decrease in epithelial cell survival and an increase in myofibroblast

invasion; the authors concluded that the process of angiogenesis driven by myeloid cell-derived VEGF was essential for prevention of fibrosis[280].There is a suggestion that VEGF expression within fibroblastic foci may be reduced[146]. While BALF VEGF levels were reported to be depressed in IPF patients in three studies[287-289] and not to be significantly different compared to healthy controls or to correlate with baseline lung function in another study[290], the levels were significantly higher in those patients who subsequently showed progressive disease or died than in those who did not suggesting that the elevated levels were of clinical significance[290]. Serum[288, 289] as well as plasma[149] levels in patients with IPF were also reported as not being different from those in healthy volunteers. Longitudinal changes in VEGF and HRCT score were also found to be positively related[149].

This study showed that baseline plasma VEGF levels were lower in patients with severe disease (though not reaching statistical significance) compared to those with milder disease and significantly lower ($p = 0.05$) in patients with subsequent disease progression as opposed to those with stable disease. This is in contrast to previous findings of Simler et al showing that patients with subsequent disease progression had higher levels of baseline VEGF compared to non-progressors. Possible explanation for this difference may be that whilst baseline disease severity was similar in both study groups (mean DLCO percent predicted 40.8 in Simler et al study versus 43.6 in our study) our patients were older (mean age 73.1 years versus 60.4 years), had shorter disease duration (2.8 years versus 4.3 years) and a smaller percent of them were on treatment for IPF including immunosuppression (30 versus 44%). The effect of age, disease duration and treatment on VEGF levels in IPF is not known (although there is a clinical observation suggesting that treatment with co-trimoxazole may reduce the levels of VEGF compared to patients not treated with co-trimoxazole[188]). It is possible that patients had different clinical phenotypes and that patients in Simler cohort had a more slow progression (considering longer disease duration) possibly with a smaller number of exacerbations.

To understand the reasons for reduction in plasma VEGF level in patients with progressive disease compared to stable patients it would be helpful to know the BAL fluid and alveolar lining VEGF level. There is an evidence of a significant gradient in alveolar VEGF concentration from epithelial broncho-alveolar surface fluid to serum and of BALF VEGF levels declining

significantly with age in healthy volunteers[288]. A phenomenon of a difference between BALF VEGF concentration (being low) and serum/plasma VEGF concentration (being high) as well as a correlation between BAL fluid VEGF concentration and DLCO have been demonstrated in the past[149, 288]. Low BALF VEGF levels could reflect damage to or apoptosis of alveolar epithelium with absent angiogenesis in the affected areas while higher plasma VEGF levels could reflect a compensatory angiogenesis in alternative areas of the lung[291]. Heterogeneity in vascular remodelling in IPF has been demonstrated with high vascular density in areas of low grade fibrosis and low vascular density in the most extensively fibrotic lesions[145]. An increased expression of VEGF in capillary endothelial cells and alveolar type II epithelial cells in highly vascularised alveolar septa in contrast to low expression of VEGF in fibroblasts and leucocytes of fibrotic lesions has also been reported[145]. In this respect it is not possible to compare radiological or histopathologic severity of the disease in terms of the extent of honeycombing and fibroblastic foci between our patients and patients recruited into Simler et al study. While it is still not clear if angiogenesis provokes fibrogenesis or is a necessary mechanism to prevent excessive fibrosis demonstration of lower VEGF levels in patients with subsequent disease progression is in support of the recent findings by Stockmann et al of a drastic increase in miofibroblast invasion associated with raised levels of hypoxia-inducible factor expression in a context of reduced VEGF expression due to myeloid cell VEGF deletion in a model of fibrosis in bleomycin treated mice[280].

A significant positive correlation between baseline levels of VEGF and baseline DLCO and FVC as well as a protective effect of higher baseline plasma VEGF levels on subsequent 18 months disease progression was observed in this study. This was contrary to the observation of Ando et al who demonstrated that higher VEGF levels were highly predictive of disease severity defined as a high alveolar-arterial difference of oxygen value and that lower baseline VEGF level correlated with smaller monthly change in percent predicted vital capacity in their study of 41 patients with IPF [289].

Of note DLCO percent predicted at baseline confirms the well accepted fact of its prognostic significance[14] by predicting both FVC decline and a combined event of FVC decline and death over subsequent 18 month follow up.

This study has a number of limitations. Firstly it did not include healthy controls. It is possible to correlate our CaNO results with those shown in healthy controls in other studies of exhaled NO in asthma, COPD and other ILD the majority of which showed mean CaNO in a range of 1.1 – 3.4 ppb but ideally controls should be matched for age as recent data shows that FeNO50 and CaNO increase significantly with age greater than 60 years which could be a result of a decrease in the capillary blood volume with reduced NO diffusion[292]. Secondly a small group of patients was on immunosuppression treatment the effect of which on CaNO in IPF and VEGF levels is not known. Thirdly HRCT data on extent and severity of fibrosis as well as longitudinal CT data would be helpful to follow up the value of baseline results of CaNO and VEGF. On the other hand CaNO and VEGF are both non-invasive markers of disease activity the use of which is not associated with an additional dose of radiation.

In conclusion CaNO and VEGF, both non-invasive markers, might complement the information obtained from three other clinically relevant investigations including HRCT, FVC and DLCO measurement. The usefulness of CaNO assessment as shown in this study is that a single measurement at baseline may predict further disease behaviour. The role of plasma VEGF in the assessment of baseline severity and subsequent behaviour of IPF requires further evaluation as the results of this study are not in line with published data.

Chapter 6
Study 4
Prognostic modelling in IPF

6.1 Introduction

Although overall prognosis of IPF is poor there is a significant variability in functional change over time ranging from improvement or minimal change in PFT over years to a significant decline leading to death over 6-12 months often preceded by an exacerbation/admission[215, 293]. A large number of individual clinical parameters are associated with poor survival in IPF including demographic, clinical, physiologic, radiologic and pathologic markers. A range of investigators have looked at combining a few parameters into clinical prediction models. Clinical prediction models are statistical models that combine clinical findings from history, physical examination, and/or test results to estimate the probability of an outcome, usually a diagnosis or prognosis[196]. The success of the model depends on the careful selection of predictor variables that are reproducibly and commonly measured in current clinical practice, and on performance of external validation and clinical impact analysis[196].

Using the identified independent determinants of survival King et al[61] developed a mathematical clinical-radiologic-physiologic (CRP) scoring system for prediction of survival time in patients with IPF. It included the following parameters: age, smoking history, clubbing, extent of profusion of interstitial opacities and presence or absence of pulmonary hypertension on the chest radiograph, % predicted TLC and pO2 at the end of maximal exercise. The CRP scoring system was used in 238 patients with new diagnosis of IPF. It was demonstrated that the CRP score correlated with the extent and severity of the important histopathologic features of IPF (fibrosis, cellularity, granulation/connective tissue, and the total pathologic derangement). The degree of dyspnoea, presence of finger clubbing, the extent of profusion and honeycombing, evidence of pulmonary hypertension on chest radiograph, the severity of impairment of lung volumes, spirometry, lung mechanics, DLCO and gas exchange while at rest and on exercise at baseline were all significant predictors of survival ($p<0.05$) as demonstrated by the study of King et al. [61]. As a result a CRP model was derived that could be used in estimation of the survival time in a patient with IPF

As mentioned previously in IPF co-existing emphysema can contribute to the PFT abnormality and this should be taken into account when quantifying the disease severity as using PFT alone might be misleading. Therefore Wells et al. constructed a composite physiologic index (CPI) against the morphologic severity of disease in order to calibrate the quantification of pulmonary fibrosis using PFT in isolation [294]. The CPI was derived in 106 patients with IPF and was tested on a further 106 patients. The following formula was used: extent of disease on CT = 91.0 – (0.65 x percent predicted DLCO) - (0.53 x percent predicted FVC) + (0.34 x percent predicted FEV1). The study demonstrated that 1) CPI correlates with the extent of pulmonary fibrosis on CT more strongly (r = 0.71) and is linked to mortality more closely than individual pulmonary function indices; 2) the CPI accounts for existing emphysema; 3) in patients without emphysema on CT the CPI reflected the extent of fibrosis no better than DLCO levels [294].

Du Bois et al in a study of 1,099 patients with definite HRCT or biopsy confirmed diagnosis of IPF used Cox proportional hazards model to derive an abbreviated clinical model comprising only 4 readily available predictors of mortality: age ≥ 70 years vs <60, HR 2.21 (95% CI 1.35-3.62), respiratory hospitalisations, HR 4.11 (95% CI 2.57-6.58), % predicted FVC ≤ 50 vs ≥ 80, HR 5.79 (95% CI 2.55-13.15), and 24 week change in % predicted FVC ≤ -10 vs > 5, HR 7.99 (95% CI 5.26-12.14). As a result they developed a practical mortality scoring system (Table 6.1)[295] which if validated would be useful in clinical practice for patients with the disease of any severity.

(1) Sum individual scores corresponding to level of each risk factor for a given patient*		(2) Find expected 1-year probability of death corresponding to total risk score	
Risk Factors	Score	Total Risk Score	Expected 1-Year Risk of Death
Age			
≥70	8		
60-69	4	0–4	<2%
<60	0	8–14	2–5%
History of respiratory hospitalization		16–21	5–10%
Yes	14	22–29	10–20%
No	0	30–33	20–30%
% Predicted FVC		34–37	30–40%
≤50	18	38–40	40–50%
51-65	13	41–43	50–60%
66–79	8	44–45	60–70%
≥80	0	47–49	70–80%
24-Week change in % predicted FVC		>50	>80%
≤ −10	21		
−5 to −9.9	10		
> −4.9	0		

Table 6.1 Mortality risk scoring system for patients with IPF[295].

Mathematical clinical-radiologic-physiologic (CRP) scoring system developed by King et al could be used for prediction of survival while composite physiologic index developed by Wells et al could be used for the assessment of the extent of the disease in IPF patient with coexisting emphysema. However these two models are confined to research only as they are largely based on the inclusion of factors that are not widely accessible in the clinical practice[295]. At present there is a lack of literature on models that include readily available simple clinical factors and there is no data available on whether patient education, income and living arrangements are important predictors of prognosis and should be included in outcome prediction models.

The purpose of the study was to identify independent predictors of both mortality at 12 months and 5% and 10% decline in FVC over 6 and 12 months the latter being a marker of poor prognosis in patients with IPF. It was also aimed at assessing if patients' social background and status affect the course of the disease.

6.2 Methods

Patients

The source population included patients who participated in the interventional study 2 (co-trimoxazole in IIP). Considering absence of effect of co-trimoxazole on lung function and survival in intention to treat population data of patients from both active and placebo groups were used (similar to patients choice in a study which developed simplified mortality risk scoring system for IPF patients[295]). Patients who died between the date of recruitment and final visit at 12 months were included.

Parameters include into a model of predictors of outcome

The following baseline characteristics were incorporated in a model:

age

gender

emphysema at recruitment

time from diagnosis to recruitment

surgical lung biopsy (includes open lung biopsy, VATs vs no biopsy

MRC dyspnoea grade

FVC, percent predicted

DLCO, percent predicted

clubbing

treatment with prednisolone

treatment with azathioprine
treatment with oxygen (any - ambulatory, long term)
SGRQ total score and domains score
education, living arrangements (lives alone or not), employment (working or not), weekly income, benefits, private insurance (available or not); data obtained from background questionnaire

The outcomes used in these models are defined as:

1. Death within 12 months of the study start date;
2. Absolute FVC decline of 5% by 6 months and by 12 months
3. Absolute FVC decline of 10% by 6 months and by 12 months

Statistical analysis

Logistic regression analysis was used to identify independent predictors of all-cause mortality as well as of 5% and 10% decline in FVC at 6 and 12 months. Unadjusted risk of all-cause mortality was estimated for patients stratified by each potential predictor separately. Continuous covariates were split into quartiles. Adjusted analysis was performed by using a forward–backward algorithm (forward selection with probability of entry of p=0.10 and then a back elimination with probability threshold of p=0.10 were used). The missing data were not imputed. An estimability problem with SGRQ scores and lung function results due to missing data was affecting the use of forward-backward algorithm in modelling predictors of FVC decline. Hence, the selection without SGRQ/PFT variables present was undertaken first, then it was checked if they significantly improved the model.

6.3 Results

Baseline characteristics

All patients (181) included into intention to treat analysis of co-trimoxazole study (study 2, Chapter 4) were included in a model of baseline predictors of death. Patients had a mean age of 71.6 ± 8.5 years, 72% were male, mean FVC% predicted was 70.7 ± 21.2% and DLCO% predicted was 37.5 ± 11.5% (Table 4.4 in Chapter 4).

Of these 138 and 113 patients had FVC measurements available at 6 and 12 months after recruitment respectively and therefore were included in models of predictors of decline of FVC.

Predictors of mortality

Thirty-seven (20%) patients had died by the end of the study. The univariate analysis showed that the following characteristics were predictive of death: age (p=0.0064), MRC dyspnoea score (p=0.0082), prednisolone (p=0.049), SGRQ symptoms score (p=0.0376), SGRQ activity score (p=0.0093), SGRQ impact score (p=0.0009), SGRQ total score (p=0.0006), DLco percent predicted (0.0332). In the multivariate analysis SGRQ total score and treatment with prednisolone were statistically significant predictors of all-cause mortality at 12 months (Table 6.2).

					Univariate analysis		Adjusted analysis	
Covariate	Level	Alive	Dead	Dead %	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, years						0.0064		
	46-65	45	4	8.2	1			
	66-72	35	14	28.6	4.5 (1.36,14.88)	0.014		
	73-78	38	6	13.6	1.78 (0.47,6.76)	0.4		
	79-96	26	13	33.3	5.63 (1.66,19.06)	0.006		
Gender								
	Female	41	9	18	1			
	Male	103	28	21.4	1.24 (0.54,2.85)	0.615		
Emphysema								
	No	131	35	21.1	1			
	Yes	13	2	13.3	0.58 (0.12,2.67)	0.481		
Time since diagnosis, days						0.2845		
	34-363	34	12	26.1	1			
	372-847	40	5	11.1	0.35 (0.11,1.11)	0.074		
	848-1624	35	10	22.2	0.81 (0.31,2.12)	0.667		
	1674-9721	35	10	22.2	0.81 (0.31,2.12)	0.667		
Surgical biopsy								
	No	121	31	20.4	1			
	Yes	23	6	20.7	1.02 (0.38,2.72)	0.971		
MRC						0.0082		
	2	27	2	6.9	1			
	3	59	11	15.7	2.52 (0.52,12.15)	0.25		
	4	47	15	24.2	4.31 (0.91,20.29)	0.065		
	5	11	9	45	11.05 (2.05,59.56)	0.005		
Finger clubbing								
	No	93	20	17.7	1			
	Yes	51	17	25	1.55 (0.75,3.22)	0.24		
FVC group						0.0770		
	<50%	19	11	36.7	1			
	51%-65%	37	9	19.6	0.42 (0.15,1.19)	0.102		
	>65%-79%	38	10	20.8	0.45 (0.16,1.26)	0.129		
	>79%	50	7	12.3	0.24 (0.08,0.72)	0.01		

Table 6.2: Predictions model for death

DLCO group						0.0332		
	<35%	46	16	25.8	1			
	>35%-45%	46	4	8	0.25 (0.08,0.81)	0.020		
	>45%	32	5	13.5	0.45 (0.15,1.35)	0.154		
Prednisolone								
	No	65	10	13.3	1		1	
	Yes	79	27	25.5	2.22 (1,4.93)	0.049	3.56 (1.34,9.48)	0.011
Azathioprine								
	No	100	23	18.7	1			
	Yes	40	14	25.9	1.52 (0.71,3.25)	0.278		
Oxygen (any)								
	No	128	31	19.5	1			
	Yes	16	6	27.3	1.55 (0.56,4.28)	0.399		
SGRQ symptoms						0.0376		
	8.56-44.89	41	3	6.8	1			
	46.05-60.44	32	11	25.6	4.7 (1.21,18.26)	0.026		
	60.45-72.57	36	8	18.2	3.04 (0.75,12.32)	0.12		
	72.89-90.09	31	12	27.9	5.29 (1.37,20.37)	0.015		
SGRQ activity						0.0093		
	21.96-60.35	39	5	11.4	1			
	60.47-79.67	38	5	11.6	1.03 (0.27,3.83)	0.969		
	79.91-92.51	53	17	24.3	2.5 (0.85,7.36)	0.096		
	92.76-100	9	8	47.1	6.93 (1.83,26.26)	0.004		
SGRQ impact						0.0009		
	0-30.02	39	3	7.1	1			
	30.13-43.70	39	3	7.1	1 (0.19,5.26)	1		
	44.36-61.11	29	13	31	5.83 (1.52,22.35)	0.01		
	61.23-100	29	13	31	5.83 (1.52,22.35)	0.01		
SGRQ total						0.0006		0.0014
	15.5-44.11	38	4	9.5	1			
	44.33-58.28	39	2	4.9	0.49 (0.08,2.82)	0.422	0.45 (0.08,2.64)	0.377
	58.41-70.45	32	10	23.8	2.97 (0.85,10.38)	0.088	2.78 (0.78,9.91)	0.115
	70.85-96.39	26	15	36.6	5.48 (1.63,18.39)	0.006	6.48 (1.86,22.66)	0.003

Table 6.2: Predictions model for death

Education						0.910		
	None/school certificate	84	18	17.6	1			
	A-Levels. CSEs, GCSE	17	5	22.7	1.37 (0.45,4.2)	0.579		
	HND/Btech \NVQ	16	3	15.8	0.88 (0.23,3.32)	0.844		
	Degree/PhD	22	6	21.4	1.27 (0.45,3.59)	0.648		
Living alone								
	No	141	35	19.9	1			
	Yes	3	1	25	1.34 (0.14,13.3)	0.801		
Paid employment								
	No	131	32	19.6	1			
	Yes	10	2	16.7	0.82 (0.17,3.92)	0.802		
Monthly household income						0.842		
	<199	27	6	18.2	1			
	200-299	21	5	19.2	1.07 (0.29,4)	0.918		
	300-399	22	4	15.4	0.82 (0.2,3.27)	0.776		
	400-499	19	5	20.8	1.18 (0.32,4.45)	0.802		
	500+	21	8	27.6	1.71 (0.52,5.7)	0.38		
State pension								
	No	98	27	21.6	1			
	Yes	46	9	16.4	0.71 (0.31,1.63)	0.420		
Disability benefit								
	No	86	23	21.1	1			
	Yes	58	13	18.3	0.84 (0.39,1.79)	0.648		
Other benefit								
	No	107	29	21.3	1			
	Yes	37	7	15.9	0.7 (0.28,1.73)	0.437		
Private health insurance								
	No	131	30	18.6	1			
	Yes	10	3	23.1	1.31 (0.34,5.05)	0.695		

Table 6.2: Predictions model for death

Predictors of FVC decline at 6 months

There were no statistically significant (at p=0.05 level) predictors of 5% decline at 6 months identified. However, there was mild evidence of an effect of emphysema (p=0.063) (Table 6.3).

					Univariate		Adjusted	
Covariate	Level	Did not decline	5% FVC decline over 6 months	% of patients with decline	OR (95% CI)	p-value	OR (95% CI)	p-value
Age						0.6609		
	46-65	21	20	48.8	1			
	66-72	18	21	53.8	1.23 (0.51,2.95)	0.651		
	73-78	21	14	40	0.7 (0.28,1.74)	0.444		
	79-96	13	10	43.5	0.81 (0.29,2.26)	0.684		
Gender								
	Female	20	18	47.4	1			
	Male	53	47	47	0.99 (0.47,2.08)	0.969		
Emphysema								
	No	64	63	49.6	1			
	Yes	9	2	18.2	0.23 (0.05,1.09)	0.063		
Time since diagnosis						0.4915		
	34-363	16	17	51.5	1			
	372-847	23	13	36.1	0.53 (0.2,1.39)	0.199		
	848-1624	18	18	50	0.94 (0.37,2.42)	0.9		
	1674-9721	16	17	51.5	1 (0.38,2.63)	1		
Surgical biopsy								
	No	59	54	47.8	1			
	Yes	14	11	44	0.86 (0.36,2.05)	0.731		
MRC						0.7883		
	2	15	10	40	1			
	3	27	29	51.8	1.61 (0.62,4.19)	0.328		
	4	25	21	45.7	1.26 (0.47,3.39)	0.647		
	5	6	5	45.5	1.25 (0.3,5.23)	0.76		
Finger clubbing								
	No	44	39	47	1			
	Yes	29	26	47.3	1.01 (0.51,2)	0.974		
FVC group						0.6799		
	<50%	10	8	44.4	1			
	51%-65%	18	22	55	1.53 (0.5,4.68)	0.458		
	>65%-79%	19	16	45.7	1.05 (0.34,3.3)	0.93		
	>79%	26	19	42.2	0.91 (0.3,2.75)	0.872		
DLCO group						0.5478		
	<35%	22	26	54.2	1			
	>35%-45%	23	17	42.5	0.63 (0.27,1.46)	0.277		
	>45%	16	16	50	0.85 (0.35,2.07)	0.715		
Prednisolone								
	No	35	24	40.7	1			
	Yes	38	41	51.9	1.57 (0.8,3.11)	0.192		
Azathioprine								
	No	49	48	49.5	1			
	Yes	22	15	40.5	0.7 (0.32,1.5)	0.355		
Oxygen (any)								
	No	68	54	44.3	1			
	Yes	5	11	68.8	2.77 (0.91,8.46)	0.073		
SGRQ symptoms						0.5608		
	8.56-44.89	20	14	41.2	1			

Table 6.3: FVC decline by 5% over 6 months

	46.05-60.44	15	18	54.5	1.71 (0.65,4.51)	0.275		
	60.45-72.57	22	16	42.1	1.04 (0.41,2.66)	0.936		
	72.89-90.09	15	17	53.1	1.62 (0.61,4.29)	0.332		
SGRQ activity						0.2752		
	21.96-60.35	18	18	50	1			
	60.47-79.67	20	13	39.4	0.65 (0.25,1.69)	0.377		
	79.91-92.51	30	26	46.4	0.87 (0.37,2)	0.738		
	92.76-100	3	8	72.7	2.67 (0.61,11.7)	0.194		
SGRQ impact						0.6418		
	0-30.02	18	14	43.8	1			
	30.13-43.70	18	19	51.4	1.36 (0.52,3.51)	0.529		
	44.36-61.11	19	13	40.6	0.88 (0.33,2.37)	0.8		
	61.23-100	14	17	54.8	1.56 (0.58,4.22)	0.38		
SGRQ total						0.4321		
	15.5-44.11	15	18	54.5	1			
	44.33-58.28	22	15	40.5	0.57 (0.22,1.47)	0.243		
	58.41-70.45	19	14	42.4	0.61 (0.23,1.62)	0.326		
	70.85-96.39	12	16	57.1	1.11 (0.4,3.07)	0.839		
Education								
	None/school certificate	39	40	50.6	1			
	A-Levels. CSEs, GCSE	13	6	31.6	0.45 (0.16,1.3)	0.141		
	HND/Btech\NVQ	8	8	50	0.98 (0.33,2.86)	0.963		
	Degree/PhD	10	11	52.4	1.07 (0.41,2.81)	0.887		
Living alone								
	No	73	65	47.1				
	Yes	0	0	0				
Paid employment								
	No	68	60	46.9	1			
	Yes	5	5	50	1.13 (0.31,4.11)	0.849		
Monthly household income						0.2140		
	<199	10	15	60	1			
	200-299	15	7	31.8	0.31 (0.09,1.04)	0.057		
	300-399	11	10	47.6	0.61 (0.19,1.96)	0.402		
	400-499	12	7	36.8	0.39 (0.11,1.33)	0.132		
	500+	10	14	58.3	0.93 (0.3,2.92)	0.906		
State pension								
	No	52	47	47.5	1			
	Yes	21	18	46.2	0.95 (0.45,1.99)	0.889		
Disability benefit								
	No	45	40	47.1	1			
	Yes	28	25	47.2	1 (0.51,2)	0.99		
Other benefit								
	No	52	51	49.5	1			
	Yes	21	14	40	0.68 (0.31,1.48)	0.331		
Private health insurance								
	No	68	59	46.5	1			
	Yes	5	6	54.5	1.38 (0.4,4.76)	0.607		

Table 6.3 FVC decline by 5% over 6 months

Treatment with prednisolone (p=0.006) and oxygen therapy (p=0.055), receipt of benefit other than state pension or disability living allowance (p=0.053) were predictors of 10% FVC decline at 6 months on univariate analysis. The final model selected only the use of prednisolone. None for the SGRQ domains were significant (Table 6.4).

					Univariate		Adjusted	
Covariate	Level	Did not decline	10% FVC decline over 6 months	% of patients with decline	OR (95% CI)	p-value	OR (95 % CI)	p-value
Age						0.0640		
	46-65	34	7	17.1	1			
	66-72	24	15	38.5	3.04 (1.07,8.57)	0.036		
	73-78	30	5	14.3	0.81 (0.23,2.82)	0.74		
	79-96	17	6	26.1	1.71 (0.5,5.9)	0.393		
Gender								
	Female	30	8	21.1	1			
	Male	75	25	25	1.25 (0.51,3.08)	0.628		
Emphysema								
	No	95	32	25.2	1			
	Yes	10	1	9.1	0.3 (0.04,2.41)	0.256		
Time since diagnosis						0.2758		
	34-363	25	8	24.2	1			
	372-847	31	5	13.9	0.5 (0.15,1.73)	0.277		
	848-1624	24	12	33.3	1.56 (0.54,4.49)	0.407		
	1674-9721	25	8	24.2	1 (0.32,3.08)	1		
Surgical biopsy								
	No	83	30	26.5	1			
	Yes	22	3	12	0.38 (0.11,1.35)	0.134		
MRC						0.6498		
	2	20	5	20	1			
	3	44	12	21.4	1.09 (0.34,3.51)	0.884		
	4	32	14	30.4	1.75 (0.55,5.6)	0.346		
	5	9	2	18.2	0.89 (0.14,5.48)	0.899		
Finger clubbing								
	No	67	16	19.3	1			

Table 6.4: FVC decline by 10% over 6 months

FVC group						0.9864		
	<50%	14	4	22.2	1			
	51%-65%	31	9	22.5	1.02 (0.27,3.87)	0.981		
	>65%-79%	26	9	25.7	1.21 (0.32,4.65)	0.78		
	>79%	34	11	24.4	1.13 (0.31,4.17)	0.852		
DLCO group						0.9552		
	<35%	36	12	25	1			
	>35%-45%	31	9	22.5	0.87 (0.32,2.34)	0.784		
	>45%	24	8	25	1 (0.36,2.81)	1		
	Yes	38	17	30.9	1.87 (0.85,4.13)	0.119		
Prednisolone								
	No	52	7	11.9	1			
	Yes	53	26	32.9	3.64 (1.46,9.13)	0.006		
Azathioprine								
	No	73	24	24.7	1			
	Yes	29	8	21.6	0.84 (0.34,2.08)	0.705		
Oxygen (any)								
	No	96	26	21.3	1			
	Yes	9	7	43.8	2.87 (0.98,8.44)	0.055		
SGRQ symptoms						0.5029		
	8.56-44.89	25	9	26.5	1			
	46.05-60.44	23	10	30.3	1.21 (0.42,3.5)	0.728		
	60.45-72.57	32	6	15.8	0.52 (0.16,1.66)	0.27		
	72.89-90.09	24	8	25	0.93 (0.31,2.8)	0.891		
SGRQ activity						0.3696		
	21.96-60.35	28	8	22.2	1			
	60.47-79.67	27	6	18.2	0.78 (0.24,2.54)	0.677		
	79.91-92.51	42	14	25	1.17 (0.43,3.14)	0.761		
	92.76-100	6	5	45.5	2.92 (0.7,12.11)	0.14		
SGRQ impact						0.3145		
	0-30.02	28	4	12.5	1			
	30.13-43.70	27	10	27	2.59 (0.72,9.27)	0.143		
	44.36-61.11	23	9	28.1	2.74 (0.75,10.06)	0.129		
	61.23-100	22	9	29	2.86 (0.78,10.54)	0.114		
SGRQ total						0.6428		
	15.5-44.11	26	7	21.2	1			
	44.33-58.28	30	7	18.9	0.87 (0.27,2.8)	0.811		

Table 6.4: FVC decline by 10% over 6 months

	58.41-70.45	23	10	30.3	1.61 (0.53,4.93)	0.4		
	70.85-96.39	20	8	28.6	1.49 (0.46,4.79)	0.507		
Education						0.1629		
	None/school certificate	57	22	27.8	1			
	A-Levels. CSEs, GCSE	17	2	10.5	0.3 (0.06,1.43)	0.132		
	HND/Btech\NVQ	14	2	12.5	0.37 (0.08,1.76)	0.212		
	Degree/PhD	14	7	33.3	1.3 (0.46,3.64)	0.623		
Paid employment								
	No	98	30	23.4	1			
	Yes	7	3	30	1.4 (0.34,5.75)	0.641		
Monthly household income								
	<199	17	8	32	1			
	200-299	18	4	18.2	0.47 (0.12,1.86)	0.283		
	300-399	16	5	23.8	0.66 (0.18,2.46)	0.54		
	400-499	14	5	26.3	0.76 (0.2,2.85)	0.683		
	500+	21	3	12.5	0.3 (0.07,1.32)	0.113		
State pension								
	No	77	22	22.2	1			
	Yes	28	11	28.2	1.38 (0.59,3.2)	0.459		
Disability benefit								
	No	66	19	22.4	1			
	Yes	39	14	26.4	1.25 (0.56,2.76)	0.587		
Other benefit								
	No	74	29	28.2	1			
	Yes	31	4	11.4	0.33 (0.11,1.02)	0.053		

Table 6.4: FVC decline by 10% over 6 months

Predictors of FVC decline at 12 months

Table 6.5 shows a univariate relationships between the covariates and a 5% decline in FVC at 12 months. SGRQ symptoms score was significant; there was a suggestion of a trend in SGRQ total score. There was some evidence for an effect with education (p=0.077) and paid employment (p=0.09).

					Univariate		Adjusted	
Covariate	Level	Did not decline	5% FVC decline over 12 months	% of patients with decline	OR (95% CI)	p-value	OR (95% CI)	p-value
Age						0.499		
	46-65	15	25	62.5	1			
	66-72	10	20	66.7	1.2 (0.44,3.24)	0.719		
	73-78	16	16	50	0.6 (0.23,1.54)	0.289		
	79-96	10	11	52.4	0.66 (0.23,1.92)	0.446		
Gender								
	Female	16	18	52.9	1			
	Male	35	54	60.7	1.37 (0.62,3.04)	0.437		
Emphysema								
	No	45	66	59.5	1			
	Yes	6	6	50	0.68 (0.21,2.25)	0.529		
Time since diagnosis						0.144		
	34-363	14	17	54.8	1			
	372-847	13	21	61.8	1.33 (0.49,3.58)	0.572		
	848-1624	7	20	74.1	2.35 (0.77,7.17)	0.132		
	1674-9721	17	14	45.2	0.68 (0.25,1.84)	0.447		
Surgical biopsy								
	No	44	59	57.3	1			
	Yes	7	13	65	1.38 (0.51,3.76)	0.523		
MRC						0.233		
	2	9	15	62.5	1			
	3	21	29	58	0.83 (0.31,2.25)	0.712		
	4	15	26	63.4	1.04 (0.37,2.95)	0.941		
	5	6	2	25	0.2 (0.03,1.21)	0.08		
Finger clubbing								
	No	36	46	56.1	1			
	Yes	15	26	63.4	1.36 (0.63,2.93)	0.438		
FVC group						0.123		
	<50%	7	9	56.3	1			
	51%-65%	7	23	76.7	2.56 (0.7,9.38)	0.157		
	>65%-79%	16	18	52.9	0.88 (0.26,2.89)	0.827		
	>79%	21	22	51.2	0.81 (0.26,2.59)	0.728		
DLCO group						0.710		
	<35%	15	25	62.5	1			
	>35%-45%	15	24	61.5	0.96 (0.39,2.38)	0.93		
	>45%	14	16	53.3	0.69 (0.26,1.79)	0.442		
Prednisolone								
	No	25	33	56.9	1			
	Yes	26	39	60	1.14 (0.55,2.33)	0.727		
Azathioprine								
	No	34	51	60	1			
	Yes	15	19	55.9	0.84 (0.38,1.89)	0.680		

Table 6.5: FVC decline by 5% over 12 months

Oxygen (any)								
	No	46	63	57.8	1			
	Yes	5	9	64.3	1.31 (0.41,4.18)	0.644		
SGRQ symptoms						0.013		0.017
	8.56-44.89	14	22	61.1	1			
	46.05-60.44	10	18	64.3	1.15 (0.41,3.19)	0.795	1.05 (0.36,3.03)	0.935
	60.45-72.57	20	12	37.5	0.38 (0.14,1.02)	0.054	0.32 (0.11,0.87)	0.026
	72.89-90.09	5	19	79.2	2.42 (0.73,7.96)	0.146	2.08 (0.62,6.93)	0.234
SGRQ activity						0.716		
	21.96-60.35	13	21	61.8	1			
	60.47-79.67	11	21	65.6	1.18 (0.43,3.23)	0.745		
	79.91-92.51	22	25	53.2	0.7 (0.29,1.73)	0.443		
	92.76-100	3	4	57.1	0.83 (0.16,4.29)	0.82		
SGRQ impact						0.591		
	0-30.02	10	22	68.8	1			
	30.13-43.70	15	19	55.9	0.58 (0.21,1.58)	0.283		
	44.36-61.11	12	16	57.1	0.61 (0.21,1.75)	0.353		
	61.23-100	11	12	52.2	0.5 (0.16,1.5)	0.215		
SGRQ total						0.626		
	15.5-44.11	11	22	66.7	1			
	44.33-58.28	13	21	61.8	0.81 (0.3,2.2)	0.676		
	58.41-70.45	13	16	55.2	0.62 (0.22,1.72)	0.355		
	70.85-96.39	10	10	50	0.5 (0.16,1.56)	0.232		
Education						0.077		
	None/school certificate	25	47	65.3	1			
	A-Levels. CSEs, GCSE	7	7	50	0.53 (0.17,1.69)	0.284		
	HND/Btech\ NVQ	5	10	66.7	1.06 (0.33,3.46)	0.918		
	Degree/PhD	12	6	33.3	0.27 (0.09,0.79)	0.018		
Live alone								
	No	50	71	58.7	1			
	Yes	1	1	50	0.7 (0.04,11.53)	0.806		
Paid work								
	No	49	63	56.3	1		1	
	Yes	1	8	88.9	6.22 (0.75,51.43)	0.090	7.62 (0.84,68.74)	0.07
Monthly household income						0.899		
	<199	10	12	54.5	1			
	200-299	8	12	60	1.25 (0.37,4.26)	0.721		
	300-399	7	11	61.1	1.31 (0.37,4.64)	0.676		
	400-499	7	6	46.2	0.71 (0.18,2.83)	0.632		
	500+	8	13	61.9	1.35 (0.4,4.57)	0.625		

Table 6.5: FVC decline by 5% over 12 months

State pension								
	No	36	48	57.1	1			
	Yes	15	24	61.5	1.2 (0.55,2.61)	0.645		
Disability benefit								
	No	30	44	59.5	1			
	Yes	21	28	57.1	0.91 (0.44,1.89)	0.799		
Other benefit								
	No	35	55	61.1	1			
	Yes	16	17	51.5	0.68 (0.3,1.51)	0.340		
Private health insurance								
	No	45	67	59.8	1			
	Yes	5	4	44.4	0.54 (0.14,2.11)	0.373		

Table 6.5: FVC decline by 5% over 12 months

There were no statistically significant predictors of a 10% decline in FVC at 12 months identified on the univariate analysis (Table 6.6).

					Univariate		Adjusted	
Covariate	Level	Did not decline	10% FVC decline over 12 months	% of patients with decline	OR (95% CI)	p-value	OR (95% CI)	p-value
Age						0.252		
	46-65	22	18	45	1			
	66-72	14	16	53.3	1.4 (0.54,3.61)	0.491		
	73-78	21	11	34.4	0.64 (0.25,1.67)	0.362		
	79-96	15	6	28.6	0.49 (0.16,1.52)	0.216		
Gender								
	Female	22	12	35.3	1			
	Male	50	39	43.8	1.43 (0.63,3.24)	0.392		
Emphysema								
	No	63	48	43.2	1			
	Yes	9	3	25	0.44 (0.11,1.7)	0.233		
Time since diagnosis						0.103		
	34-363	18	13	41.9	1			
	372-847	15	19	55.9	1.75 (0.66,4.69)	0.263		
	848-1624	16	11	40.7	0.95 (0.33,2.71)	0.927		
	1674-9721	23	8	25.8	0.48 (0.16,1.41)	0.183		
Surgical biopsy								
	No	61	42	40.8	1			
	Yes	11	9	45	1.19 (0.45,3.12)	0.726		
MRC								
	2	11	13	54.2	1			

Table 6.6: FVC decline by 10% over 12 months

	3	31	19	38	0.52 (0.19,1.39)	0.192		
	4	23	18	43.9	0.66 (0.24,1.82)	0.425		
	5	7	1	12.5	0.12 (0.01,1.14)	0.065		
Finger clubbing								
	No	50	32	39	1			
	Yes	22	19	46.3	1.35 (0.63,2.88)	0.438		
FVC group						0.323		
	<50%	8	8	50	1			
	51%-65%	15	15	50	1 (0.3,3.37)	1		
	>65%-79%	24	10	29.4	0.42 (0.12,1.42)	0.162		
	>79%	25	18	41.9	0.72 (0.23,2.28)	0.576		
DLCO group						0.977		
	<35%	23	17	42.5	1			
	>35%-45%	23	16	41	0.94 (0.38,2.3)	0.894		
	>45%	18	12	40	0.9 (0.34,2.36)	0.834		
Prednisolone								
	No	35	23	39.7	1			
	Yes	37	28	43.1	1.15 (0.56,2.36)	0.701		
Azathioprine								
	No	49	36	42.4	1			
	Yes	21	13	38.2	0.84 (0.37,1.9)	0.680		
Oxygen (any)								
	No	64	45	41.3	1			
	Yes	8	6	42.9	1.07 (0.35,3.29)	0.910		
SGRQ symptoms						0.656		
	8.56-44.89	21	15	41.7	1			
	46.05-60.44	15	13	46.4	1.21 (0.45,3.28)	0.703		
	60.45-72.57	21	11	34.4	0.73 (0.27,1.96)	0.537		
	72.89-90.09	12	12	50	1.4 (0.5,3.96)	0.526		
SGRQ activity						0.762		
	21.96-60.35	17	17	50	1			
	60.47-79.67	19	13	40.6	0.68 (0.26,1.81)	0.445		
	79.91-92.51	29	18	38.3	0.62 (0.25,1.52)	0.295		
	92.76-100	4	3	42.9	0.75 (0.15,3.87)	0.731		
SGRQ impact						0.843		
	0-30.02	17	15	46.9	1			
	30.13-43.70	20	14	41.2	0.79 (0.3,2.1)	0.641		
	44.36-61.11	16	12	42.9	0.85 (0.31,2.36)	0.755		
	61.23-100	15	8	34.8	0.6 (0.2,1.82)	0.371		

Table 6.6: FVC decline by 10% over 12 months

SGRQ total						0.745		
	15.5-44.11	17	16	48.5	1			
	44.33-58.28	19	15	44.1	0.84 (0.32,2.19)	0.72		
	58.41-70.45	18	11	37.9	0.65 (0.24,1.79)	0.404		
	70.85-96.39	13	7	35	0.57 (0.18,1.8)	0.339		
Education						0.723		
	None/school certificate	39	33	45.8	1			
	A-Levels. CSEs, GCSE	9	5	35.7	0.66 (0.2,2.15)	0.487		
	HND/Btech\NVQ	8	7	46.7	1.03 (0.34,3.15)	0.953		
	Degree/PhD	12	6	33.3	0.59 (0.2,1.75)	0.342		
Living alone								
	No	70	51	42.1	1			
	Yes	2	0	0	-			
Paid employment								
	No	67	45	40.2	1			
	Yes	3	6	66.7	2.98 (0.71,12.52)	0.137		
Monthly household income						0.733		
	<199	15	7	31.8	1			
	200-299	12	8	40	1.43 (0.4,5.07)	0.581		
	300-399	10	8	44.4	1.71 (0.47,6.24)	0.414		
	400-499	8	5	38.5	1.34 (0.32,5.61)	0.689		
	500+	10	11	52.4	2.36 (0.68,8.15)	0.175		
State pension								
	No	50	34	40.5	1			
	Yes	22	17	43.6	1.14 (0.53,2.45)	0.744		
Disability benefit								
	No	40	34	45.9	1			
	Yes	32	17	34.7	0.63 (0.3,1.32)	0.216		
Other benefit								
	No	50	40	44.4	1			
	Yes	22	11	33.3	0.63 (0.27,1.44)	0.270		
Private health insurance								
	No	65	47	42	1			
	Yes	5	4	44.4	1.11 (0.28,4.34)	0.885		

Table 6.6: FVC decline by 10% over 12 months

6.4 Discussion

Although overall prognosis of IPF is poor there is a significant variability in functional change over time ranging from improvement or minimal change in PFT over years to a significant decline leading to death over 6-12 months often preceded by an exacerbation/admission[215, 293]. A number of individual clinical, radiological, pathological parameters and biomarkers obtained both at baseline and over time have been associated with poor prognosis in IPF. Clinical prediction models have been previously produced in an attempt to combine these parameters/predictors in order to accurately predict prognosis and help to decide on treatment. However two of these models and scoring systems (clinical-radiologic-physiologic (CRP) scoring system and composite physiologic index (CPI)) are confined to research only as they are largely based on the inclusion of factors that are not widely accessible in the clinical practice[295]. The most recently published abbreviated prediction model and based on it scoring system include readily available parameters and could be easily used in clinical practice to assess 1 year risk of mortality[295]. This scoring system could be applied to patients with the disease of any severity but at present it requires validation before it is recommended for a routine use.

The results of this study show that treatment with prednisolone at baseline was predictive of both death at 12 months and a 10% decline in FVC at 6 months but not at 12 months. Both SGRQ symptoms domain score and being in paid employment were predictive of 5% FVC decline at 12 months while SGRQ total score at baseline was predictive of death at 12 months. There were no baseline predictors of 5% FVC decline at 6 months and 10% FVC decline at 12 months identified.

10% decline in FVC at 6 and 12 months was chosen as an outcome measure as it has a prognostic significance. A number of studies demonstrated that this change during this time scale is highly predictive of death[62, 65] and that it is more predictive of prognosis than most baseline characteristics including histopathologic diagnosis[196]. Though as a result ≥10% FVC change has been considered clinically significant, recent data suggest that even marginal decline in FVC of 5% at 6 months is associated with more than two-fold increase in the risk of death over

subsequent 12 months[295]. This magnitude of change has previously been considered to be within normal limits. Since the prospective follow up was limited to 12 months it seemed to be reasonable to use changes in FVC as a surrogate marker of mortality.

Baseline characteristics used in this modelling were chosen based on its practicality and availability during routine clinical consultation (with an exception of SGRQ which is normally not a part of a standard evaluation of patients with ILD). Change in DLCO % predicted over time was not included in modelling as it is not readily available in clinical practice (only 62% of patients who had FVC measurements at 12 months after recruitment had DLCO measurements done also) and is known to possess significant variability.

Though consistent with previous research age, MRC dyspnoea score, DLCO percent predicted, SGRQ scores, and the use of prednisolone were predictive of death on univariate analysis it was unexpected to see that only the latter two markers were included into a final model of predictors of death. At the same time this might mean that longitudinal data reflecting disease behaviour over a period of time is at least equally if not more relevant than clinical predictors obtained at a single time point. The result of the study of du Bois et al[295] aimed at identifying individual risk factors of mortality for IPF patients is in line with this showing that four out of seven clinical factors significantly predictive of all cause mortality were of longitudinal nature (history of respiratory hospitalisation, 24-week change in FVC percent predicted, DLCO percent predicted and HRQL (SGRQ) (alongside age, FVC percent predicted and DLCO percent predicted).

An important observation adding to a recently accumulating data about the effect of steroid treatment on the course of IPF is the fact that the use of prednisolone at baseline appears to be a significant predictor of both 10% decline in FVC at 6 months and death at 12 months. This means that patients receiving treatment with corticosteroids not only continue to progress but are at a higher risk of death than those who do not, more likely due to associated side effects, on the first place possibly increased risk of infections. It is likely that patients with severe disease or rapidly declining condition were more often treated with corticosteroid therapy than patients with mild or stable disease. Corticosteroid therapy could

therefore be a marker of increasing disease severity and of increasing likelihood of death. However corticosteroid therapy was predictive of death even in the adjusted analysis which was corrected for age and available makers of severity (namely FVC) but the decision to when to instigate corticosteroid therapy is complex and involves more aspects than we can include in the prediction model. Of the patients included in co-trimoxazole study 60% were receiving corticosteroids at recruitment. Only 25% of recruited patients were incident cases which means that the majority of corticosteroid treated patients had been on this treatment for over 12 months by the time of recruitment. This is particularly relevant in a view of the BTS national interstitial lung disease survey with data collected during late 2010 and early 2011 demonstrating that around 50% of chest physicians (from a total of 120) continued to use prednisolone for the treatment of IPF[254] which means that this treatment continued to be a routine practice at least until very recent past. Though a recent recommendation of BTS and ERS [296] is not to commence newly diagnosed patients on immunosuppression and to consider withdrawal of corticosteroids in patients who have been commenced on it previously there will be a large proportion of patients in who their attending physician would feel reluctant to withdraw this long term medication either due to potential withdrawal risks (adrenal insufficiency) or anecdotal risk of exacerbation of underlying IPF following the withdrawal of corticosteroids.

Treatment with immunosuppression has recently been demonstrated to increase mortality in two major studies - a retrospective study assessing predictors of mortality in IPF and in an interventional study assessing the effects of N-acetylcysteine. As shown by du Bois et al treatment with prednisolone in any dose as well as with azathioprine was associated with increased risk of death in univariate analysis of 1099 patients with a wide severity spectrum disease[295]. At the same time the interim safety analysis from the three arm PANTHER-IPF study assessing the efficacy of N-acetylcysteine compared to placebo and a combination of Prednisone, Azathioprine, and N-acetylcysteine reported that treatment with immunosuppression (the latter arm) was associated with increased mortality compared to placebo (11% versus 1%) as well as higher frequency of hospitalizations (29% versus 8%), serious adverse events (31% versus 9%) and showed no difference in lung function test[297]. As a result recruitment into the triple therapy arm has been discontinued. It is

possible that those patients died from infections. In this respect the treatment effect in co-trimoxazole study (Chapter 4) was significantly related to those receiving immunosuppressive therapy.

Population based studies have looked at the impact of race and ethnicity on survival in IPF and showed that non-Hispanic black and Hispanic patients with IPF have worse survival than white patients after listing for a lung transplant both in a single and a multicentre (94 centres in the US) studies[27, 298]. Though some ILD disease registers' data form along with basic socio-demographic information (gender, age, smoking history) contain more extended information for example on years of education[299] none of the epidemiological or interventional studies reported on the role of social factors such as education, employment and family arrangements in survival in IPF. Only one study in its original abstract report demonstrated that in a cohort of long term lung transplant survivors (among who 11% patients had an underlying diagnosis of IPF) both bilateral lung transplant and HLA matching as well as higher education may portend improved survival [300] (this data was not included in the final full text paper[116]).

This study is the first one to determine the role of education, living arrangements, employment, and welfare benefit in the prognosis of IPF. It showed that patients with degree with or without a PhD are less likely to exhibit a 5% decline in their FVC over 12 months while those with a school certificate alone without the subsequent education were more likely to decline over this time period. It is possible that patients with a higher education are more vigilant to infections and are more open to additional treatments such as pulmonary rehabilitation (even though so far pulmonary rehabilitation was shown to improve only functional exercise capacity in IPF as measured by 6 minute walk distance[120]). At the same time being in paid employment increased the risk of a 5% decline in FVC over 12 months. This may reflect the fact that patients in paid employment who are more likely to be younger than those who do not work have a more severe disease and therefore progress quicker.

Alongside a lack of use of longitudinal predictors of deterioration in IPF mentioned previously this study has a number of other limitations. First, it had a limited duration of follow up of 12 months. At the same time we

ensured that the status of patients who withdrew from the co-trimoxazole study prematurely was established at a 12 months time point and for those who remained alive all attempts were maid to obtain their lung function data. Second, the study included a relatively small group of patients which could partly explain why the final models were including only a small number of parameters. Third, large proportions of patients were older and had severe disease therefore whether the results would be applicable to those younger with less severe disease is not clear. Fourth, radiological parameters (CT fibrosis score) were not included in the baseline characteristics of the model.

In conclusion, this study provides further evidence that treatment with prednisolone is predictive of a significant decline in FVC and death in patients with IPF over a limited period of observation of 6-12 months and suggests that commencement of long term corticosteroids should be avoided in this condition.

Chapter 7
Overall discussion

7.1 Diagnostic accuracy

As shown by audit and radiological review of TIPAC study there is a degree of variability in diagnosing IPF. Only 10 out of 108 cases involved in the audit project had confidently excluded identifiable cause for the ILD. Particularly weak areas included evaluation of previous and current hobbies, previous medical history, medication exposure and family history. While occupational history enquiries were made in 75% of patients this was incomplete in most of cases. Similarly while 66% of patients had serological connective tissue disease screen performed most of them did not have an evaluation of symptoms undertaken.

In both the audit (93.5%) and the TIPAC study (84%) the majority of diagnosis of IPF was made without histology. This leads one to the next question of the accuracy and reliability of diagnostic assessment of UIP HRCT pattern. In the TIPAC study in the absence of surgical lung biopsy IPF was diagnosed by an investigator based on clinical-radiological data with radiological evaluation having been performed by a study site radiologist at the time of patient's diagnosis. Where available the same (87% of cases) diagnostic scans were subsequently used in the retrospective radiological review that was undertaken by two specialist respiratory radiologists using published criteria[164]. Interestingly 7 patients who were assigned the diagnosis of NSIP by the local investigator/radiologist were felt to have a UIP HRCT pattern (3 typical and 4 probable) by the study radiologist. Similarly 15 patients who were assigned the diagnosis of UIP by the local investigator/radiologist were felt to have NSIP by the study radiologist (study radiologists were blinded to patients' clinical diagnosis). This had an implication on deciding which patients would be included in the sensitivity analysis for definite/probable diagnosis of IPF (biopsy, definite/probable UIP on HRCT) with the latter patients being excluded from it. At the same time when following an algorithm to predict a biopsy confirmation of IPF described by Fell et al[165] the HRCT scans of 15 patients who were diagnosed by study radiologists as NSIP were also scored according to the degree of interstitial changes, only 4 scans scored as intermediate probability of IPF

and the remaining 11 were consistent with a high probability diagnosis of IPF.

This diversity of approaches and re-classification using different criteria reflects that even in the presence of detailed guidelines there is no full consistency in diagnostic approach and it is still challenging to establish a correct diagnosis in some cases.

7.2 Poor survival and longitudinal changes in lung function

Twelve months follow up in the TIPAC study confirmed the previous data that older patients with more advanced disease have a high mortality rate - 20% of patients died over this observation period. Though median survival in IPF is reported to be no greater than 3 years some patients live longer and some do not exhibit evidence of functional decline for prolonged period of time. Flaherty et al [13] was the first to demonstrate that although overall survival in IPF is poor, a large proportion of patients (up to a third in the study by Flaherty et al) had stable disease over 12 months of observation. The analysis of lung function trends of TIPAC study patients over 12 months showed that 40% of patients have ≥10% decline in FVC whilst 50% had changes that in routine clinical practice would be considered as evidence of non-progressive disease. The latter results were similar in the group including both treatment arms and in the group including placebo arm patients only and was in line with the previous observation of Flaherty (Chapter 4, Table 4.11).

7.3 Predictors of outcome

Considering a diversity of behaviour of IPF it would be valuable for both patients and attending physicians to have a way of predicting at diagnosis how the disease would behave over time. This requires biomarkers as individual predictors of survival as well as for use in clinical prediction models that combine a number of parameters. Individual predictors include clinical, radiological, physiological, pathological, and biomarker predictors[196]. Changes in some of these parameters over time (physiological and radiological) could be particularly helpful in identifying patients with progressive disease. This thesis reported two prospective studies looking at the role of clinical-physiological parameters as well as two biomarkers in predicting disease behaviour in patients with idiopathic pulmonary fibrosis. It was shown that alveolar nitric oxide concentration has a strong predictive value for subsequent clinically significant decline

in DLCO and that plasma VEGF level is a strong predictive factor of a clinically significant FVC decline over time. It was also demonstrated that treatment with prednisolone at baseline was predictive of both death at 12 months and a 10% decline in FVC at 6 months and that SGRQ total score at baseline was predictive of death at 12 months.

There is accumulating prospective evidence that individual physiological markers are responsive measures of disease status[68, 301]. FVC is a reliable and valid parameter for assessing disease status in patients with IPF and even a small change of 5-10% over time (24 weeks) is highly predictive of mortality at 1 year[197, 301]. At the same time the significance of 2-6% magnitude of change in FVC percent predicted as a minimal clinically important difference[301] would be difficult to interpret in isolation due to the test variability. Therefore changes in individual parameter should be used in conjunction with other markers of the disease progression which may be done within the frames of a prediction model. Indeed, du Bois[295] has suggested a mortality scoring model that includes age, history of respiratory hospitalisations, %predicted FVC, and 24 week change in % predicted FVC .

7.4 Future studies arising from this thesis

Many questions have arisen from the results of this thesis. The effect of co-trimoxazole on survival was unexpected and taking into account the associated reduction in infections it would be interesting to know whether any antibiotic would have such an effect and whether this is related to the treatment with steroids or not. To answer such question a new study would need to recruit ideally treatment naive patients and to use two treatment arms, one using co-trimoxazole and one using another antibiotic class. It would also be important to know if co-trimoxazole treats colonisation or provides early treatment for acute infections. To answer this question a study with thorough assessment of microbiological profile at recruitment and during any infective episode would be required. Such study may be challenging to conduct as ideally microbiological specimens would need to be obtained using broncho-alveolar fluid. Alternatively co-trimoxazole may have a non-antibiotic role and mechanistic studies would be required to investigate this. Co-trimoxazole reduced a number of admissions to hospital due to any reason and due to a respiratory causes; it would be interesting to see if the drug affects the rate of acute exacerbations in which case a precise definition of exacerbation would need to be given in

the protocol. The positioning of co-trimoxazole therapy is not clear: should all patients receive co-trimoxazole at diagnosis or should it be reserved for patients who have had an exacerbation or recurrent respiratory tract infections? A role of longitudinal changes in CaNO and VEGF in predicting prognosis of IPF is not known. Given the ease of measuring exhaled nitric oxide this parameter could be included within a prediction model however a larger long-term prospective mortality study would be required.

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Appendix 1

National Research Ethics Committee approval of study 2 (Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole)

NHS
National Research Ethics Service
Cambridgeshire 4 Research Ethics Committee
Victoria House
Capital Park
Fulbourn
Cambridge
CB21 5XB

Telephone: 01223 597685
Facsimile: 01223 597645

04 September 2007

Dr Andrew Wilson
Clinical Senior Lecturer
Biomedical Research Centre
School of Medicine
University of East Anglia
Norwich
NR4 7TJ

Dear Dr Wilson

Full title of study:	**The efficacy and safety of co-trimoxazole therapy in patients with idiopathic interstitial pneumonia**
REC reference number:	**07/MRE05/45**
Protocol number:	**7**
EudraCT number:	**2007-002043-25**

Thank you for your letter of 20 August 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Sub-Committee of the REC held on 28 August 2007 by Dr Leslie Gelling, Chair and Mr Ron Driver, Lay member.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the research sites taking part in this study. The favourable opinion does not therefore apply to any site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at sites requiring SSA.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application	AB/107014/1	25 May 2007
Investigator CV - Dr Andrew Wilson		23 May 2007
Protocol	7	15 August 2007
Covering Letter		23 May 2007
Peer Review of EATS Fellowship application		
Compensation Arrangements UEA Norwich-Zurich Municipal. (Policy number NHE-09AC01-0013)		23 July 2007
Questionnaire: EQ-5D incl. patient initials, centre No. and Visit No.		
Questionnaire: St Georges Respiratory incl. patient initials, centre No. and Visit No.	Original	
Questionnaire: Health service use and personal expenditure resource diary	2	25 July 2007
Questionnaire: Background Information	2	25 July 2007
Questionnaire: Cost Questionnaire-Follow up	2	25 July 2007
Questionnaire: Cost Questionnaire-Baseline	2	25 July 2007
GP Letter	2	14 August 2007
Participant Information Sheet	5	13 August 2007
Participant Consent Form	3	13 August 2007
Response to Request for Further Information		25 July 2007
Response to Request for Further Information		20 August 2007
Request for Authorisation from MHRA (Annex 1 to ENTR/CT1)		
Details of Data Monitoring		
Annex 2 Notification of Amendment (CTIMPs)		20 July 2007

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Feedback on the application process

Now that you have completed the application process you are invited to give your view of the service you received from the National Research Ethics Service. If you wish to make your views known please use the feedback form available on the NRES website at:

https://www.nresform.org.uk/AppForm/Modules/Feedback/EthicalReview.aspx

We value your views and comments and will use them to inform the operational process and further improve our service.

07/MRE05/45	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Leslie Gelling
Chair

Email: emma.clark@eoe.nhs.uk

Enclosures: *Standard approval conditions*

Copy to: Mrs Sue Steel
Research Contracts Manager
Research and Business Services
University of East Anglia
Research and Business Office
Norwich
NR4 7TJ

Appendix 2

Medicines and Healthcare products Regulatory Agency approval letter of study 2 (Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole)

Safeguarding public health

MHRA

Direct Line: 0207 084-2456
Facsimile: 0207 084-2443
Room 12- 242

Our Reference: 31701/0001/001-0001
Eudract Number: 2007-002324-15

Dr A M Wilson
UNIVERSITY OF EAST ANGLIA
BIOMEDICAL RESEARCH CENTRE
EARLHAM ROAD
NORWICH
NR4 7TJ
UNITED KINGDOM

24/08/2007

Dear Dr A M Wilson

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 1031
Product Type: General Medicinal Product
Product: SEPTRIN TABLETS
Protocol number: P01092

NOTICE OF ACCEPTANCE OF AMENDED REQUEST

I am writing to confirm that the Licensing Authority, acting under regulation 18(6)(b) or (c), or 19(7)(a) or (8), or 20(4)(a) or (5), according to the type of medicinal product involved[1], accepts your amended request to carry out a clinical trial in accordance with your application 21/08/2007 subject to you receiving a favourable opinion from the relevant ethics committee in accordance with regulation 15(1). You may therefore carry out the trial as notified, but I must remind you of the Authority's powers under regulation 31 to suspend or terminate a clinical trial if the conditions set out in regulation 31(1)(a) and (b) are satisfied

The authorisation is effective from the date of this letter and may continue under this authorisation. In accordance with regulation 27, you must notify the Licensing Authority within 90 days of the conclusion of the trial, that has ended.

Yours sincerely

Dr Martyn Ward
Head of Clinical Trials Unit

[1] The Licensing Authority's authorisation powers for clinical trials are regulation 18 for those involving general medicinal products, regulation 19 for those involving medicinal products for gene therapy etc., and regulation 20 for those involving medicinal products with special characteristics.

Medicines and Healthcare products Regulatory Agency
Market Towers 1 Nine Elms Lane London SW8 5NQ
T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk

An executive agency of the Department of Health

Appendix 3

STUDY PROTOCOL (version 13)

TREATING INTERSTITIAL PNEUMONIA WITH THE ADDITION OF CO-TRIMOXAZOLE (TIPAC) STUDY

Full title

The efficacy and safety of co-trimoxazole therapy in patients with idiopathic interstitial pneumonia

Investigators

Andrew M Wilson - Clinical Senior Lecturer

Orion Twentyman - Consultant Physician

Tony Davison – Consultant Physician

Veronica Varney – Consultant Physician

Allan Clark – Medical Statistician

John Curtin – Consultant Radiologist

Ed Wilson – Health Economist

1) BACKGROUND AND RATIONALE

Idiopathic interstitial pneumonia, a type of diffuse parenchymal lung disease, consists of conditions of unknown aetiology that result in fibrosis, with or without inflammation, of the lung parenchyma. Clinically it is recognised as idiopathic pulmonary fibrosis (IPF), also called cryptogenic fibrosis alveolitis. Recent epidemiological data suggest that the incidence is 6.8-16.3/100,000(1). The median survival from diagnosis of is only 2.9 years(2). During this time individuals become increasingly dyspnoeic such that simple activities of daily living become difficult even with continuous oxygen therapy, and the disease often ends with a distressing death from respiratory failure. There is no cure, no treatment has been proven to be effective and the mortality rate in the UK is increasing(2). There is therefore a considerable unmet need.

Corticosteroids are the most widely used treatment for IPF, and are recommended in current guidelines(3). However a Cochrane review failed to demonstrate any advantage of this form of therapy(4). Recent review articles consistently state that there is no clear evidence that corticosteroids are beneficial(5;6). Given the significant adverse effects of corticosteroids; azathioprine or cyclosporin are prescribed concomitantly as steroid sparing agents. These immunotherapies given alone or in combination with corticosteroids also have adverse effects with no clear survival advantage(7;8). More recently newer therapies have been evaluated including interferon-γ-1b, n-acetylcysteine and pirfenidone. These have shown modest beneficial effects, the clinical significance of which is unknown(9;10).

Co-trimoxazole is an antibiotic that has been available for more than 20 years. It is the first-line treatment for pneumocystis carini pneumonia and is also used long–term as prophylaxis against this infection. It is often used in the management of Wegner's granulomatosis – which may involve the lung parenchyma – and has been shown to reduce the incidence of relapse in this condition(11). Co-trimoxazole has also been shown to have beneficial effects in rheumatoid arthritis(12). In a small randomised, double blind, study of 20 patients with idiopathic pulmonary fibrosis, randomised to receive co-trimoxazole or placebo, there were clinically and statistically significant improvements in FVC, shuttle walking distance and symptom scores after 3 months of active therapy(13). The improvements in the treatment group were maintained at one year, and similar improvements were seen when the original placebo group were crossed over to an open extension treatment period and received therapy with co-trimoxazole. Given the lack of efficacy of standard therapies and modest improvement with newer expensive therapies, validation of a trial that showed remarkable improvements with an inexpensive, well tolerated therapy is required.

We will assess the effects of co-trimoxazole by measuring forced vital capacity. Forced vital capacity (FVC) is a standard breathing test that is performed routinely as part of clinical care and is therefore appropriate for this type of multicentre study. Furthermore, FVC correlates closely with health related quality of life and breathlessness scores in patients with idiopathic pulmonary fibrosis(14) and change in FVC is the best predictor of survival(15).

Secondary outcomes will include the six minute walk test and St Georges Respiratory Questionnaire. The six minute walk is a reproducible procedure that has been shown to relate to full cardiopulmonary exercise testing in patients with pulmonary fibrosis(16) and that the change oxygen saturation during the six minute walk is a good predictor of survial(17;18). The St Georges Respiratory Questionnaire is a tool for assessing health related quality of life that has been validated for use with patients with idiopathic interstitial pneumonitis(19). It is a responsive tool that has three domains: symptoms, activity, and impacts (on daily life)(20).

2) OBJECTIVE

The primary objective is to compare the efficacy and safety of 12 months therapy with co-trimoxazole 960 mg twice daily to placebo in a double-blind placebo-controlled study of patients with fibrotic idiopathic interstitial pneumonia. The secondary objective is to estimate the incremental cost effectiveness of co-trimoxazole plus standard care compared with standard care alone.

3) ENDPOINTS

3.1 The primary endpoint of the study will be change in forced vital capacity after 12 months of study drug.

3.2 Secondary outcomes will be

1. change in MRC breathlessness score.
2. change in total lung capacity.
3. change in total lung diffusing capacity of carbon monoxide.
4. change in St Georges Respiratory Questionnaire.
5. change in 6 minute walking distance and desaturation.
6. change in EuroQol (EQ-5D) score.

3.2 Other endpoints will be

1. all cause mortality and mortality due to IPF.
2. the requirement for escalation of therapy. This includes commencement of prednisolone or azathioprine (in patients who had not been on immunossupression prior to recruitment) or increase or decrease in the dose of prednisolone or azathioprine (in those who had been on immunosuppression prior to recruitment), addition of other treatments including acetylcystein and the commencement of oxygen therapy.
3. the number of hospitalisations.

3.3 Safety endpoints will be

1. Blood haematology and biochemistry.

2. Drug related adverse events.

4) DESIGN

This will be a 12 month double-blind placebo-controlled, randomised multicentre study of oral co-trimoxazole when added to standard care in 200 patients (100 in each arm) with fibrotic idiopathic interstitial pneumonia. Patients will attend for a screening visit to ensure that inclusion and exclusion criteria are met and obtain consent. The screening visit will be within 6 weeks of commencing therapy. Baseline measurements will be made as detailed below and repeated at 6 weeks, 6, 9 and 12 months following randomisation. Randomisation will be performed centrally with stratification for baseline therapy. The study centres will be responsible for identification and recruitment of subjects including obtaining written informed consent. Investigations will be performed as part of routine clinic appointments. An intention to treat analysis will be performed at the conclusion of the study. There will be an interim safety analysis after 50% of patients have completed 6 months of therapy.

All patients participating in the TIPAC study shall receive their supply of study medication following documentation of any side effects and other adverse events, clinical assessment and confirmation of the patient's consent to continue in the study. This assessment may be undertaken by the local principal investigator or a designee. Following receipt of a signed study drug prescription, the pharmacist shall dispense the medication to the participant directly or to the research team, who will dispense the medication to the participant. Wherever possible, the study drug prescription shall be signed, and the study medication shall be dispensed from the pharmacy on the day of patient's study visit. On some occasions this is not possible and the prescription may be signed in advance of the study visit. The research team shall document, in the study workbook, the amount of study drug supplied, and by whom

5) STUDY POPULATION

SAMPLE SIZE

A sample size of 63 subject in each arm will have an 80% power to detect a mean difference of 200ml in forced vital capacity at a significance level of $p = 0.05$, assuming a standard deviation of 400 ml. In order to accommodate a withdrawal rate of 37% we will recruit 200 patients into the study.

INCLUSION CRITERIA

1. Male or female, aged greater than 40 years.
2. Female subjects must be of non-childbearing potential, defined as follows:
   - postmenopausal females who have had at least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhoea with serum FSH>40mIU/ml.
   - females who have had a hysterectomy or bilateral oophorectomy for at least 6 weeks.
3. Able to provide informed consent.
4. A clinical labelled diagnosis of fibrotic idiopathic interstitial pneumonia with HRCT scan features compatible with Usual Interstitial Pneumonia (UIP) or Fibrotic Non-specific Interstitial Pneumonia (NSIP). The following criteria adapted from the ATS/ERS consensus statement will be used for the diagnosis the clinical manifestation of UIP (idiopathic pulmonary fibrosis):
   - Major Criteria (All present)
     - Exclusion of other known causes of interstitial lung disease, such as drug toxicities, environmental exposures, and collagen vascular diseases
     - Abnormal pulmonary function studies that include evidence of restriction with or without impaired gas exchange
     - Bibasal reticular abnormalities with minimal ground glass opacities on HRCT
   - Minor criteria (two out of three features)
     - Insidious onset of otherwise unexplained dyspnoea on exertion
     - Duration of illness 3 months
     - Bibasal inspiratory crackles (dry or "Velcro-" type in quality)

   Patients with clinical diagnosis of non-specific interstitial pneumonia will be entered if fibrotic features are predominant on HRCT. Histology will not be required as an entry criterion however histology from lung biopsy or autopsy will be reviewed if available.

5. Patients may have had initial treatment of prednisolone +/- azathioprine, as indicated and described in the current BTS guidelines, without a significant response to immunosuppressive therapy that would make the physician doubt the diagnosis of fibrotic idiopathic interstitial pneumonia.
6. Patients should be on stable treatment regimen for at least 6 weeks. Patients may be on no immunosuppressive medication or may be receiving immunosuppressive medication in the form of oral prednisolone up to a dose of 20mg per day +/- azathioprine. Patients receiving higher doses of up to 0.5mg/kg may be enrolled in exceptional circumstances after discussion with the principal investigator.
7. Those patients who are not on immunosuppressive therapy and have not had steroid treatment in the past due to concern of potential adverse effects or for other reasons, but who have a significant deterioration in their lung function, as determined by the attending physician and investigator would be invited to participate in the study.
8. Patients may be receiving treatment with n-acetylcysteine or other anti-oxidants.
9. MRC dyspnoea score of ≥2.
10. A normal serum folate and B12 (to ensure no bone marrow or neurological adverse effects occur with folate therapy to B12 deficient individuals) is required at screening.
11. Subjects have a 12 lead ECG recording that does not demonstrate any clinically important abnormality that, in the opinion of the investigator, would make the subject unsuitable for participation in the study.

5.3 EXCLUSION CRITERIA

1. A secondary cause for pulmonary fibrosis including a diagnosis of asbestosis, drug induced pulmonary fibrosis, collagen vascular disease or other secondary pulmonary fibrosis.
2. A recognised significant co-existing respiratory disorder.

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3. A respiratory tract infection within the last 2 months.
4. Overt and persistent heart failure, a myocardial infarction within 12months, ischaemic heart disease requiring more than one regular therapy or a clinically significant uncontrolled arrhythmia (including Mobitz type II or third degree heart block).
5. Significant medical, surgical or psychiatric disease that in the opinion of the patients' attending physician would affect subject safety or influence the study outcome.
6. Women who are pregnant or are breast-feeding.
7. Patients receiving immunosuppressant medication (with the exception of prednisolone and azathioprine according to guidelines).
8. Co-trimoxazole allergy or intolerance and patients receiving medication known to interact with co-trimoxazole.
9. Untreated folate or B12 deficiency.
10. Glucose-6-phosphate dehydrogenase deficiency as measured at screening (in males only).
11. Receipt of an investigational drug or biological agent within the 4 weeks prior to entry in to this study.
12. Patients with evidence of drug or alcohol misuse.

6.1 STUDY ASSESSMENTS

At screening, assessment will be made for glucose-6-phosphate deficiency and will be performed unless previously documented. An ECG will be taken unless performed within the last 6 months. A brief questionnaire will be administered to assess baseline health and social care resource utilisation and costs. An additional questionnaire will assess baseline socioeconomic status.

The following will be performed at screening and 6 weeks, 6 months 9 months and 12 months after randomisation:

1. Spirometry – this will be performed according to American Thoracic Society criteria and represented as absolute values(21).
2. MRC Breathlessness score.
3. Full blood count, Urea and Electrolytes and Liver function tests (this is unlikely to be additional to standard care).
4. The EuroQol EQ-5D (a 1 page self administered questionnaire)
5. A health and social care resource utilisation and costs questionnaire (3 pages).

The following will be performed at screening and 6 months and 12 months after randomisation:

6. Six minute walking test as described previously with assessment of desaturation during the test and distance walked(22) – in a subgroup of patients only.
7. St George's Respiratory Questionnaire (SGRQ). This patient completed questionnaire has been previously validated in idiopathic pulmonary fibrosis(19).
8. Total lung diffusing capacity of carbon monoxide (DLCO).
9. Static lung volumes including total lung capacity (TLC) by body plethysmography or helium dilution.
10. Blood will be stored for vascular endothelial growth and KL-6 in a subgroup of patients only.

For the duration of the study an assessment will be made of

11. all cause mortality and mortality due to IPF.
12. the requirement for escalation of therapy. This includes an increase or decrease in the dose of prednisolone or azathioprine, addition of other treatments including acetylcystine and the commencement of oxygen therapy.
13. adverse events.
14. hospitalisations.

The 6 week assessment will be undertaken between 4 and 8 weeks and the 6 month assessment will be conducted between 5 and 7 months, the 9 month assessment will be between 8 and 10 months and the 12 month assessment between 11-13 months to permit study visits to coincide with routine medical follow-up.

6.2 SAFETY

6.2.1 Laboratory values

Screening for glucose-6-phosphate deficiency will be performed (as described in 6.1 above)

Full blood count, Urea and Electrolytes and Liver function tests will be measured at screening, at 6 weeks, 6 months, 9 months and at 12 months of therapy (as described in 6.1 above).

Patients on Azathioprine or Mycophenolate Mofetil will require additional monitoring of full blood count on two weekly basis due to potential risk of neutropenia. Patients on Mycophanolate Mofetil will have their Urea and Electrolytes and Liver function tests checked two weeks after recruitment.

Details of adverse events will be collected (as describe in 6.1 above).

Additional investigations will be requested as deemed appropriate by the investigator on an individual patient basis

6.2.2 Pregnancy

6.2.2.1 Action to be taken if pregnancy occurs

Female subjects with the potential to become pregnant will be excluded from entry into the study.

6.2.2.2 Action to be taken if pregnancy occurs in a female partner of a male study subject

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The investigator will record pregnancy information and submit it to the principle investigator within 2 weeks of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the principle investigator. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

7. LIFESTYLE CHANGE

There will be no lifestyle changes required

8. INVESTIGATIONAL PRODUCT

Patients will be randomised to receive either of the following treatments for 12 months:

1) Co-trimoxazole (non-proprietary) 960mg twice daily as 2 tablets of 480mg twice daily.

Or

2) Placebo tablets (manufactured from pharmacy at Guy's and St Thomas's Hospital – to be identical to co-trimoxazole 480mg) 2 tablets twice daily

Plus

Folic acid (non-proprietary) 5mg once daily

9. CONCOMITANT MEDICATION

Permitted Therapy

1. Patients may be receiving oral prednisolone at a stable dose (up to 20 mg per day) for 6 weeks prior to the start of the study. Patients receiving prednisolone will continue this dose unless clinically indicated. Any change in prednisolone dose will be recorded

2. Some patients will also be receiving azathioprine (1-3 mg/kg/day). They will continue this dose unless clinically indicated. Any change in azathiorpine dose will be recorded.

3. Acetylcysteine or other anti-oxidant therapy

Non-permitted therapy on entry

1. Cyclophosphamide
2. Methotrexate
3. D-penicillamine
4. Colchicine
5. Gamma-interferon

Concurrent therapy requiring caution or increased monitoring

1. Digoxin
2. Warfarin
3. Phenytoin
4. Sulphonylureas
5. Procainamide hydrochloride

10 WITHDRAWAL

Patients will be withdrawn for any of the following reasons

1. Patient choice.
2. Intolerance to study drugs.
3. Co-trimoxazole related haematological disease (e.g. blood dyscrasia, thrombocytopaenia).

11. ADVERSE EVENTS ANDADVERSE REACTIONS

The local investigator at the study site is responsible for the detection and documentation of events meeting the criteria and definition of adverse events or adverse reactions including reporting to the sponsor.

11.1.1 "adverse event" (AE) means any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

11.1.2 "adverse reaction" (AR) means any untoward and unintended response in a subject to an investigational medicinal product, which is related to any dose administered to that subject.

11.1.3 "serious adverse event" (SAE) or "serious adverse reaction" (SAR) or "unexpected serious adverse reaction" means an adverse event/reaction that fulfils at least one of the following criteria:

A) Results in death

B) Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe

C) Requires hospitalisation or prolongation of existing hospitalisation

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the GP clinic or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

D) Results in persistent or significant disability or incapacity or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

E) Consists of a congenital anomaly or birth defect

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.1.4 "unexpected adverse reaction" means any adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product, or summary of product characteristics [SMPC] for an authorised product).

11.1.5 Severity: The term "severe" is used to describe the intensity of a specific event. This is not the same as "serious" which is based on patient/event outcome, or action criteria.

11.1.6 "Suspected Serious Adverse Reaction (SSAR)"

Means an adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question set out

(a) In the case of a licensed product, in the summary of product characteristics (SMPC) for that product
(b) In the case of any other investigational medicinal product, in the Investigator's brochure (IB) relating to the trial in question.

11.1.7 "Suspected Unexpected Serious Adverse Reaction (SUSAR)"
means an adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out

(a) In the case of a licensed product, in the summary of product characteristics (SMPC) for that product
(b) In the case of any other investigational medicinal product, in the Investigator's brochure (IB) relating to the trial in question.

11.2.1. Clinical Laboratory Abnormalities and Other Abnormal Assessments
Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, and vital signs) that are judged by the investigator as **clinically significant** will be recorded as AEs or ARs if they meet the definition's above. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or ARs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or ARs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

11.3. Time Period, and Frequency of Detecting AEs and ARs
From the time a subject consents to participate in the study until he or she has completed the study (including any follow-up period), all SAEs assessed as related to study participation (e.g., protocol-mandated

procedures, invasive tests, or change in existing therapy) will be reported promptly to the principle investigator.

11.4. Reporting of Adverse events
In compliance with Article 16 of the European Directive 2001/20/EC, the investigator will report all SAEs promptly to the sponsor (Ms Sue Steel, RBS, UEA, Norwich Fax 01603 591550) within 24 hours of being identified. The immediate report will be followed by detailed written reports. The immediate and follow-up reports will identify subjects by unique code numbers assigned to the latter. The investigator will report AE's to the sponsor within 3 months. For reported deaths of a subject, the investigator shall supply the sponsor and the Ethics Committee with any additional information requested. The sponsor shall keep detailed records of all adverse events which are reported to him by the investigators. These records shall be submitted to the Medicines and Healthcare Products Regulatory Agency, UK if they so request.

11.5 Reporting of Serious adverse reactions
11.5.1 In compliance with Article 17 of the European Directive 2001/20/EC, the sponsor (Ms Sue Steel, RBS, UEA, Norwich) shall ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the Medicines and Healthcare products Regulation Agency (MHRA), the Data Monitoring and Ethical Committee (DMEC) and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

11.5.2 All other suspected serious unexpected adverse reactions shall be reported to MHRA, DMEC and Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor (Ms Sue Steel, RBS, UEA, Norwich).

11.5.3 The sponsor shall also inform all investigators.

11.5.4 Once a year throughout the clinical trial, the sponsor (Ms Sue Steel, RBS, UEA, Norwich) shall provide the MHRA, DMEC and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

12 STATISTICAL ANALYSIS

There will be central randomisation with stratification for baseline treatment at entry into the study. The primary endpoint will be the change in Forced Vital Capacity (ml) from baseline to 12 months of therapy. Assuming a residual SD of 400ml (from data from ISOLDE and TRISTAN study courtesy of J. Anderson, GSK, Greenford), then with 63 patients in each group this study has an 80% power to detect a mean difference of 200ml at a significance level of $p = 0.05$. The value of 200ml for the mean difference in FVC from baseline was used to power the study since this represents the minimum change required for a favourable or unfavourable response to treatment as proposed in the ATS/ERS International Consensus statement (1999). The study will be analysed on an intention to treat base. A mixed-effect model with centre and centre-by-treatment included as random effects with outcomes FVC, FEV1, FV6, 6 min walking distance, change in oxygen saturation during 6 minute walk, MRC, Borg dyspnoea and SGRQ scores, steroid dose, total lung diffusion capacity of carbon monoxide and total lung volume. This assumes the baseline values are similar for both groups, if they are not a suitable adjustment will be used. This also assumes that the residuals will be normally distributed, if this is not the case then a suitable transformation will be used. An adjustment may also be used if a the correlation between baseline and the final value is high The number of patients with abnormal renal function, liver function or full blood count or the number of patients with a significant escalation in therapy, adverse event or hospitalisation in each group and the number of deaths in each group will be compared using a chi squared test.

A cost-effectiveness and cost-utility analysis will be performed to determine the costs and outcomes (point improvement in FVC and QALYs gained) of treating a patient with or without co-trimoxazole, measured from the viewpoints of both the health service and society. Health service costs will be taken as drug costs, hospital costs and GP practice costs. The societal analysis will include NHS costs plus costs arising from social care providers, patient out of pocket costs and informal carer time.

Quality Adjust Life Years (QALYs) will be calculated by converting the EQ-5D questionnaire results into utilities using UK health state valuations(23), then measuring the resulting area under the curve.

A point estimate of the Incremental Cost Effectiveness Ratio (ICER) will be calculated and confidence intervals around differences in cost and outcome generated using a non-parametric bootstrap approach. The results will be presented as a cost-effectiveness acceptability curve.

13 STUDY CONDUCT CONSIDERATIONS

13.1 Regulatory considerations

The study will also be conducted in accordance with "good clinical practice" (GCP), all applicable subject privacy requirements, and, the guiding principles of the Declaration of Helsinki. This includes, but is not limited to, the following:

- MREC review and favourable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Subject informed consent
- Investigator reporting requirements

Written informed consent will be obtained for each subject before he or she can participate in the study.

13.2. Quality Control (Study Monitoring)

This study will be managed by the East Anglia Thoracic Society (EATS) clinical fellow. The EATS fellow will have training in Good Clinical Practice. Prior to enrolment of a site, the EATS fellow will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory and ethical requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

A monitoring committee will be formed and will monitor the study consistent with the demands of the study and site activity to verify that the:

- All outcomes and resource use data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

13.3 An independent trial steering committee will be formed. It will be comprised of an Independent Chairman (no direct trial involvement), two additional independent expert members, Chief Investigator and a patient/lay representative

13.4 A data monitoring and ethical committee will comprise a statistician and a researcher with special interest in interstitial lung disease. This committee will monitor the serious adverse events and mortality.

13.5 Contacting patients after the end of their participation in the study

For the purpose of accurate data collection and follow up of adverse events and reactions reported by the patients at the last visit of the study, patients might need to be contacted after their last study visit. It will be aimed at doing this as soon as possible when it is identified that some questionnaire questions are not filled in or in terms that are felt by the attending team to be relevant when a follow up of AE/AR is required. Patients will be contacted either over the phone or in writing. The status of a patient will be checked with hospital Patient Administration System (PAS) first to ensure that families of deceased patients are not disturbed.

Time and events table

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	0	6 weeks	6 months	9 months	1 year
Consent	**X**				
History & Examination	**X**	X	**X**	**X**	**X**
Drug dispensed	**X**	**X**	**X**	X	
Adverse events	**X**	**X**	**X**	**X**	**X**
Concomitant medication	**X**	**X**	**X**	**X**	**X**
Spirometry	**X**	**X**	**X**	**X**	**X**
MRC score	**X**	**X**	**X**	**X**	**X**
FBC, U&E, LFT	**X**	**X**	**X**	**X**	**X**
6 Min Walk	X		X		X
SGRQ	**X**		**X**		**X**
DLCO	X		X		X
TLC	**X**		**X**		X
KL-6	X		X		X
EQ-5D	**X**	**X**	**X**	X	X
Socioeconomic status questionnaire	**X**				
Cost questionnaire - baseline	**X**				
Cost questionnaire – follow-up		**X**	**X**	X	X

Bold indicates measurements that will be performed in all subjects. Other measurements are will be performed in a subgroup of patients.

Appendix 4

LOCAL HOSPITAL HEADED PAPER TO BE USED

PATIENT INFORMATION SHEET

PART 1

1. Study title:
The efficacy and safety of co-trimoxazole therapy in patients with idiopathic interstitial pneumonia TIPAC Study

2. Invitation paragraph
We are inviting you to participate in a research study being conducted by Chief Investigator, Dr Andrew Wilson, and his colleagues. Before you make your decision it is important for you to understand why the research is being done and what it would involve for you if you took part.
Your participation in this study is entirely voluntary. If you decide not to take part, or want to withdraw at any stage without giving a reason, you can do so without this affecting the standard of care that you receive.
Please take time to read this information and discuss it with your GP or relatives or friends.

- Part 1 of this information sheet tells you the purpose of the study and what would happen if you took part,
- Part 2 gives more detailed information about how the study will be conducted.

3. What is the purpose of the study?
The purpose of this study is to investigate whether the use of an antibiotic (called co-trimoxazole) improves the breathing function of patients with pulmonary fibrosis .

4. Why have I been chosen?
You have been chosen because you have a lung condition called pulmonary fibrosis (also called idiopathic interstitial pneumonia). If you agree to participate, you will be one of 180 patients from England and Wales who are helping with this study.

5. Do I have to take part?
It is up to you to decide. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show that you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

6. What will happen to me if I take part?
When we don't know which way of treating patients is best we need to compare the new way of treating you with the old way. The best way to do this is to put people into groups and give each group different treatment. The results are then compared to see if one is better. To try to make sure the groups of people are the same to start with, each patient is put into a group by chance (randomly). This is like tossing a coin to decide which group you will be in. You will have an equal chance of getting the co-trimoxazole treatment or the placebo. A placebo is a 'dummy treatment' that looks like the genuine medicine but contains no active ingredient.

7. What do I have to do?

PLEASE READ APPENDIX 1 – INFORMATION ABOUT CO-TRIMOXAZOLE

You will be invited to attend for a screening visit at the clinic. At the visit you will have some breathing tests done, a test to see how far you can walk in 6 minutes, a blood sample will be taken and you will be asked some questions about your breathing. The breathing tests will be the same ones that you usually have when you attend the Respiratory Clinic ie no additional breathing tests will be necessary. They will include a forced breathing test when you have to breathe hard and a gentle breathing test – you may need to enter a Perspex box for this test. The questionnaires are

standard questionnaires and will not take long to complete. During the 6 minute walking test you will have to walk as fast and as far as you can. During this test we will measure the oxygen in your blood by clipping a peg on your finger. You will also have a heart wave tracing done. You will be given a short questionnaire to complete that asks questions about your employment etc and about your contact with the NHS - doctors, nurses, hospital, etc

There is a rare condition, that only effects males, which causes their red blood cells (oxygen carrying cells in the blood) to break up if they are exposed to certain medications including co-trimoxazole. We therefore are required to take a blood test from all male patients who are interested in helping with the study to check that they do not have this condition before they take the study medication. If you are a man then we will need to take an additional blood test during the screening visit. If you are shown to be positive for this condition then we will refer you to a specialist haematologist for further information/advice.

You will then be allocated to either receive the active drug or the dummy drug, which you will need to take in the morning and at night. You will also be prescribed with a vitamin called Folic acid which you will need to take in the morning which will help to protect your bone marrow (which produces blood cells) from potential rare risk of affecting the number of certain blood cells. You will then be followed up in the clinic in the normal way. After six weeks, 6 months and 9 months of taking the study drug you will be asked to return to the clinic for a blood test, a breathing test and to complete a short questionnaire. After twelve months of taking the study drug you will be invited back to the clinic to repeat the tests that were done at the beginning of the study.

You will need stop taking the study medication and contact your hospital consultant or family doctor immediately if you experience:

- Sudden wheeziness or difficulty in breathing
- Swelling of the eyelids, face or lips
- Blisters with a skin rash

8. What is the drug being tested?
Co-trimoxazole is an antibiotic that is used routinely to treat and prevent certain types of respiratory infections.

9. What are the alternatives for treatment?
You will already either be receiving optimal (best possible) treatment for your condition or not be on any treatment but be followed up by your Consultant to ensure early signs of deterioration are picked up and acted on so the study drug will be in addition to your usual medication (if you are taking any). You will not be excluded from taking any recommended treatment for your condition.

10. What are the possible disadvantages and risks of taking part?
You may not get the active treatment and may receive the dummy treatment.
The active drug (co-trimoxazole) sometimes causes unwanted effects in some people. We have classified these into common, less common and very rare to give you an idea of the chances of an unwanted effect occurring. However all side effects are listed in the patient information sheet which comes with the tablets.

Common:	Nausea, Diarrhoea, Headache, Rash
Less common:	Thrush, Vomiting
Very Rare	Sore mouth, Lack of appetite, Problems with liver, pancreas, lungs, intestine or kidneys, Depression, fits, nerve problems, dizziness, ringing in ears Blood cell and chemical abnormalities or a serious skin rash

If you experience any unwanted side-effect, either those mentioned above or not, you should contact your hospital consultant or family doctor.

It is likely that you will require increased monitoring of your blood clotting tests if you are receiving warfarin.

There is an increased risk of a problem with your blood cells, liver and kidney tests if you take co-trimoxazole and azathioprine or mycophenolate mofetil together. Although this risk is low the effects may be severe and therefore we will increase the monitoring of your blood count from every

four weeks (required for azathioprine or mycophenolate treatment when given alone) to every two weeks. You will also have an additional liver and kidney test two weeks after starting a study drug.

It may be necessary for you to attend the hospital on visits in addition to your clinic visit. If you are required to make an additional visit, we will reimburse your traveling expenses at a rate of 22p/mile if traveling by car or bus/train/taxi fares against receipts if using public transport

11. What are the possible benefits of taking part?
It cannot be guaranteed that the active drug will improve your breathing and ability to exercise, although we think that it might.

12. What happens when the research study stops?
Co-trimoxazole is not currently used to treat patients with pulmonary fibrosis however if we find out that you have been taking co-trimoxazole and that you have had a noticeable benefit from it your doctor may be in a position to prescribe it for you. If you are taking the dummy tablet and the results of this study are very encouraging your doctor may prescribe it for you. If the results are disappointing then you would continue with your usual treatment.

13. **What if something goes wrong**?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. (Further detailed information in Part 2).

14. Will my taking part in this study be kept confidential?
Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

15. Contact details
If you have any queries about your participation in this study, please contact one of the following.

Dr……..,
Consultant Respiratory Physician, Tel: ……..…

Dr Ludmila Shulgina
Study co-ordinator Tel……

If the information in Part 1 has interested you and you would consider participating please read the additional information in Part 2 before making a decision

PART 2

16. **What if new information becomes available?**
Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study he may ask you to sign an updated consent form.

17. **What will happen if I don't want to carry on with the study?**
If you decide at some point that you no longer wish to take part in the study, you may withdraw at any time. You may decide that you no longer want to take the study medication, but we would still ask that you return for your follow-up visits at 6 and 12 months after starting treatment, but you are not obliged to do so.
If you withdraw from the study, we will destroy all your identifiable samples, but we will need to use the data collected up to your withdrawal.

18. What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from your hospital.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed during the research due to someone's negligence then you may have grounds for legal action for compensation against your hospital, but you may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you.

19. Will my taking part in this study be kept confidential?

Your data will be collected by your hospital consultant or members of clinical staff at your hospital and by members of the research team. It will be used to assess whether you have had any benefit or side effects with the study medication. All information that is collected about you during the course of this study will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised. Representatives of the sponsor or the Trust R&D department will have access to identifiable data to ensure the study is being corrected properly. This anonymised information will be accessible to the research team and may also be looked at by representatives of regulatory authorities and by authorized people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant. It will be stored securely and Dr Wilson will be the custodian. It will be kept for your 15 years after which it will be disposed of securely. Use of your data will be in compliance with the Data Protection Act.

With your permission, your GP will be informed of your participation in this study.

20. What will happen to the results of the research study?
This study should be completed by the end of 2010 when a report will be completed and we will also publish our findings in research journals. You will not be named or identified in any way in any report of the study. If you would like information about the results of the study please contact the Principal Investigator named below.

21. Who is organising and funding the research?

This research study is being organised and conducted by Dr Andrew Wilson and is sponsored by The University of East Anglia. The study is supported by a grant from the East Anglian Thoracic Society and the Research for Patient Benefit programme. The study co-ordinator will be Dr Ludmila Shulgina. Dr Shulgina will be working on this study as part of an educational qualification. Your Doctor is not being paid for including you in this study.

22. Who has reviewed the study?
This study was given a favourable ethical opinion for conduct in the NHS by the Cambridgeshire 4 Research Ethics Committee.

23. Contact for further information
If you have any queries about your participation in this study, please
contact one of the investigators (contact details below).

Principal Investigator:

Co-investigator:

Dr Ludmila Shulgina
Study co-ordinator
Tel……
Thank you for considering taking part in this study!

If you decide to participate you will be asked to sign a consent form and given a copy of this information sheet and consent form to keep.

APPENDIX 4.1

INFORMATION ABOUT CO-TRIMOXAZOLE – adapted from datasheet

- Please read this leaflet carefully before you start to take your medicine.
- It gives you important information about your medicine.
- If you want to know more, or you are not sure about anything, ask your pharmacist or doctor.
- Keep the leaflet until you have finished the medicine.

What's in co-trimoxazole

One of the active ingredients in this medicine is Sulfamethoxazole.

This is the new name for Sulphamethoxazole.

The ingredient itself has not changed.

ABOUT YOUR MEDICINE

Before taking your medicine

Do not take Co-trimoxazole tablets if you:

- are sensitive to any of the ingredients in the product
- have severe liver damage or are jaundiced (yellowing of the skin and whites of the eyes)
- have any blood disorder. If you keep getting infections or nosebleeds or notice any unusual bruising tell your doctor
- have the metabolic disease porphyria
- have severe kidney damage or disease
- are giving the tablets to children under 6 years as they are not suitable. Co-trimoxazole must not be given to new born babies under 6 weeks of age.

Check with your doctor or pharmacist before taking Co-trimoxazole tablets if you:

- have a history of severe allergic reactions or bronchial asthma
- have been told you have a reduced amount of the enzyme glucose 6 phosphate dehydrogenase. You may react badly when you eat certain types of foods such as fava beans
- have a protein disorder called phenylketonuria
- have Group A beta-haemolytic streptococcia (a bacterial infection)
- are elderly as you may suffer with more side effects.

Check with your doctor or pharmacist if you are taking any of the following:

- ace inhibitors used to treat high blood pressure (e.g. captopril, lisinopril)
- anaesthetics such as prilocaine
- antiarrhythmics used to treat some heart conditions such as procainamide, amiodarone, dofetilide
- antibiotics such as rifampicin, dapsone, methenamine
- anticoagulants drugs used to prevent your blood clotting (eg warfarin)
- sulphonylureas used to treat diabetes
- phenytoin used to treat epilepsy
- pyrimethamine used to treat malaria
- antivirals such as lamivudine, zidovudine, zalcitabine
- amantidine used to treat parkinsonism or some viral infections

- clozapine used to treat mental health problems
- cytotoxic drugs such as methotrexate, azathioprine, mercaptopurine (used to treat some cancers, severe psoriasis or severe rheumatoid arthritis)
- cardiac glycosides (used to treat heart conditions e.g. digoxin)
- diuretics such as bendroflumethiazide or hydrochlorothiazide
- ciclosporin used to prevent rejection after transplantation
- potassium aminobenzoate
- any other medicines that you have bought without a prescription.

Driving and using machines:

Co-trimoxazole tablets may make you feel drowsy or dizzy, see things that are not there, cause ringing in the ears or sleeplessness. Make sure you are not affected before you drive or operate machinery.

- You MUST STOP taking the tablets immediately and contact your doctor if you experience sudden wheeziness, breathlessness; swelling of the eyelids, face or lips; or blisters and a skin rash.

If you see another doctor or go into hospital, let them know what medicines you are taking because Co-trimoxazole tablets may effect some medical tests. Please tell them that you are participating in a clinical study under the supervision of …….. phone number……

TAKING YOUR MEDICINE

Swallow the tablets preferably with food or a drink at the same times each day. This medicine should be taken for as long as your doctor tells you to, it may be dangerous to stop without their advice.

If you (or someone else) swallow a lot of the tablets at the same time, or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty unit or tell your doctor immediately. Please tell them that you are participating in a clinical study under the supervision of …….. phone number……

If you forget to take a dose, take one as soon as you remember, unless it is nearly time to take the next one. Never take two doses together. Take the remaining doses at the correct time. DO NOT take two doses at the same time.

If you are worried ask your pharmacist or hospital consultant or family doctor for advice.

TAKING YOUR MEDICINE

This medicine sometimes causes unwanted effects in some people. These effects may include skin rashes, these can be serious. If you get a skin rash you must stop taking the tablets and consult your doctor immediately. These skin rashes may be itchy, red or your skin may become sensitive to light.

Effects on the blood: co-trimoxazole can alter the number and type of certain blood cells. If you get increased bruising, nose bleeds, sore throats or infections you should consult your doctor.

Allergic reactions: these can be serious, if you notice any symptoms such as swelling, difficulty breathing or fever tell your doctor. Other allergic reactions can include inflamed heart or blood vessels, fever and systemic lupus erythematosus (SLE characterised by skin rash, hair loss, difficulty breathing and joint pains).

Aseptic meningitis can occur in some patients. This may show as a combination of symptoms such as headache, fever, stiff neck, tiredness, feeling ill and your eyes become very sensitive to bright light. If you experience any of these symptoms seek medical attention immediately.

Effects on the nervous system: headaches which may be severe, depression, dizziness, giddiness, hallucinations (seeing things that are not there), fits, lack of co-ordination, numbness of fingers or toes, drowsiness, fatigue, sleeplessness and increase pressure in the skull. Consult your doctor if any of these effects are severe or prolonged.

Effects on the stomach: feeling or being sick, diarrhoea, loss of appetite and sore tongue or mouth and rarely colitis.

Effects on the liver: rare but serious effects can include jaundice, changes in liver function and liver damage or an inflamed pancreas. If you notice yellowing of your skin or eyes, get severe diarrhoea or severe abdominal pain you should consult your doctor immediately.

Other effects: cough, difficult or painful breathing, sensitivity to light, vertigo, ringing in the ears, overgrowth of some fungal organisms, kidney damage, crystal in the urine and changes in body chemicals (especially potassium and sodium) can also occur. If you have difficulties passing water, pain or blood in your urine, or difficulties breathing tell your doctor.

If you are concerned about any of these effects or get any other unusual effects, tell your doctor or pharmacist immediately.

STORING YOUR MEDICINE

Do not use the tablets after the end of the expiry month shown on the product packaging.

- Keep the tablets stored below 25°C in a dry place and protected from light
- Do not transfer them to another container.
- Keep CO-TRIMOXAZOLE out of the reach and sight of children in a secure place.
- Remember that this medicine is for you only. Never give it to anyone else. It may harm them, even if their symptoms are the same as yours.
- Return all unused medicines to your pharmacist for safe disposal.

Appendix 5

LOCAL HOSPITAL HEADED PAPER TO BE USED

PATIENT CONSENT FORM

Patient Identification Number for this trial:

Title of Project:

Treating Interstitial Pneumonia with the Addition of Co-trimoxazole (TIPAC) Study

.

Name of Researcher: Dr Andrew M Wilson

Please initial box

1. I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3 I give permission for my General Practitioner to be informed about my participation in the study ☐
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
5. I agree for my data to be stored securely in an anonymised form ☐
6. I agree to undergo screening for glucose-6-phosphate deficiency (males only) ☐
7. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes Version 3 13 August 2007

Appendix 6

ILD PROFORMA

Patient's name_____

Demographics

DOB_____
Age_____
Race: Caucasian☐ African Descent ☐
Mediterranean ☐
Other_____(specify)
Weight_____(kg) Height_____(cm)
Gender: F☐ M☐

Smoking history
Never smoked☐
Ex-smoker☐
Current smoker ☐

Pack-years _____
Year started_____ Year finished_____

Respiratory hazard

Inorganic:	Organic:
1. Asbestos: • Construction worker • Shipyard worker • Power station construction • Maintenance worker • Naval boiler man • Garage worker (brake lining) • Joiner • Electrician • Carpenter 2. Coal mining 3. Metal exposure 4. Sandblasting 5. Talc 6. Aluminium oxide 7. Wood work 8. Other	1. Birds (describe, length of exposure) 2. Farmers lung 3. Sugar cane 4. Coffee 5. Tobacco (tobacco growers lung) 6. Fishmeal (fishmeal worker's lung) 7. Mushroom 8. Maple bark stripper 9. Malt 10. Tea grower 11. Cheese 12. Wine 13. Other

Occupational history (see respiratory hazard box above)

Employer	Job type, activities	Occupational hazard	Respiratory protection	Respiratory symptoms at the time

Domestic/environmental exposure
(See respiratory hazard box above, **including exposure to domestic mould and humidifiers)**
_____
_____

Spouse employment_____
_____

Hobbies:
Birds Yes ☐ No ☐
age of exposure_____duration of exposure_____birds indoors/outdoors
respiratory symptoms at the time Yes ☐ No ☐
Isocyanates, age and length of exposure
Other (see respiratory hazard box above)_____

Family history of ILD_____ _____
Family history of CTD_____

Medical history other than possible ILD

Diagnosis	Details
Previous malignancy Tx with Radiotherapy +/-Chemotherapy	
Connective tissue disease	
Inflammatory bowel disease	
Cardiac disorders	
Other	

Drug history

Drug	**Dose and duration of Tx**	**Respiratory symptoms at the time of drug use**
Nitrofurantoin		
Disease modifying antirheumatic drugs(Sulphasalazine, MTX, Gold, Penicillamine, Leflunomide, Etanercept)		
Cardiovascular (Amiodarone, ACEI, Statin)		
Chemotherapeutic agents (bleomycine, Cyclophosphamide)		
Ilicit drugs (heroin, methadone, talc)		
Miscellaneous (oxygen, radiation, aspirin, interferons)		
Over the counter/herbal medicines		

Clinical symptoms/examination at Diagnosis

Respiratory symptoms (list):	**Connective tissue disease symptoms:**	
	Ocular symptoms Sicca symptoms Oral ulcers Alopecia Recurrent fevers Weight loss Photosensitivity Raynaud's phenomenon	Skin thickening Rash Teleangiectasia Arthralgia Myalgia Proximal muscle weakness Dysphagea/acid reflux
Cyanosis Yes☐ No ☐ *Finger clubbing* Yes☐ No ☐ *SaO2_____(%) on_____l/min*	*Auscultation of the chest* Wheeze☐ Crepitations☐ Other(specify)_____ *Auscultation of precordium* _____ *Hepatomegaly* Yes☐ No ☐ *Peripheral oedema* Yes☐ No ☐	

MRC dyspnoea grade: _____ (use table for guidance)

Grade	*Degree of Breathlessness Related to Activities*
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness or has to stop for breath when walking at own pace
4	Stops for breath after walking about 100 meters or after a few minutes on level ground
5	Too breathless to leave the house or breathless when dressing or

Autoantibodies

RhF, result_____
ANA_____negative ☐ positive ☐ Titre_____
In patient with raised ANA titre is **Lupus Anticoagulant** Positive ☐ Negative ☐
In patient with raised ANA titre are **Anticardiolipin Antibodies** Positive ☐ Negative ☐
Anti-double stranded DNA (dsDNA) Antibodies: Negative ☐ Positive ☐ Titre_____
ENA Negative ☐ Positive ☐
Anti-SSA (Ro) Antibodies Negative ☐ Positive ☐
Anti-SSB (La) Antibodies Negative ☐ Positive ☐
Anti-Sm Antibodies Negative ☐ Positive ☐
Anti-RNP Antibodies Negative ☐ Positive ☐
Anti-Scl-70 Antibodies Negative ☐ Positive ☐
Anti-Jo 1 Antibodies Negative ☐ Positive ☐
Cryoglobulins checked Yes ☐ No ☐
ESR_____ CRP_____ Avian Precipitins Positive ☐ Negative ☐ Framers Lung precipitins Positive ☐ Negative ☐

Lung function tests

6 Minute Walk at diagnosis

Distance_____(metres) Max SaO2_____% Min SaO2_____
HRCT requested Yes☐ No ☐

Appendix 7

Study protocol (version 4)

Are alveolar nitric oxide and plasma VEGF markers of disease severity and progression in patients with idiopathic pulmonary fibrosis

Authors

Andrew M Wilson
Ludmila Shulgina
Helen Parfrey

1 Introduction

Interstitial lung diseases (ILD) are a group of lung disorders which may be acute or chronic and can involve varying degrees of pulmonary inflammation and fibrosis(1) The commonest ILD of all is Idiopathic Pulmonary Fibrosis (IPF) with Usual Interstitial Pneumonia (UIP) histology pattern and Idiopathic Nonspecific Interstitial Pneumonia (NSIP). The prognosis is usually poor (median survival of 2-3 years)(2). Patients usually die from gradually progressive disease, some have rapidly fatal course due to acute exacerbation(3). Previously much of the research into ILD had been hampered as there was no uniform international diagnostic criteria or classification of disease. However, the American Thoracic Society and European respiratory society (ATS/ERS)(1) have now published a guideline and joint international consensus statement. The guidelines define IPF as a ‘’progressive chronic ILD of unknown cause associated with histopathologic pattern of UIP’’(4) .

Although the median survival is poor, there is considerable variability in disease progression with only a proportion of patients showing evidence of decline at 6 and 12 months from diagnosis. Flaherty et al (5) showed that whilst 32% of patients with IPF had a 10% decline in FVC at 6 months and 54% had a similar decline at 12 months, 68% and 31% remained within 10% or had a 10% improvement in their FVC at 6 and 12 months respectively. Even with this enormous variability, the best method to assess disease progression and hence to predict outcome is serial pulmonary function over a 6 to 12 month period. Biomarkers, biochemical tests which predict prognosis or response to treatment, are required to help identify those patients with a good or poor outlook. Two potential biomarerks are exhaled nitric oxide or vascular endothelial growth factor (VEGF).

Current concept of pathogenesis of IPF suggests that repetitive injury to alveolar epithelium and endothelial injury causes chemokines and growth factors release which in turn drives recruitment of fibroblasts and endothelial cells which leads to collagen-matrix remodelling with little evidence of inflammation. Nevertheless there is evidence of inflammatory cell involvement with an alveolar septal infiltrate of lymphocytes, plasma cells, and histiocytes associated withtype II pneumocytes hyperplasia (ATS/ERS consensus Classification). It is thought that free radicals are involved in the role of fibrogenesis of human lungs in ILD and the activation of inflammatory cells leads to the production of reactive oxygen species: a strong expression of nitrotyrosine (a byproduct of protein nitration caused by a potent oxidant peroxinitrate) and nitric oxide synthase is seen in macrophages, neutrophils and alveolar epithelium of lungs of patients with early to intermediate stage of IPF compared to normal control subjects(6).

NO is a gaseous signalling molecule and can act as a bronchial and vascular smooth muscle dilator(7). NO is produced by constitutive NO synthases (cNOS) in the physiological state and during inflammation inducible NO synthase (iNOS) is produced in higher quantities(8). Previous studies of patients with asthma show that inhaled steroids reduce the levels of exhaled NO in the asthmatic airways, that these levels correlate well with the disease activity in a form of sputum eosinophilia and that they could well be used successfully to guide titration of the dose of inhaled steroids(9).

Although a number of studies have investigated the role of exhaled NO in patients with systemic sclerosis with and without its complications in a form of interstitial lung disease and/or pulmonary hypertension, in patients with asbestosis(10) and stage 1-4 sarcodosis(8); there is a paucity of research investigating the role of NO in patients with idiopathic pulmonary fibrosis. Some of this studies looked at alveolar rather than total exhaled NO. Modley et al(11), demonstrated that alveolar NO was elevated in patients with scleroderma without ILD compared to those with ILD suggesting presence of subclinical inflammation (confirmed by higher neutrophil and eosinophil count in broncho-alveolar lavage fluid in Scleroderma patients compared to healthy controls) before the clinical and radiological evidence of it becomes apparent. Girgis et al(2) demonstrated increased concentrations of alveolar NO in Scleroderma patients with ILD with and without concomitant pulmonary hypertension. It had also been shown that in patients with scleroderma the levels of alveolar NO are related to the extent of ILD as evidenced by the CT scan fibrosis score and inversely related to the severity of ILD as evidenced by diffusing capacity for carbon monoxide(12;13). Alveolar NO has been suggested for use as a noninvasive marker for assessment of severity of inflammation in asbestosis(10).

A study by Paredi et al(14) showed that patients with fibrosing alveolitis had elevated total exhaled NO levels and this correlated well with activity in broncho-alveolar lavage fluid (as indicated by any of the following: lymphocytes >14%, neutrophils >4%, eosinophils >3%); patients treated with corticosteroids had lower levels of NO than untreated patients. Lehtimaki et al's(7) study of patients with IPF suggests that there was an increased alveolar concentration of NO in patients with IPF and that it correlated negatively with DLco percentage of predicted which is a marker of disease severity.

Vascular endothelial growth factor (VEGF) is a potent mediator of vascular regulation in angiogenesis and vascular permeability(15). Plasma concentrations of VEGF correlate with HRCT thoracic scan fibrosis scores(16). In support of its role in the development of pulmonary fibrosis, a VEFG receptor antagonist attenuated bleomycin-induced lung fibrosis in a murine model(17). Although its concentration is higher in patients with progressive disease (defined as those with a 10% change in FVC after 6 months), the usefulness of VEGF as a survival indicator has not been evaluated.

2 Objectives

Is there an association between the disease severity (as assessed by DLco) of patients with idiopathic pulmonary fibrosis and alveolar NO or plasma VEGF?

Is there an association between alveolar NO and/or plasma VEGF and disease progression (as measured by % change in FVC) at 6 and 18 months?

3 Methods

3.1 Study design

This is a prospective observational study to evaluate the concentration of small airways nitric oxide and levels of vascular endothelial growth factor in 30 patients with idiopathic pulmonary fibrosis and relate this to pulmonary function measures of disease severity and progression. Participants will be identified from clinical notes of patients with ILD attending the respiratory out patients department at the Norfolk and Norwich University Hospital NHS Trust (NNUH) and will be approached by their attending physician. Patients will attend the clinic for a screening visit and baseline measurements including history, medical examination, and assessment of alveolar nitric oxide, and a venepuncture to collect blood for VEGF analysis, following informed consent. All other data will be obtained from the medical notes. Patients will attend clinic for visit 2 which will take place between four and eight months and visit 3 which will take place between sixteen and twenty months after the screening visit for repeat pulmonary function tests, repeat NO measurements and blood collection for VEGF levels(4 months time span for each follow up visit will be given to permit study visits to coincide with routine medical review). General Practitioners (GP) responsible for patients care will be informed of the patients participation in the study by the means of GP letter.

Clinical Assessment

A full medical history and examination will be undertaken. Details of age, gender, diagnosis, length of diagnosis, time of onset of illness (first noticed breathlessness), main symptom (e.g. breathlessness, cough), treatments, environmental exposure to known aetiological factors, drug

history, key examination findings, autoantibody screen including rheumatoid factor will be obtained. A blood sample will be taken and plasma stored for subsequent analysis of VEGF.

Review of Medical Notes

A review of the medical notes will be completed to ensure they meet the entry criteria. Details of previous pulmonary function tests, from time of diagnosis, including spirometry and gas transfer will be obtained from the clinic notes or pulmonary function laboratory database.

Exhaled Nitric Oxide

This will be measured using a NIOX nitric oxide analyzer at visit 1 and 2 (Aerocrine, Chicago, Illinois USA), with an expiratory flow rate of 50ml/sec according to American Thoracic Society guidelines (18). The mean of three separate measures of nitric oxide will be used in the analysis. In addition, measurements will be made at expiratory flow rates of 30, 100 and 200 ml/sec. The analyser will be calibrated daily using a cylinder of nitric oxide at concentration of 208ppb. At visit 3 nitric oxide will be measured using a NIOX mino rather than NIOX machine as the NIOX machine is no longer serviced and is not safe for patient use as of March 2011. Niox mino is the a calibration and maintenance free device with built in control that displays measurement results from correctly performed procedures only, it measures nitric oxide with an expiratory rate of 50ml/sec according to American Thoracic Society guidelines (18).

Vascular endothelial growth factor (VEGF)

Levels of VEGF in plasma will be assessed using a commercially available validated VEGF ELISA kit.

Assessment of disease severity

This will be based on assessment of impairment of diffusing capacity for carbon monoxide (DLco) as a well recognised marker of disease severity (levels below 40% of predicted value reflect severe disease). This will be performed, as required for routine clinical assessment, at the same time as the measurement of exhaled nitric oxide and VGEF

Assessment of disease progression.

This is based on percentage change in Forced Vital Capacity (FVC) within 6 to 18 months of follow up. All patients with pulmonary fibrosis undergo routine pulmonary function assessment (forced vital capacity and gas transfer) at least annually. Details of pulmonary function will be obtained from the respiratory department pulmonary function database. Date and cause of death will be obtained from medical records.

3.2 Sample size estimation

This study is a pilot study and the results from the study could potentially provide information for a future study which will enable a power calculation. Thirty patients should be sufficient to gain sufficient data for this study.

3.3 Patient Recruitment

3.3.1 Inclusion criteria

1. male or female: aged greater than 40 years
2. able to provide informed consent
3. Clinically labelled diagnosis of fibrotic idiopathic pulmonary fibrosis with HRCT scan features compatible with Usual Interstitial Pneumonia (UIP) or Fibrotic Non-specific Interstitial Pneumonia (NSIP) according to current guidelines(19)

3.3.2 Exclusion criteria

1. A secondary cause for pulmonary fibrosis including a diagnosis of asbestosis, drug induced pulmonary fibrosis, collagen vascular disease or other secondary pulmonary fibrosis.
2. A recognised significant co-existing respiratory disorder.
3. A respiratory tract infection within the last 2 months.
4. Significant medical, surgical or psychiatric disease that in the opinion of the patients' attending physician would affect subject safety or influence the study outcome.
5. Women who are pregnant or are breast-feeding as pregnancy itself might alter levels of VEGF(20)
6. Patients with clinical evidence of right heart failure
7. Current smokers

4 Ethics

Research governance and ethical committee approval will be obtained before commencement of the study. Written informed consent will be obtained from all participants involved in the study (appendix 2). Patients will be given a unique identification number and no-patient identifiable information will be available. All data will be stored at the NNUH which will be password protected and only accessible by student, supervisor and a study co-ordinator. The study will be conducted at the NNUH and no patient identifiable data will leave the NNUH site. The investigations are not onerous but do require the patient to blow at a predetermined flow. Some patients may become light headed during the procedure and they will be given time to recover. Patients might have a bruise at a venepuncture site.

5 Data analysis and statistical analysis:

Alveolar NO will be calculated using a linear interpolation of the NO versus flow curve as described by George et al(21). Linear regression analysis (using Pearson correlation coefficient or Spearman's rank correlation coefficient) will be used to evaluate relationship between alveolar NO/VEGF and (1) gas transfer corrected for alveolar volume and (2) 6 and 12 months decline in FVC in the preceding year and (3) a decline in FVC in the forthcoming 6 months and 18 months.

A T test or distribution-free tests will be undertaken to compare the differences between patients with or without a decline in FVC greater or less than 10% from previous records. Multivariate analysis will be used to investigate the contributing role of previous smoking, age and gender. All statistical analysis will be completed using statistical analysis using SPSS (Statistical Package for the Social Sciences).

Appendix 8

PATIENT INFORMATION SHEET

Study title:
Are alveolar nitric oxide and plasma VEGF markers of disease severity and lung function decline in patients with idiopathic pulmonary fibrosis

You are being invited to take part in this research study, but before you decide to do this it is important to understand why the research is being done and what you will be required to do. Please read the information provided carefully and if necessary discuss it with others. If there is any aspect which appears unclear please do not hesitate to ask for more information. Please feel free to take time in deciding whether you wish to participate in the study.

Thank you for reading this.

What is the purpose of the study?

The purpose of the study is to find out how the amount of a gas that patients with pulmonary fibrosis breathe out and a level of certain blood test (marker called Vascular Endothelial Growth Factor, VEGF) compares to patients' breathing tests. We know that the breathing tests of some patients with interstitial lung diseases deteriorate quicker than others. We want to know whether the gas breathed out and a level of blood test can be used to tell which patients will have a quicker deterioration than others.

Why have I been chosen?

You have been chosen because you have a lung condition called pulmonary fibrosis. Thirty patients are required for the study and all these patients must comply with several study entry criteria. These include details of your medical history and surgery you have had in the past and certain examination findings (if you want to know these then we can provide this information).

Do I have to take part?

No, you are not under any obligation to take part. It is completely up to you whether or not you take part and if you do decide to take part you will be given this information sheet to keep along with a consent form that will need signing. If you decide to take part you are still free to withdraw from the study at any time and without giving reason. If you do decide to withdraw from this study this will not affect your future treatment at the respiratory department.

What will happen to me if I take part?

If you enter the study you will be asked to come into the lung function laboratory at the Norfolk and Norwich University Hospital NHS Trust. Here we will assess your breathing tests as you do when you have your outpatient clinic appointments. The test will be slightly different than normal as you will be asked to exhale into the tube at five different flow rates (at visit 1 and 2 only) and at one flow rate at visit 3 so that we can measure the level of the gas we are investigating- nitric oxide.

Before this happens you will have some baseline assessments. These will be:

- Confirming your consent to take part by signing the consent form
- Confirming that you meet all the criteria for the study.
- Collection of information relating to you, your medical history and your lung disease
- Collection of information relating to all the medications you are taking.

We will also take a small sample of blood from you approximately equivalent to a table spoonful which will be analysed for the study.
After an initial assessment you will be invited for the second clinic assessment which will take place between four and eight months and then for the third clinic assessment which will take place

between sixteen and twenty months after your first visit to perform the lung function test. You might spend approximately 1 hour at the department for your first visit and half an hour for the second and third one. We will analyse the results following your initial assessment and then after your second and your final visit.
We would like to ensure the female patients are not pregnant as pregnancy itself might alter levels of VEGF therefore if you are a woman we will ask you to confirm in a consent from that you are not pregnant and are not planning to become pregnant during the period of the study. If you do become pregnant during the study you will be withdrawn from the study but the information collected until then will be used for analysis.

What is being tested?

The study is looking to see whether there is an association with pulmonary fibrosis and the exhaled gas and levels of blood test; and whether the gas and a level of blood test are indicators of how severe the disease is.

What are the possible disadvantages and risks of taking part?

The trial is not intended to cause pain or harm but you may feel tired, breathless or light headed after the test. There are no major disadvantages or risks from taking part in the study. It will be a similar feeling to when you have your yearly lung function test. Taking a blood sample might leave you with a small bruise.

What are the possible benefits of taking part?

There are no direct benefits to you but it is hoped that the study will provide insight and understanding about this group of diseases as there is a lack of information on how and why these diseases progress the way they do. We hope the information will be useful for future studies into this field. It will also give you more information with regards to your condition and this may help you understand the condition better.

What happens when the research study stops?

Once the research is conducted some results will be presented as a part of a student's medical degree as a part of their assessment and subsequently as a part of postgraduate degree of a medical doctor and if the results prove beneficial will be adapted to be published in a journal that will be read by other healthcare professionals.

Once you have completed the study your doctor will continue to manage your interstitial lung disease in the usual way.

What if something goes wrong?

All efforts will be made to prevent injury from participation in the trial, your right to legal action in the event of an injury will not be affected by consenting to the participate in the study. Your right at law to claim compensation for injury where you can prove negligence is not affected. Copies of these guidelines are available on request.

Will my taking part in this study be kept confidential?

All information collected will be made anonymous (your personal data such as name and date of birth will not be used) and you will be given a unique identification number (for example the first patient entering the study will be allocated number 1, the second – number 2 etc) at the start. Data will only be available to those who are involved in the study and stored securely.

With your permission, your GP will be informed of your participation in this study.

What will happen to the results of the research study?

The data collected will be analysed and a report will be written on the findings of the study which will be read by University of East Anglia medical school assessors. If the results prove beneficial there will be potential to submit results to a journal for publication for wider access to other healthcare professionals, you will not be identified in these publications.

Should you decide to withdraw from the study at any time, the information collected on you up to that point will be used in the results of the study.

Who is organising and funding the research?

The Norfolk and Norwich University Hospital NHS Trust (NNUH) Respiratory department will fund the study.

Who has reviewed the study?

The study protocol has been reviewed by the Norfolk and Norwich University Hospitals NHS Foundation Trust, and the Norfolk Research Ethics Committee.

Contact for further information

If you would like to discuss this information in more detail or want further information please contact:

Dr Andrew M Wilson
Senior Clinical Lecturer in Respiratory Health
Biomedicine Group
School of Medicine, Health Policy and Practice
University of East Anglia
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Dr Ludmila Shulgina
Research Fellow
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University of East Anglia
Norwich UK NR4 7TJ
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Email: Ludmila.shulgina@nhs.net

If you decide to take part in this study you will be given a copy of information sheet and a signed consent form to keep.

Thank you for taking the time to read this information leaflet.

Appendix 9

PATIENT CONSENT FORM

Patient Trial Identification Number:

Protocol Title:

Is alveolar nitric oxide a marker of disease severity and lung function decline in patients with interstitial lung disease

Name of Researcher: Dr Andrew Wilson

Please initial box

I confirm that I have read and understood the information sheet dated …….. (version…….) for the above study and have had the opportunity to ask questions.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I understand that sections of any of my medical notes may be looked at by responsible individuals from the study monitors where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐
I give permission for my blood samples to be stored in anonymized form at the Norfolk and Norwich Hospital for further analysis.	☐
I give permission for my General Practitioner to be informed about my participation in the study	☐
I agree for my data to be stored securely in an anonymised form.	☐
I confirm that I am not pregnant, am not planning to become pregnant during the period of the trial, and that if I become pregnant I will notify you and be withdrawn from the trial.	☐
I agree to participate as a part of the above study.	☐

_____	_____	_____
Name of Patient		Signature
	Date	
_____	_____	_____
Name of Person Taking Consent	Signature	Date
_____	_____	_____
Researcher		Signature
	Date	

3 copies, 1 for patient, 1 for researcher and 1 to kept with hospital notes