Efficacy of pharmacological intervention (pirfenidone with N-acetylcysteine) of idiopathic pulmonary fibrosis (2006-2016) - A Meta-analysis

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CHAPTER I: INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF) as the name suggests is a progressive disorder with no known aetiology. It is characterised by the thickening of the alveoli due to scarring resulting in cough. It is known to primarily occur in older adults over 60 years of age. The findings of IPF have a known association of Usual Interstitial Pneumonia (UIP) (Raghu *et al*., 2011; Kawano-Dourado & Kairalla, 2013; Wells, 2013). It has been deemed that the prognosis is generally poor when UIP has been confirmed (King *et al*., 2001b). The median survival rate of IPF is 50%, typically around two years after diagnosis (Raghu *et al*., 2011; King *et al*., 2001b).

The effects of IPF are known to be high in male than male wherein the condition affects patients aged 60. Such prevalence of IPF and its increased over the years are predominant; however, the cause of such a disease could not be clearly specified (Navaratnam *et al*., 2011; Raghu *et al*., 2006c). Furthermore, the prognosis of the disease is also poor wherein the mean estimated survival is between 2 and 5 years. It is further evident from NICE (2013) that the condition has become a focus with the new guidlines set by the UK towards the diagnosis and management of IPF.

IPF which is a condition difficult to manage worsens even further in the latter stages of the disease's progress. Hence it is important for the condition to be diagnosed in the early stages so as to maximise the outcome potential; however, there are no extensive treatment methods available which could increase the outcome of the treatment NICE (2013). Patients with no contraindications require lung transplantation which is the only treatment method for survival (Christie *et al*., 2012). However, with the deficiency in donor organs and shortness of supply of these organs, there is a need to examine the other treatment methods which would modify the rate of mortality and increase the rate of survival.

The mortality rate for IPF is high due to the lack of effective treatment modalities available. High efficacy pharmacological interventions have become the need of the hour in order to effectively treat IPF (Bando *et al*., 2010; Behr *et al*., 2009; Demedts *et al*., 2005; Homma *et al*., 2012; Martinez *et al*., 2014; Tomioka *et al*., 2005) . The main stay management which is the use of anti-inflammatory drugs in conjunction with corticosteroids

have not shown any significant decrease in the mortality rates for patients diagnosed with IPF(Xaubet *et al*., 2003b; Pinheiro *et al*., 2008; Taskar & Coultas, 2006; Lee *et al*., 2011). Other more novel drugs that have been upcoming in the past few decades such as nintedanib, etanercept, warfarin, gleevec and bosetan still present conflicting evidence (Luppi *et al*., 2012). Of this, Pirfenidone is another novel drug that was given approval by the European Medicines Agency (EMA) in 2011 for treating IPF (Behr *et al*., 2009; Taniguchi *et al*., 2010; Jiang *et al*., 2012; Behr & Richeldi, 2013).

There are several researches which attempt to elaborate the mechanisms and the progress of the disease wherein there is still no definitive mechanism identified for the disease. It is hence likely to know that there exist several progressing mechanisms through which the disease progress which further states that no single specific mechanism has been proved to be effective for the treatment. Therefore, though several clinicians and researchers have been examining the disease for decades, the clinical outcomes are still unchanged (Fioret, 2012).

1.1 Background of the Study

The development of two important IPF treatment drugs namely Pirfenidone and NAC has been elucidated briefly by Myllärniemi and Kaarteenaho, (2015) wherein the previous researchers has examined the time frame of development of each of the drug. The time frame elaborated for each of the treatment drug showed variations from their discovery till their initial use for the treatment of IPF.

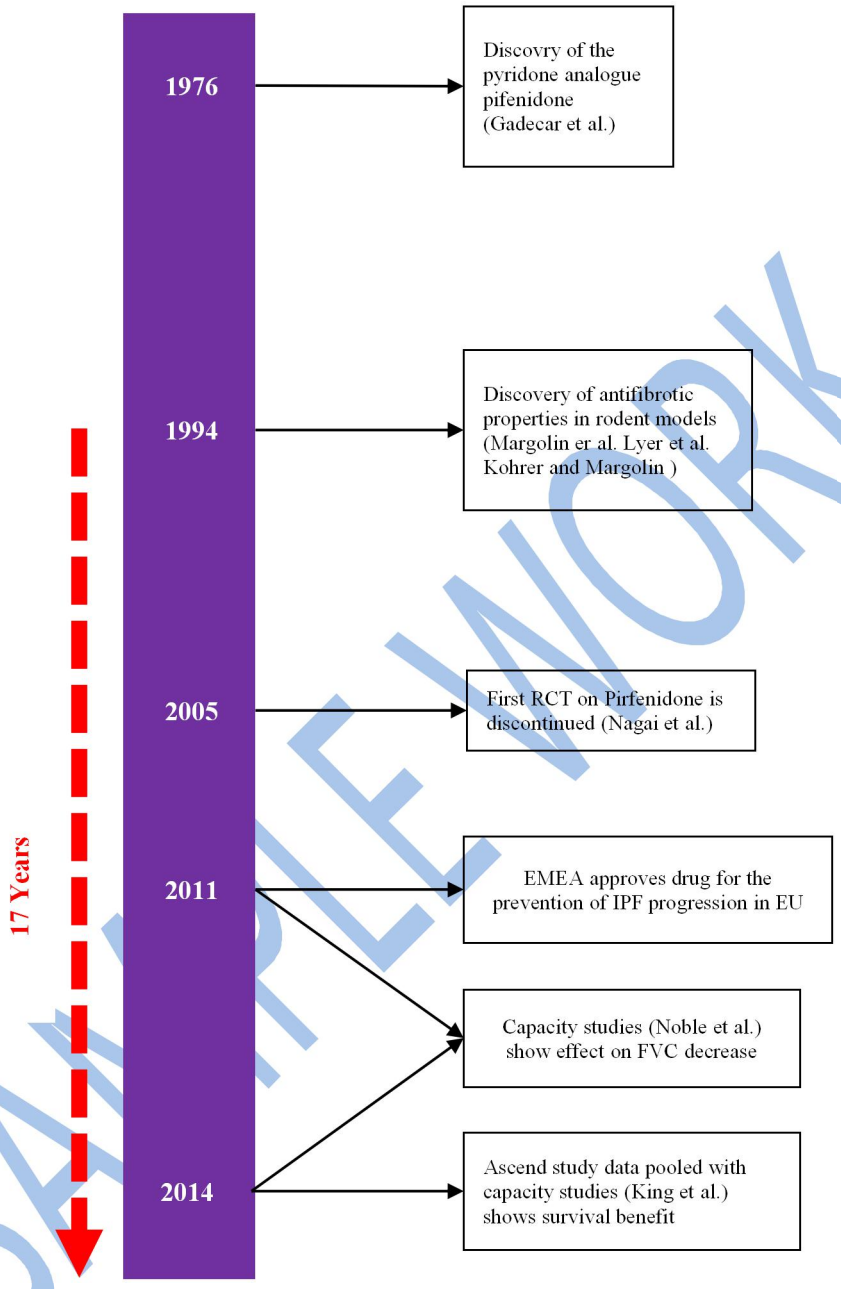
1.2 Pirfenidone

Pirfenidone is found to possess anti-oxidant, anti-fibrotic and anti-inflammatory effects in the experimental models wherein the same potential is also found to be in IPF human patients. Pirfenidone is Found To Inhibit The Growth Factor-B (TGF-β) in vitro and functions as an anti-fibrotic by altering the synthesis, expression and accumulation of collagen (Iyer *et al*., 1999b; Misra & Rabideau, 2000; Oku *et al*., 2008a). Pirfenidone is found to possess the properties of an anti-oxidant wherein the action involves reactive oxygen species scavenging (Mitani *et al*., 2008). Furthermore, prifenidone was found to be better than placebo towards preservation of Forced Vital Capacity (FVC) and improvisation of

Progression-Free Survival (PFS) in patients. However, the effects of pirfenidone have not been extensively investigated till date in patients suffering from advanced stages of IPF.

The early studies on the treatment of IPF using pirfenidone which was conducted in the early 1990s used the model of bleomycin-induced pulmonary fibrosis in hamsters wherein the previous research revealed that pirfenidone could actively involved in the reduction of severe profibrotic lung tissue factors and bronchoalveolar lavage fluid expression. Pirfenidone is shown to reduce or prevent the accumulation of inflammatory cells, hydroxyproline, procollagen I and III and Transformation of Growth Factor-Beta (TGF-β) in the bronchoalveolar lavage and in the lung tissues (Iyer *et al*., 1995, 1998, 1999a, 2000; Giri *et al*., 1999; Schelegle *et al*., 1997; Mansoor *et al*., 1999). Similar findings were acquired in the mice and cats wherein models such as bleomycin and amiodarone are used (Card *et al*., 2003; Kakugawa *et al*., 2004; Tian *et al*., 2006; Oku *et al*., 2008b). Pirfenidone is further shown to reduce the pool of fibrocyte and migrates the cells in the the bleomycin-induced lung fibrosis lung model (Inomata *et al*., 2014). Over the recent years, several findings of experiments involving cell culture revealed that in human lung fibroblasts, the drug is found to exert effects such as decrease in the proliferation of fibroblasts, reduced TFG-β stimulated reactions, lessened myofibroblast marker alpha smooth muscle actin (α-SMA) levels, and reduced heat shock protein 47 expression (Nakayama *et al*., 2008; Conte *et al*., 2014).

Figure 1: Timeline of Pirfenidone



Source: Adopted from Myllärniemi and Kaarteenaho (2015)

The time-frame for the development of the drug namely pirfenidone and the several preclinical studies conducted all over the world as the first choice among drugs in the treatment of IPF is depicted in figure 1. Several international studies have been conducted which act as promising results for the treatment of IPF (Raghu *et al.*, 1999a; Nagai *et al.*, 2002). The first extensive study was conducted in Japan wherein a randomised control study

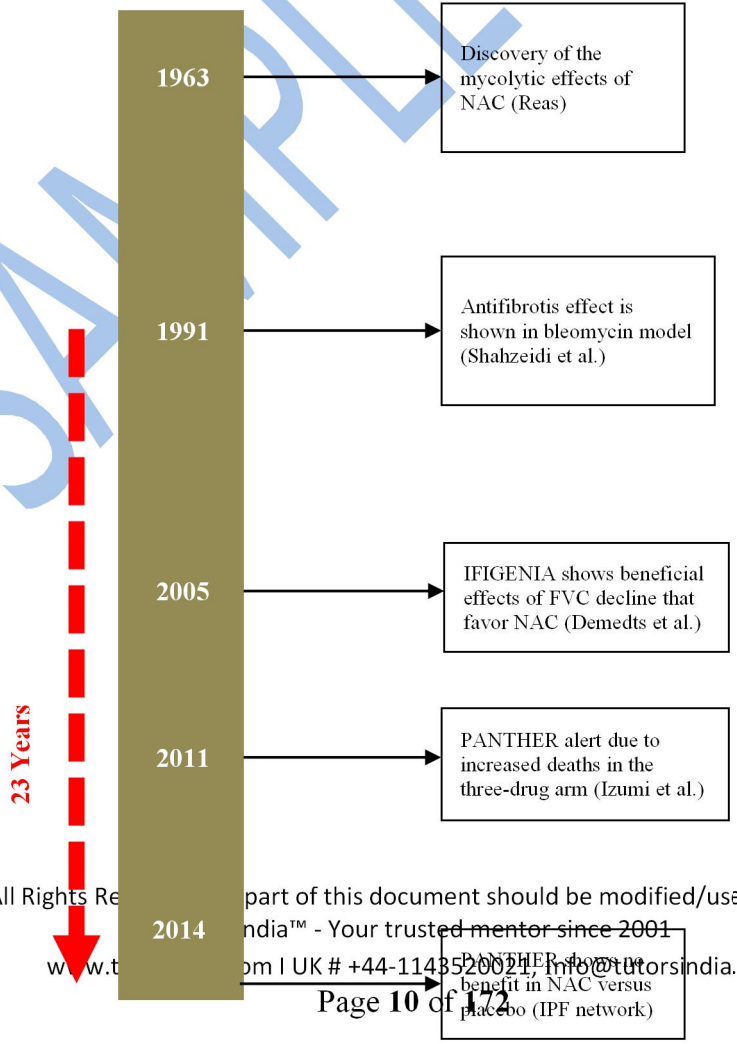
is used (Azuma *et al*., 2005). The previous study's primary endpoint which is based on the low oxygen saturation using the pulse oximetry SpO2 on a test based on six minutes exercise was unable to be achieved due to the actions of the drug authority of Japan. A 6 month interim analysis of the secondary endpoint which is acute exacerbation further led the termination of the trial due to ethical reasons. IPF acute exacerbation was manifested in the 14 per cent of the placebo when compared to zero patients in the intervention group for the nine months. Considering the results after the nine months recommended that pirfenidone could be administered to all patients suffering from IPF by Japan drug authority. Such a trial and the cessation which is premature led to the utilisation and acceptance of pirfenidone for IPF treatment in Japan. However, some drug authorities of Japan find weakness in supporting IPf for the treatment of IPF and hence the drug was not approved to be used until another study conducted in Japan (Taniguchi *et al*., 2010). which is a randomised study and other studies that were published in the year 2011 which demonstrates the reduction in FVC by 30 percent decline at 52 weeks in one among the two trails which further led the approval of the drug by the European Drug Authority (EMEA). With only one among the two different US studies stated positive, the Federal Drug Administration (FDA) in the United States requested for conducting another placebo-controlled study which demonstrated Pirfenidone's efficacy in the treatment of IPF. Henceforth, a study was performed in collaboration with the FDA which at the end confirmed that pirfenidone has better effects for the prevention of FVC decline (King *et al*., 2014b). Additionally, an analysis of the capacity of several studies revealed the positive outcome of pirfenidone as treatment based on the reduction of mortality. It is further deemed that the overall IPF mortality to be low which is based on the analysis of previous researches (King *et al*., 2014a; Atkins *et al*., 2014).

1.3 N-Acetylcysteine

The actions of NAC with respect to its mucolytic effects were first discovered in the year 1963 wherein the mucolytic drug is highly used for the treatment of cystic fibrosis (Reas, 1963). Several decades after the previous study, a research was conducted based on bleomycin-induced lung fibrosis in rat models which revealed that NAC is a viable inhibitor of collagen accumulation in lungs (Shahzeidi *et al*., 1991). However, in the late 1990s, several researchers examined the efficacy of the NAC short-term treatment in patients

suffering from different pulmonary fibrosis variations, IPF, sarcoidosis wherein it is noted that NAC improved BAL fluid glutathione of the considered patients for the researches (Meyer *et al*., 1994; Behr *et al*., 1997). In studies which utilised the rat and mice models of bleomycin-induced fibrosis revealed that NAC acts as a inhibitor of different mechanism of profibrosis such as the amounts of collagen, hydroxyproline, cytokines, mucus secretory cells and the mucin subtype 5ac (Behr *et al*., 1997; Cortijo *et al*., 2001; Serrano-Mollar *et al*., 2003; Mata *et al*., 2003). NAC is also known to inhibit the transition of epithelial–mesenchyma in the alveolar epithelial cells of rat models (Felton *et al*., 2009). wherein it is also known to reduce the contraction of TGF-β-induced gel, production of VEGF and the expression of α-SMA in the fibroblasts of human lungs (Sugiura *et al*., 2009). Furthermore, NAC tends to reduce the concentrations of cytokines in IPF patients generated by alveolar macrophages (Radomska-Leśniewska *et al*., 2010)(Patel *et al*., 2012). Several recent studies involving animal models revealed that NAC reduced the score of fibrosis, protects lung injury, decreases the content of reactive oxygen species in the macrophages of alveolus (Wang *et al*., 2013; Zhang *et al*., 2013, 2014).

Figure 2: Timeline of N-acetylcysteine



Source: Adopted from Myllärniemi and Kaarteenaho (2015)

Though several studies have been conducted to examine the efficacy of the NAC and its anti-fibrotic effects with results found to be convincing, only one placebo-controlled trial has been conducted previously which is based on the efficacy of NAC as a monotherpy based IPF treatment (Izumi *et al*., 2012; Martinez *et al*., 2014). The initial reports on the efficacy and the use of NAC were based on the previous study by (60) which revealed that a drug regimen which combines three drugs namely prednisone, azathioprine, and NAC was found to be efficient for the treatment of IPF than a drug regimen which combines prednisone and azathioprine. However, the previous placebo controlled study by Martinez *et al*. (2014) did not reveal any positive effect on the endpoints of the study. On the contrary, it was revealed that IPF patients treated using NAC tends to exhibit some side effects; however, no side effects in the gastrointestinal tract were evidences. In this regard, it is evident that no studies have proved the efficacy of the treatment of IPF using NAC alone and hence a combined treatment modality has always been a topic of interest for researchers and clinicians.

1.4 Problem Statement

Several animal and Phase-I studies that initiated the evaluation of novel drugs in the 90's and 2000's depicted poor efficacy especially demonstrated at the phase-III stage (Ahluwalia *et al*., 2014). The present decade however showed much promise when the clinical trial protocols with more defined endpoints were used for discerning effective treatment for IPF. More recently, trials have evidenced that the three drug regimen that is used for management of IPF today combining the use of prednisone, azathioprine and N-acetylcysteine is either harmful or ineffective in patients with IPF thereby not significantly contributing to the increase in survival rates of IPF (Izumi *et al*., 2012).Contrastingly, pirfenidone have been found to be effective in IPF patients(Azuma *et al*., 2005; Taniguchi *et al*., 2010; Noble *et al*., 2011; King *et al*., 2014b; Richeldi *et al*., 2014). While these studies

mark the beginning of novel therapy for IPF, more scrutiny is required to ascertain the drug efficacy as well as the effects on the reduction of mortality. Besides this, a comparative efficacy of pirfenidone in combination N-acetylcysteine can shed light on more effective treatment of IPF so as to reduce the mortality. Additionally, there is paucity in the literature that assesses the effect of these drugs on the reduction of mortality. With this view, the present study aims to assess the present evidence on the efficacy of combination therapy of pirfenidone with NAC.

1.5 Research Aim and Objectives

The study aims to assess the efficacy of Pirfenidone in combination with NAC. In this regard, the following objectives are framed:

- To evaluate the efficacy of pirfenidone with NAC
- To assess the likelihood of combination therapy in decreasing the mortality rate of IPF
- To derive a management framework for IPF from the above and make recommendations for effective treatment

1.6 Research questions

1) What is the likelihood of combination therapy (pirfenidone with NAC) in decreasing the mortality rate of IPF?
2) Can a management framework be derived for IPF which could recommend effective treatment of the disease using the combined drug therapy?

1.7 Motivation of the Research

There are several studies which evidenced the effectiveness of different drug treatment therapies for IPF wherein these evidences further enhanced the interest of researches, clinicians and patients for the treatment of the disease. IPF is no normal condition; it is a devastating disease which progresses with scar tissue deposition in the lungs which further leads to shortness of breath and at the end results in total failure of the lungs thereby leading to death. It has been documented seriously over the years that the incidence of the

disease is increased; however, no specific reasons are evident. In this regard, it is also reported that the rates of mortality are high wherein based on a 5-year survival report, it is stated that IPF stands to be the seventh severe fatal disease (Raghu *et al*., 2011, 2006c). In the recent years several treatment options have been made available wherein the concentration of majority of treatment has been control of symptoms and palliation (Raghu *et al*., 2014). Previous researches by Raghu *et al*., (2015); Loveman *et al*., (2015); Aravena *et al*., (2015) revealed that pirfenidone which is license in the year 2011 in Europe on the evidences of the RCTs conducted shown great improvements to slow the progression rate of IPF(Atkins *et al*., 2014). Furthermore, another agent named N-acetylcysteine (NAC) also has been used to reduce IPF wherein studies particularly focused on the treatment on the basis of combined drug treatment (Rogliani *et al*., 2016). The strength of utilization of these two drugs (NAC and pirfenidone) is at first is based on the strength of data that these drugs are approved by the US Food and Drug Administration (FDA) wherein the combined treatment procedure may likely offer new hope for patients to improve their life. In this regard, it is imperative to note that a research that combines all evidences pertaining to these drugs would act as compiled evidence which motivated the research to review the effectiveness of the treatment methods using pirfenidone with N-acetylcysteine and present the results of the research on the basis of a meta-analysis. The motivation to conduct the research hence supported the researcher to conduct a meta-analysis.

1.8 Scope and Significance of the Research

The present research will be a significant contribution to the research community wherein there is a significant lack of previous researches that would examine the combined efficacy of pirfenidone and NAC. Several previous researches have been conducted as meta-analysis examining the efficacy of prifenidone and nintedanib whereas prifenidone and NAC efficacy is least examined. In this regard, the study will be a significant addition to researches. Furthermore, the scope of the study is limited to the examination of combined efficacy of prifenidone and NAC wherein previous studies were examined.

1.9 Chapterisation

Chapter 1- Introduction: This chapter discusses the background of the study followed by the problem statement. From the problem statement, the research aims and objectives of the study are stated. This chapter also includes the scope, significance and chapter scheme of the dissertation.

Chapter 2- Review of Literature: The review of literature begins with the concepts and definition of IPF along with the signs, symptoms, clinical presentation, pathogenesis, diagnosis and management of the disease. The current modes of management along with previous literature are discussed. The research gap is then extracted and debriefed.

Chapter 3- Materials and Methods: The chapter includes the search strategy, inclusion and exclusion criteria and the methods of analysis for the extracted data. A quality assessment of the included studies is also included here.

Chapter 4- Results and Discussion: The results contain a review of the selected studies along with the statistical analysis of the extracted data. Besides this a critical review of all the papers coupled with the implications of the findings of the study is discussed.

Chapter 5- Summary, Conclusion, Contribution to Knowledge, Suggestion for Future Research: The chapter contains the findings of the study in brief. It also explains how the findings relate to achieving the objectives of the study.

CHAPTER II: LITERATURE REVIEW

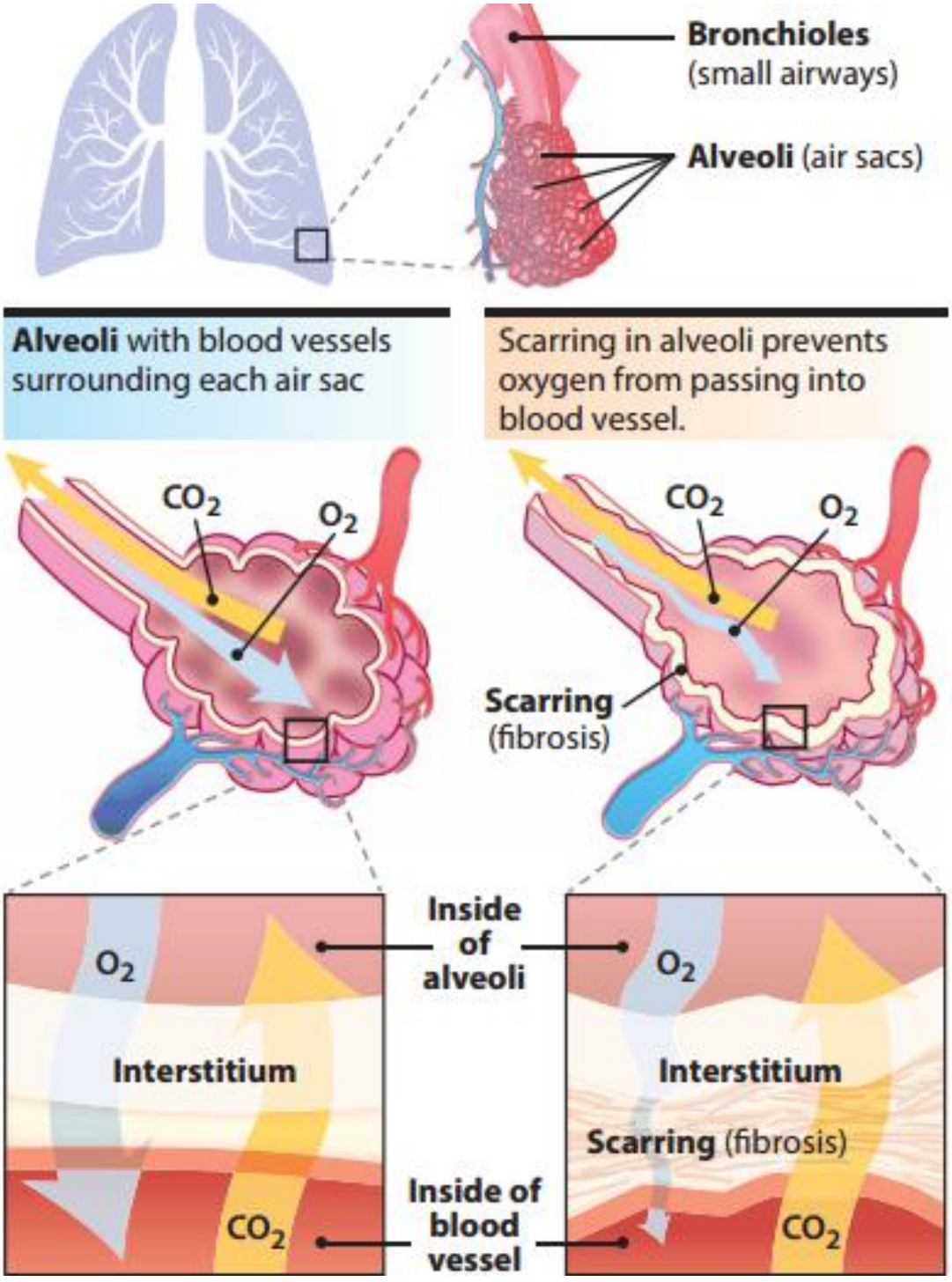
2.1 Introduction

The emphasis of the literature review in the current chapter is on the Idiopathic pulmonary fibrosis, its pathophysiology, the definitions provided by numerous medical researchers for the disease, the signs and symptoms of the disease, the management of disease, diagnostic criteria and earlier experimental studies performed to evaluate the nature, diagnosis and treatment of the disease.

2.2 Idiopathic pulmonary fibrosis

The disease in which deeper tissues of the lungs becomes scarred, or thick and stiff over time is termed as Pulmonary Fibrosis (PULL-mun-ary fi-BRO-sis). Fibrosis is the term given for the formation of scar tissue (National Institutes of Health, 2011). The condition that leads to chronic and progressive scarring of the tiny air sacs (alveoli) in the lungs is termed as Idiopathic Pulmonary Fibrosis (IPF). The crucial action of the alveoli is to conduct the shifting of oxygen to your blood stream through the air you breathe in, and shifting the unwanted product, carbon dioxide from the your blood, to the air you breathe out. The scar tissue quantity irrevocably enhances over time. The rate of progression of the disease is highly inconsistent, with few patients continuing to be steady for many years while others may worsen quickly (Lung Foundation, 2012). In patients with the histologically established UIP pattern of IPF the prognosis is notably inferior as compared to those with other histological patterns of chronic interstitial pneumonia (King *et al*., 2001b).

Figure 3: Idiopathic Pulmonary Fibrosis



Source: Adopted from Raghu *et al.* (2011)

The dangerous disease basically attacking middle-aged and older adults is the IPF. It differs from one individual to other. Fibrosis occurs rapidly in few individuals. The procedure is much slower in others. The disease remains same for years in few individuals. Though there is no treatment for IPF still. After the diagnosis most individuals survive for only around 3 to 5 years. Respiratory failure is the most frequent reason of death associated to IPF. The other reasons of death comprise of heart failure, pulmonary embolism (EM-bo-lizm), pulmonary hypertension (HI-per-TEN-shun), pneumonia (nu-MO-ne-ah), and lung cancer. IPF may also be associated to genetics. If IPF is present in more than one member of your family, the disease is termed as familial IPF (National Institutes of Health, 2011).

The global incidence of IPF has no inclination for race or ethnicity (Morrisey, 2003). In North America and Europe the conventional computation of incidence are between 3 and 9 cases annually per 100,000 individuals, based on the analysis of published studies since 2000 (Hutchinson *et al*., 2015). Globally the mortality rates of IPF remain to enhance evenly (Hutchinson *et al*., 2014). This can in portion be ascribed to broader similarity apparently with the condition (and thus its diagnosis) and wider agreement on the mechanics of such diagnosis. Another contributing component that is related is basically the certainty that individuals are surviving longer now than ever before, and this disease is mainly represented in an older population. Though, the worldwide incidence and prevalence of IPF differs, which is probably inferable to local distinctions in diagnosing the condition, as well as the methodology, sample size and statistics employed in the studies from which such inferences are obtained (Nalysnyk *et al*., 2012).

The upward shift worldwide in IPF nevertheless over time is apparent in the literature. In a review, for instance, the large health insurance claims database in the U.S. over the period of 1996-2000, the annual incidence was concluded as 6.8 per 100,000 seeking an approximately narrow IPF diagnostic standard, and 16.3 per 100,000 under a wider test, while the prevalence was 14.0 per 100,000 under the rigid standards and 42.7 per 100,000 under the wider standards (Raghu *et al*., 2006b). In the HealthCore Integrated Research Database -- a most current review of patient files between 2006–2012 using a newly-advanced screening algorithm for U.S. adults (restricted in execution to patients older than 50 years of age) -- generated an computed incidence (for the population, and not only the 50+

cohort) of 14.6 per 100,000, while prevalence was 58.7 per 100,000 (Esposito *et al*., 2015). The computed annual incidence/prevalence per 100,000 in Europe was 0.22/1.25 in Belgium, 0.94/6.5-12.1 in the Czech Republic, 0.93/3.38 in Greece, 2.17/NA in Denmark, 3.0/NA in Spain, 4.3/23.4 in Norway, and 7.94/NA in the United Kingdom (Kuwano *et al*., 2016). A study described the incidence/prevalence as 2.23/10.0 per 100,000 in Japan (Kuwano *et al*., 2016).

The cause of IPF is unknown but is expected to be related with a variety of risk factors, comprising of cigarette smoking, viral infections and occupation (Baumgartner, 2000). The most common collection of risk factors is exposure to inhalation agents, with extended, repeated injury to the lungs substantially causing the fibrotic approaches (Kuwano *et al*., 2016). IPF has also been perceived to appear in a familial pattern (influencing two or more individuals of an immediate family), though the appearance of such familial cases differs in studies between 2% and 25% of all IPF cases (Tang *et al*., 2003). One study inference that among all the risk factors related with IPF, the highest single risk factor was to have a parent or sibling with IPF (odds risk (OR) = 6.1) (García-Sancho *et al*., 2011).

Other than the genetic and environmental factors described above, there are numerous medical conditions that incline to represent parallel to IPF. The 126 studies examined by literature review conducted from 1990 to 2015, described remarkable comorbidities related with IPF. The respiratory comorbidities were as follows: pulmonary hypertension (34%), chronic obstructive pulmonary disease (18%), lung cancer (15%), obstructive sleep apnea (6%), and pulmonary embolism (2%). The non-respiratory comorbidities comprised of cardiovascular disease (27%), metabolic disease (24%), and gastro-esophageal reflux disease (18%) (Raghu *et al*., 2015a). The category of these relations, whether they are causal or share common risk factors (e.g., age), has not been described.

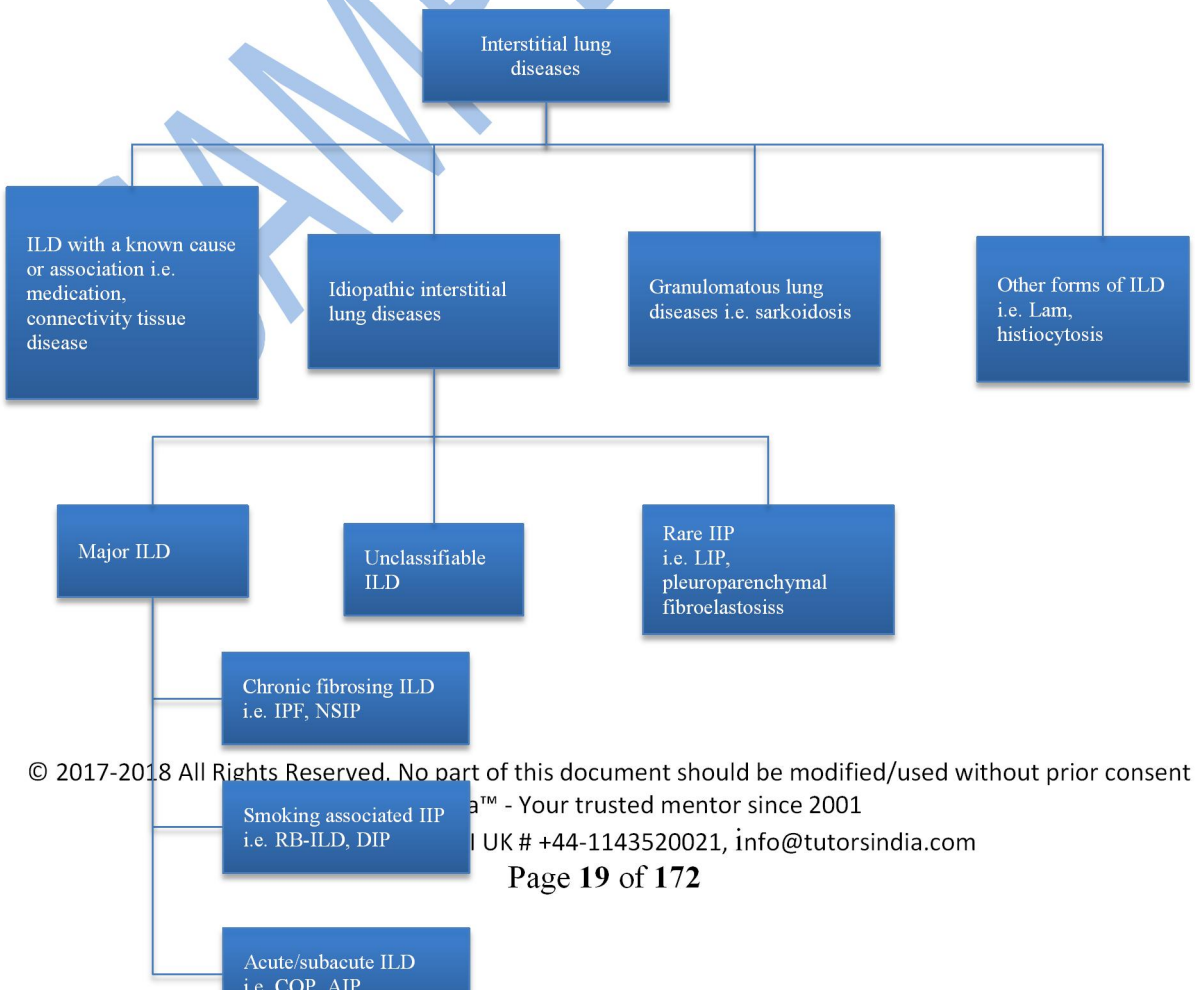
2.2.1 Idiopathic pulmonary fibrosis as an Interstitial Lung Disease

New international definitions, guidelines, classifications and treatment probabilities in current years, have progressed in interstitial lung disease (ILD) and precisely in IPF. The word ILD describes more than 200 different establishments. In 1960's the first pathologic categorization was defined, and in the subsequent 20-30 years no clear differentiation was

made between the inflammatory and fibrotic ILDs which caused a magnified hope on the effect of steroid treatment. It was recognized in 1990's that not all ILDs were steroid sensitive; which caused a new pathological classification and new guidelines in 2000 and 2002 in which the differentiation between the distinct kinds of ILD were described for the first time (Katzenstein & Myers, 2000; American Thoracic Society & European Respiratory Society, 2002).

In 2011, the first guideline precisely for IPF was published and provided a new description of the disease based on the exclusion of all known causes for ILD and the recognition of particular combinations of radiological and histological patterns of UIP (Raghu *et al*., 2011). A surgical lung biopsy therefore was no longer required for making an optimistic diagnosis in patients with a certain UIP pattern on a high resolution computed tomography (HRCT). The most current multidisciplinary classification of ILD was published in 2013 wherein, for the first time, it was a accepted that not all patients can be sub-classified and the term "unclassifiable ILD" was established (Figure 2) (Travis *et al*., 2013). However, the most common of the idiopathic interstitial pneumonias continues to be idiopathic pulmonary fibrosis.

Figure 4: Classification of ILD



Source: Adopted from Bendstrup (2014)

2.2.2 Etiology

The basic issue of patients exhibiting pulmonary fibrosis is its diminishing features. The etiology of pulmonary fibrosis comprehension will give long-term typical reduction and potential alteration of the disease. There are presently various familiar hazards till date that are related with pulmonary fibrosis which will be explained below.

2.2.2.1 Radiation and chemotherapy-induced lung injury

The treatment of breast, lung, oesophageal and lymphoid cancers is done using Thoracic Radiation Therapy (RT). A general dose-restricting obstacle of RT nevertheless is the evolution of pulmonary interstitial damage and infection, frequently described to as radiation pneumonitis and appearance of fibrotic foci (Burkhardt, 1989; Carver et al., 2007; Vågane et al., 2008). In RT-originated fibrosis various procedures have been recognized, comprising enhanced Reactive Oxygen Species (ROS), alveolar injury (Ghafoori et al., 2008) and the toxic impact of ROS on parenchymal cells (Beinert et al., 1999; Rødningen et al., 2008), obstruction of multiplication-related transcription components (Lemay & Haston, 2008), and the inflow of infection cells, like lymphocytes and macrophages (Johnston et al., 2004; Westermann et al., 1999). Dysregulated pro-inflammatory and pro-fibrotic cytokines, IL-6, MMPs, TGFβ (Barthelemy-Brichant et al., 2004; Matej et al., 2007; Hill, 2005; Molteni et al., 2007; Yang et al., 2007) and chemokines (Johnston et al., 2002) moreover additionally decrease the anti-inflammatory cytokines subsequent to radiation (Haase et al., 2007) can also intensify the infection and wound-healing reaction. Genetic determinants of RT-originated fibrosis have been exhibited by animal prototypes (Sharplin & Franko, 1989; Lemay & Haston, 2008) comparable to the analogous genotype-associated relations in humans

(Giotopoulos et al., 2007). RT of the thoracic section generally can lead to remarkable injury to the radiation-receptive alveolar sections of the lung inducing a dysregulated infection overflow, abundant in pro-inflammatory and pro-fibrotic intercessors. Transcription components, dysregulated chemokines and anti-infection pathways can additionally blend this unconfined reaction, causing pulmonary fibrosis.

Chemotherapy analogous to radiation therapy can lead to lung damage with inconstant outcomes based on duration, dose rate, previous lung disease and consequent use of steroids (Abid *et al*., 2001; Sleijfer, 2001). Bleomycin (BLM) (Umezawa *et al*., 1967), the *Streptomyces verticullatus*-acquired antibiotic is successful against skin tumours and squamous cell carcinomas (Umezawa, 1974); An adverse side effect comprises infection and fibrotic reactions in the lung nevertheless like RT. In around 46% of patients treated, BLM-originated infection happens (Van Barneveld *et al*., 1984) with obstacles in the skin and lung because of the deficiency of bleomycin hydrolase, the endogenous bleomycin-inactivating enzyme, in these tissues (Onuma *et al*., 1974).

The evolution of animal models helps our comprehension of BLM-originated fibrosis which may replicate many, but not all, of the features of the human disease (Onuma *et al*., 1974). Cell death (Doelman & Bast, 1990) may be instantly caused by BLM and that will minimize O_2 into free radicals, leading to deterioration of DNA (Burger *et al*., 1981). The epithelial and endothelial cells are few of the primary cells affected, based upon the route of administration (Adamson & Bowden, 1974), leading to a leukocyte-rich infection reaction. In animal models the impediment of this inection reaction with anti-CD11 Ab-inhibiting cellular discharge, considerably minimizes pulmonary collagen and fibrosis, denoting the remarkable benefaction of infection cells on the evolving fibrotic reaction (Piguet *et al*., 1993a). The FAS-L-expressing cells which assist the inflammatory cytokines, TNFα (Piguet *et al*., 1989), IL-1β (Scheule *et al*., 1992), IL-6 (Smith *et al*., 1998) and pro-fibrotic TGFβ (Santana *et al*., 1995; Zhang *et al*., 1995) cause more apoptosis (Hagimoto *et al*., 1997; Kuwano *et al*., 1999). The infection and sequent fibrotic reaction subsequent to BLM discharge can be minimized by the impediment of TNFα, IL-1, FAS-Ligand or TGFβ (Giri *et al*., 1993; Piguet *et al*., 1993b, 1989; Hagimoto *et al*., 1997). TNFα, IL-1, IL-6, and TGFβ therefore are few of the probably many intercessors intricate in BLM-originated fibrosis. To analyze the

collaboration of many cytokines in the pulmonary fibrotic reaction the BLM model has been employed. The collaboration of type-2 cytokines is rarely evident, with IL-4 and IL-5 exhibiting no remarkable role (Hao *et al*., 2000; Izbicki & Breuer, 2003; McKay *et al*., 1975), while IL-13, either directly (Jakubzick *et al*., 2003) or indirectly through TGFβ (Fichtner-Feigl *et al*., 2007; Kolodsick *et al*., 2004), imparts to the fibrotic reaction. It is also clear that Type-1 cytokines are intricated (Segel *et al*., 2003), with lesser infection cells, weight loss, mortality and lung hydroxyproline content seen in IFNγ$^{-/-}$ mice (Chen *et al*., 2001). Analogous outcomes were observed by impeding the IFNγ-advocating cytokine IL-12 or germ line abolition of IL-12 (Sakamoto *et al*., 2002). Though supplicating a remarkable infection reaction, BLM can also directly enhance fibroblast multiplication (Moseley *et al*., 1986) and TGFβ creation from endothelial cells (Phan *et al*., 1991). BLM therefore seems to have various features, leading to cell death and apoptosis directly, supplicating an infection reaction and enhancing fibroblast multiplication and TGFβ creation. The mouse prototype of BLM-originated fibrosis directly gives a great device to analyze the comparable benefaction of the many cells, pathways and intercessors intricated in drug-originated fibrosis.

2.2.2.2 Asthma and allergic airway inflammation

There has been an extraordinary advancement in the quantity of persons agonizing from asthma and allergic airway infection over the previous 30 years, basically within the urban sections of both developing and developed countries (Eder *et al*., 2006). Allergic asthma is a polygenic disorder (Martinez, 2005), indicated by allergen-specific IgE and IgG1, mucus secretion, airway hyper-reactivity and airway and interstitial eosinophilia (Cohn *et al*., 2004). Recurrent attacks of allergen exhibition and dysregulated infection at the mucosal surfaces associated chronic asthma can cause goblet cell hyperplasia, angiogenesis, smooth muscle hyperplasia and hypertrophy and eventually subepithelial fibrosis (Broide, 2008; Huang *et al*., 1999; Ward *et al*., 2002).

Many features of allergic inflammation can be managed by CD4^{+} Th2 cells, precipitated by dendritic cell or basophil-derived IL-4 and IL-25 (Angkasekwinai *et al*., 2007; Owyang *et al*., 2006; Sharkhuu *et al*., 2006; Min *et al*., 2004; Voehringer *et al*., 2004; Webb *et al*., 2007). Confined cellular influx is disseminated by the activation and regression of cytokine-secreting Th2 cells into the interstitium and mucosal surfaces of the lung. Th2-

derived cytokines, IL-5 and IL-9, more basically mature, deploy and raise eosinophils and mast cells (Hauber *et al*., 2004; Woodman *et al*., 2008; Takatsu & Nakajima, 2008) into the airspaces and tissue, and specifically these cells are observed in biopsies of asthmatic persons. In human asthmatics there is a remarkable increase in the TGFβ (Zagai *et al*., 2007; Balzar *et al*., 2005; Batra *et al*., 2004; Levi-Schaffer *et al*., 1999; Sagara *et al*., 2002) with the level of subepithelial fibrosis associating with a deprivation of forced expiratory volume (FEV_1). Flood-Page *et al*. (2003) after these findings of elevated TGFβ, eosinophils and subepithelial fibrosis evaluated the particular cellular origin of TGFβ. 86% of TGFβ $mRNA^+$ cells in the bronchial mucosa of asthmatics basically were eosinophils, and differentiating eosinophils was a remarkable origin of pro-fibrotic TGFβ in the allergic lung (Ohno *et al*., 1996). Various studies additionally have recognized the association of collagen deposition with enhanced quantity of tissue eosinophils and myofibroblasts (Hoshino *et al*., 1998; Minshall *et al*., 1997) as well as the assertion of submucosal MMP9 and MMP12 (Kang *et al*., 2007).

Various clinical trials with little victory were done subsequent to these findings and treatment process employing anti-IL-5 antibodies to obstruct tissue eosinophilia. Treatment of atopic dermatitis patients as well as allergic asthmatic patients (Phipps *et al*., 2004), with anti-IL-5 antibodies (mepolizumab) caused remarkable minimizations in tissue eosinophilia (Menzies-Gow *et al*., 2003; Flood-Page *et al*., 2003a), regardless of no alteration in the late-stage of cutaneous allergic responses. A decreased thickness and density of the extracellular matrix (lumican, tenascin and pro-collagen III (COL3A)) was obvious subsequent to anti-IL-5 treatment, recommending that IL-5-mediated tissue eosinophilia was remarkably accountable for ECM deposition. Regardless of these inspiring consequences, the exact role and association of eosinophils in human asthmatics is argued though, with many clinical trials of anti-IL-5 mAb describing little or no clinical development (Flood-Page *et al*., 2003b; O'Byrne, 2007).

Few animal studies conducted employing either IL-5-lacking mice (Cho *et al*., 2004) or eosinophil-eroded mice (Humbles *et al*., 2004; Lee *et al*., 2004) have shown a remarkable role for eosinophils, with minimized airway remodeling, comprising of smooth muscle thickness and peri-bronchial fibrosis, additionally with various other characteristics of allergic asthma subsequent to chronic airway exhibition. Impeding TGFβ (McMillan *et al*.,

2005) or obstructing with TGFβ signalling (Le *et al*., 2007) also may remarkably impair airway remodeling subsequent to chronic allergen exhibition.

Animal prototypes taken concurrently have exhibited an evident role for eosinophils and eosinophil-acquired TGFβ in airway injury and remodeling. Nevertheless human studies have generated a spectrum of outcomes and supplementary studies are needed, with precise outcomes to convey the role of IL-5 and eosinophils in the advancement and determination of subepithelial fibrosis in asthmatic airways.

In allergic persons IL-13 may also be a harmful cytokine. Most of the pathological situations recognized in allergic asthmatics can be indicated to IL-13. IL-13 for instance can reconcile goblet cell hyperplasia in local epithelia (Kondo *et al*., 2006) and enhance mucus generation (Malavia *et al*., 2008) that can obstruct the small airways (Fanta, 1985; Ramalingam *et al*., 2008). Epithelial repair (Allahverdian *et al*., 2008; Booth *et al*., 2001), fibroblast growth (Ingram *et al*., 2004; Saito *et al*., 2003), EMT (Richter *et al*., 2001), and collagen deposition (Malavia *et al*., 2008) can also be supported by IL-13. IL-13 also leads to smooth muscle hyperplasia (Chiba *et al*., 2009) and subepithelial fibrosis (Yang *et al*., 2004) afar the airway epithelium. IL-13 can harmonize with and enhance profibrotic TGFβ (Wen *et al*., 2002; Zhou *et al*., 2005) eotaxin production (Wenzel *et al*., 2002), and TIMP expression (Zhou *et al*., 2007) analogous to the process suggested employing the bleomycin prototype. Within the subject of allergic asthma, eosinophils, TGFβ, and IL-13 consequently may all confer to airway remodeling and pulmonary fibrosis.

2.2.2.3 Other pulmonary fibrotic conditions with known etiologies

There can be toxic outcomes on the mucosal surfaces of the lung from the environmental particulates of occupational exposure or smoking. Work that comprises mining or that subject workers to metal dust, silica dust or asbestos for instance can lead to pulmonary fibrosis (Paris *et al*., 2004). Exposure to organic and inorganic materials (Schenker, 2000; Von Essen *et al*., 1990), fumes (Buerke *et al*., 2002), or moldy hay (Che *et al*., 1989) leading to allergic infection and fibrosis, frequently regarded as Farmer's Lung (Cormier *et al*., 2000; Lalancette *et al*., 1993; Toubas *et al*., 1995) can strike agricultural workers. The worldwide incidence of 16.5−19/100,000is observed with sarcoidosis and

granulomatous lung disease, hence it is less usual (Hillerdal *et al*., 1984). These diseases are remarkably governed by genetic and environmental components. The causative agents have not been recognized till date (Nunes *et al*., 2007). The involvement of bacteria has been considered by an alveolar macrophage gene-transcript profile (Gaede *et al*., 2004) which is analogous to *Mycobacterium tuberculosis* infection. Though, bacteria have not yet been obscured from sarcoidosis patients till date. The parenchymal design, the alveolar spaces and endothelial cells of sarcoidosis patients are greatly distorted by chronic infection and the evolution of infection cell-rich pulmonary granulomas (Abehsera *et al*., 2000; Roman *et al*., 1995), that are abundant in type-1 cytokines and chemokines (Hutyrová *et al*., 2002a; Müller-Quernheim, 1998; Rottoli *et al*., 2005; Ziegenhagen *et al*., 1998) and T cells (Iida *et al*., 1997). An increased collagen and fibronectin in granulomas of sarcoidosis patients (Roman *et al*., 1995) have been observed by immunohistochemical evaluation of human and animal lung biopsies and post-mortem histological components. Co-expression of pro-fibrotic TGFβ moreover within the granulomas was also noticed in sarcoidosis granulomas (Limper *et al*., 1994; Marshall *et al*., 1996). Repeated lung damage and infection (Kline *et al*., 1993) is general to many of these fibrotic situations regardless of these differing etiologies, and may widely underlie the pathogenesis of pulmonary fibrosis.

2.2.3 Mortality

A poor prognosis is conveyed in IPF (American Thoracic Society. Idiopathic pulmonary fibrosis, 2000; American Thoracic Society & European Respiratory Society, 2002). The enhancement in death rates with enhancing age, are persistently higher in men than women, with the highest death rates happening in the winter and undergo seasonal discrepancy even when infections are eliminated (Olson *et al*., 2009). The amended diagnostic norms for IPF were employed in studies wherein only 20 to 30% of subjects were existing 5 years after the diagnosis (Bjoraker *et al*., 1998; Flaherty *et al*., 2002; Nagai *et al*., 1998; Daniil *et al*., 1999; Park *et al*., 2000). The advancement of lung fibrosis caused most of the deaths rather than from generally happening comorbid situations (Martinez *et al*., 2005; Mannino *et al*., 1996; Panos *et al*., 1990; Olson *et al*., 2007; King *et al*., 2009). Respiratory complications cause repeated hospitalizations for general occurrences and are usually related with death (Fernández Pérez *et al*., 2010; Martinez *et al*., 2005; King *et al*., 2009). In published clinical trials patients with IPF-associated deaths recorded prospectively, subacute

decline was observed in most patients (exacerbation over a period of > 4 wk to months) prior to their death. A considerable minority of patients although witnessed acute decline resulting in death (instant exacerbation of less than 4 wk time) (Raghu *et al*., 2008; Daniels *et al*., 2010; Fernández Pérez *et al*., 2010; Martinez *et al*., 2005; King *et al*., 2009). The significant reasons of mortality in IPF include ischemic heart disease, heart failure, infection, pulmonary embolism and bronchogenic carcinomas (Hubbard *et al*., 2008; Martinez *et al*., 2005; Olson *et al*., 2007; King *et al*., 2009).

2.2.4 Risk factors associated with IPF

2.2.4.1 Acquired risk factors

IPF is a disease of unspecified division by description, since no particular reason has been strongly recognized so far. Number of possible risk factors although have been described which may have some relation to the evolution of this disease (Raghu *et al*., 2011).

- Cigarette smoking: It is assumed that heavy smoking may be related with IPF, and this relation is comparable to both sporadic and familial IPF (Baumgartner *et al*., 1997; Steele *et al*., 2005; Antoniou *et al*., 2008).
- Environmental exposures: A remarkable risk for evolution of IPF includes exposure to metal dusts, in specific lead, brass and steel as well as wood dust (Hubbard *et al*., 1996; MIYAKE, 2005; Gustafson *et al*., 2007). Relation to IPF has also been observed with few occupational hazards that are associated to farming, hair dressing, stone cutting/polishing, bird raising and livestock (Baumgartner *et al*., 1997).
- Microorganisms: The instigation of IPF is also observed to have close relation to chronic viral infections, specifically, Epstein-Barr-Virus (EBV) (Egan *et al*., 1995; Stewart *et al*., 1999; Tsukamoto *et al*., 2000; Lok *et al*., 2001; Kelly *et al*., 2002) and hepatitis C virus (Ueda *et al*., 1992; Meliconi *et al*., 1996) infections. It was observed in a study conducted on 33 IPF patients that in 97% of IPF cases confirmation of herpes virus infection comprising of EBV, cytomegalovirus, Human Herpes Virus (HHV)-7 and human HHV-8 (Tang *et al*., 2003). On the contrary, some other studies although described no association between viral

infection and IPF (Wangoo *et al*., 1997; Zamò *et al*., 2005). No ultimate inference on the role of EBV infection in the evolution of IPF has been drawn regardless of the large number of studies. This is mainly due to the high prevalence of viral infection in general population (Raghu *et al*., 2011).

- Gastroesophageal reflux: The relation of microaspiration in gastroesophageal reflux is observed with IPF (Tobin *et al*., 1998; Raghu *et al*., 2006b).
- Diabetes Mellitus (DM): The relation of DM with IPF has been observed in a current study as well (Gribbin *et al*., 2006).

2.2.4.2 Geneti risk factors

Familial idiopathic pulmonary fibrosis: A strong relation with familial IPF is observed with mutation in the Surfactant Protein-C (SFTPC) gene (Thomas *et al*., 2002); while, this mutation is unfamiliar in sporadic IPF (Selman *et al*., 2003; Lawson *et al*., 2004). One of the reasons of type II Alveolar Epithelial Cell (AECII) injury is considered to be the SFTPC gene mutation (Thomas *et al*., 2002). Familial IPF is also described due to a rare mutation in gene encoded for surfactant protein-A2 (SFTPA2) (Wang *et al*., 2009). Current studies on familial IPF recognized a mutation in the Human Telomerase Reverse Transcriptase (hTERT) gene (Armanios *et al*., 2007; Tsakiri *et al*., 2007; Alder *et al*., 2008; Diaz de Leon *et al*., 2010). This mutation results in the compression of telomere which may eventually cause the alveolar epithelial cell apoptosis (Raghu *et al*., 2011).

Sporadic idiopathic pulmonary fibrosis: There is no genetic component recognized till date which is persistently related with sporadic IPF (Raghu *et al*., 2011). Polymorphisms of genes encoding Interleukin (IL)-1α, IL-4, IL-6, IL-8, IL-10, IL-12,), Transforming Growth Factor-β1 (TGF-β1), Tumour Necrosis Factor-α (TNF-α angiotensin converting enzyme and Matrix Metalloproteinase-1 (MMP-1) although have been perceived, in some cases of sporadic IPF unpredictably (Riha *et al*., 2004; Vasakova *et al*., 2007; Hutyrová *et al*., 2002b; Renzoni *et al*., 2000; Pantelidis *et al*., 2001; Xaubet *et al*., 2003c; Whittington *et al*., 2003; Morrison *et al*., 2001; Checa *et al*., 2008).

2.2.5 Signs and symptoms

The diagnosis of IPF is rare before the age of fifty and its incidence enhances with age and the mean age at diagnosis is 67 years. Nearly 75% of the patients are males and 2/3 are smokers or previous smokers (Hyldgaard *et al*., 2014; Raghu *et al*., 2011).

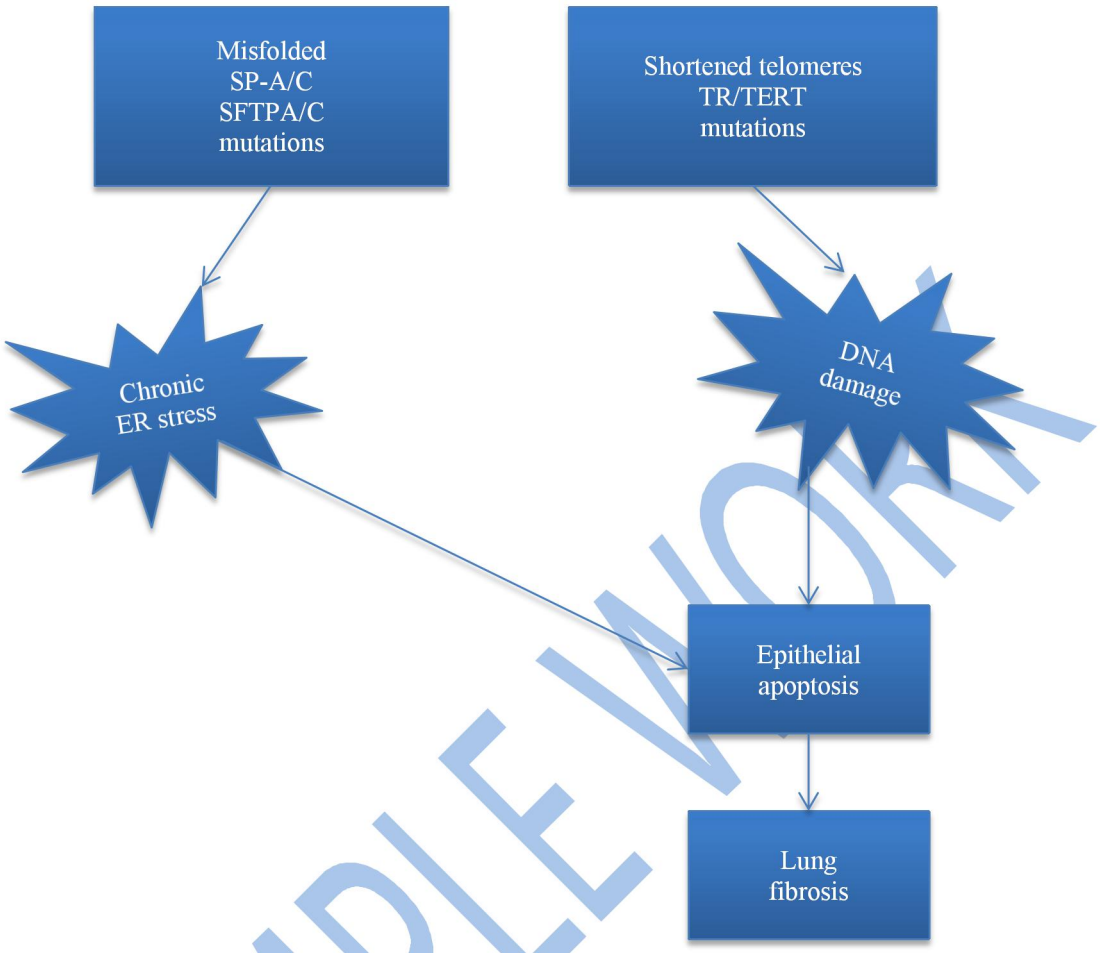
IPF comprises of classic signs like progressive dry cough and dyspnea, basically diminishing over months. The symptoms are present for many years in few patients before they contact a physician or are referred for investigations. Initially, the symptoms are generally experienced with regards to exercise, but later even the slightest movement can result in severe cough, dyspnea and desaturation. Though weight loss is not classical, it may be observed in the extreme stage of the disease when the respiratory work load enhances. Cancer needs to be always excluded in such cases. Few patients have experienced repetitive "airway infections" previous to the diagnosis frequently characterized by enhanced cough and phlegm, dyspnea and crackles at lung auscultation, but without exceptionally increased C-reactive protein or fever. The symptoms are rarely refined with antibiotic therapy and should possibly be depicted as minor acute worsening of IPF (Bendstrup *et al*., 2014).

There are few subtle or non-existing clinical findings during the initiation of the disease, but may comprise of clubbing and basal velcro crackles (Cordier & Cottin, 2013). These observations may be previous to the respiratory symptoms for numerous months. It is significant to look for extra pulmonary indications of connective tissue disease, as this may exclude IPF but rather classify the lung disease as associated to the rheumatologic disease. The differential diagnosis is significant since prognosis and treatment of ILD associated to connective tissue diseases are distinct from that of IPF. The chronic respiratory deficiency usually evolves with cyanosis when pulmonary function becomes severely diminished, during the start of exercise, but may exist later also at rest. Pulmonary hypertension may lead to peripheral increased dyspnea, edemas, need of oxygen and diminishing diffusion capability, which is a comparatively common complication to severe IPF and a dangerous prognostic sign (Raghu *et al*., 2011).

2.2.6 Pathophysiology

Though the pathophysiology of the disease is not completely understood, yet chronic injury of Alveolar Epithelial type II cells (AECII) is contemplated to be the answer. It is currently believed that IPF arises subsequent to the repetitive injury to the epithelial alveolar cells, the Alveolar Epithelial type II cell (AECII) in specific, therefore, stimulating responses related with normal tissue repair and scar formation. Nevertheless, in the pathogenesis of IPF, this scarring procedure remains persistent (du Bois, 2010). The risk factors for epithelial alveolar cell damage comprise of exposure to metal or wood dust, smoking and genetic disposition, as well as age, amongst others (Raghu *et al*., 2011). Particularly, it is assumed currently that chronic injury of AECIIs is a crucial occurrence in the IPF. The damaged AECIIs are prone to apoptosis. It was described by Korfei *et al*. (2008) that the cell markers prosurfactant protein (SP)-C and p20 caspase-3, in stained sections of IPF lungs, exhibited that 70-80% of the AECIIs manifest constant signs of apoptosis.

Figure 5: Possible Mechanisms of Familial IPF



Source: Adopted from Gunther *et al.* (2012)

2.2.7 Clinical Course of IPF

2.2.7.1 Subclinical IPF

The symptoms forego diagnosis that is well observed by a median of 1 to 2 years (Nagai *et al*., 1999; Nicholson *et al*., 2000; King *et al*., 2001a; Collard *et al*., 2003; Jegal *et al*., 2005; Bjoraker *et al*., 1998; Nagai *et al*., 1998), and radiographic confirmation of the disease may even forego the symptoms, indicating "subclinical" intervals of disease that are not well described (Nagai *et al*., 1998). The development of asymptomatic to symptomatic IPF may happen over years to decades (El-Chemaly *et al*., 2011). Early lung fibrosis is asymptomatic and has been progressively identified and described in family members of the affected individuals with familial pulmonary fibrosis, basically in those with a history of

smoking (Rosas *et al*., 2007; Steele *et al*., 2005). The samples of lung biopsy from individual with early asymptomatic lung disease exhibit several histologic subtypes of interstitial lung disease (ILD) (Rosas *et al*., 2007). A familiar risk factor for few idiopathic interstitial pneumonias including IPF is cigarette smoking (Baumgartner *et al*., 1997), it may result in subclinical parenchymal lung disease that is observable by spirometry and computed tomography (CT) imaging, even amidst a conventionally healthy cohort (Lederer *et al*., 2009; Washko *et al*., 2010). A high-resolution CT (HRCT) scanning emerges to be more sensitive than measurements of pulmonary function and cardiopulmonary exercise test parameters in recognizing subjects with asymptomatic ILD (Rosas *et al*., 2007).

It is uncertain presently that how patients with incidental, subclinical IPF should be attended and supervised. It is significant to have enhanced comprehension since the prevalence of subclinical IPF is probable to expand with expanding tendency in the operation of chest CT imaging for non-ILD diseases, like the diagnosis of pulmonary embolism and coronary artery disease. Considering the comparable low prevalence of IPF and deficiency of successful therapies, it is also unknown how to recognize those at high risk for progressing IPF in the general population and if the screening attempts to modify the results perceive in the subclinical stage IPF. It is probable additionally that subclinical IPF is not a benign procedure. The subclinical IPF may be exhibited as a risk factor for the progression of acute aggravation, basically after invasive process or (Chida *et al*., 2008; Araya *et al*., 2008; Takeda *et al*., 2008) .

2.2.7.2 Slowly Progressive IPF

In the IPF's traditional phenotype there is gradually continuous decrease in the lung function and aggravating dyspnea causing death within some years of diagnosis (Selman *et al*., 2007; King *et al*., 2001b). In aggravating disease the mean annual rate of decrease, ranges from 0.13 L to 0.21 L as measured by the FVC (King *et al*., 2008; Raghu *et al*., 2004; Azuma *et al*., 2005; Demedts *et al*., 2001; Taniguchi *et al*., 2010; Raghu *et al*., 2008; Daniels *et al*., 2010). It is observed that the gradually continuous clinical path may basically be less usual than classically defined. According to a current population-based cohort study in Olmsted County, Minnesota, 47 incident cases of IPF were evaluated over a term of 9-years and

observed that only 21% of these patients exhibited a gradually continuous path without confirmation of acute decompensation (Fernández Pérez *et al*., 2010).

2.2.7.3 Rapidly Progressive IPF

A subgroup of patients with IPF were recognized by Selman and coworkers , who exhibited a quickly continuous disease (< 6 mo of symptoms prior to first appearance) and displayed reduced survival in contrast to patients subsequent to the gradually continuous clinical path (Selman *et al*., 2007). These were essentially massive cigarette smoking men (Selman *et al*., 2007). The patients with a hastened clinical path impressively exhibited a gene expression description that varied from those with obtuse development and extended survival in spite of having related lung functions, chest imaging and histologic observations during the period of diagnosis. It was demonstrated by Boon and colleagues that lung molecular indications during the period of diagnosis may recognize patients with substantial IPF in contrast with those having quickly continuous disease (Boon *et al*., 2009).

2.2.7.4 Acute Exacerbations of IPF

Intervals of acute respiratory decrease are witnessed in patients with IPF either due to familiar complications, like infections, or of unrevealed reason (i.e., acute aggravation of IPF). Our comprehension of these occurrences has enhanced due to the creation of predefined norms for acute aggravation and disease development in patients with IPF. It is described that the acute aggravation of IPF causes the emergence of quick decline (within few days to weeks) in symptoms, lung function, and radiographic occurrence (bilateral ground-glass opacities and fusion overlapping a reticular pattern on HRCT) in the lack of infection, pulmonary embolism, heart failure or other recognizable reason (Collard *et al*., 2007b; Tomioka *et al*., 2007; Silva *et al*., 2007). A very poor result is exhibited in patients with acute aggravations of IPF.

2.2.8 Diagnosis

The IPF conclusive diagnosis of needs:(a) the expulsion of diffuse parenchymal lung diseases of known reason (connective tissue diseases, drug toxicity, environmental or occupational exposure) or other described clinical establishments and (b) the existence of a

histological pattern of UIP in the examination of lung tissue acquired by surgical lung biopsy, or radiological confirmation of a UIP pattern on the high resolution computed tomography (HRCT) or both.

The pulmonologists, pathologists and radiologists accomplished that the multidisciplinary assessment in the diagnosis and management of DILD can enhance the diagnostic precision, which currently is a broadly assumed proposal for demonstrating the diagnosis (Flaherty *et al*., 2007; Raghu *et al*., 2011).

2.2.8.1 Clinical Characteristics and Additional Tests

The clinical representation of IPF is generally indicated by progressive dyspnea on exertion and has a subtle onset, usually assisted by non-productive cough. The occurrence of the symptoms is gradual, but aggravates over time. There is an inconsistent retard between the onset of symptoms and the final diagnosis, and it may occur between 6 months and two years (Kim, 2006). An auxiliary diagnosis is traced to be caused by the existence of systemic symptoms/signs. In 90% of patients crackles can be heard on auscultation and in 50% of patients acropachy is determined (Xaubet *et al*., 2003a).

No particular laboratory deformities exist for this disease. Nevertheless, certain signs or symptoms of connective tissue diseases in their deprivation, serological autoimmune tests should be conducted in all patients.2 The positive rheumatoid factor or anti-nuclear antibodies can be discerned in up to 20% of IPF cases (Xaubet *et al*., 2003a). The existence of serum specific IgG should be evaluated consistently against the antigens that can most frequently cause hypersensitivity pneumonitis, since its clinical illustrations are at times similar to those of IPF. If any of these are positive, in the situation of reasonable exposure and bronchoalveolar lavage (BAL) with an enhanced lymphocyte count, an irritation test against the antigen in question and/or surgical lung biopsy should be conducted, in order to affirm or reject the diagnosis of chronic hypersensitivity pneumonia (Xaubet *et al*., 2003a). The probability of employing new biomarkers in the depiction and diagnosis of this disease has also obtained concern in the current years. Few biomarkers like KL-6, SP-A and SP-D, circulating fibrocytes and metalloproteinases 1 and 7 are being presently researched (Rosas *et al*., 2008; van den Blink *et al*., 2010).

2.2.8.2 Bronchoalveolar Lavage and Transbronchial Biopsy

In the study of DILD, Bronchoalveolar lavage (BAL) has been broadly employed. Its examination in IPF basically exhibits distinct neutrophilia with or without eosinophilia, and its use has been typically associated with its capability to rule out other establishments (Raghu *et al*., 2011). The latest international unison demonstrated that BAL cellular analysis should not be conducted consistently in all patients in the diagnostic process, though it may be suitable for a few (Raghu *et al*., 2011). However, BAL may be very helpful in particular cases in the differential diagnosis with other establishments such as chronic hypersensitivity pneumonitis or non-specific interstitial pneumonia.

In diseases with lymphatic and centrilobular distribution transbronchial biopsy is employed, or in those that represent characteristic diagnostic components and which have a dispersed distribution (Leslie *et al*., 2007). It has being employed growingly for the diagnosis of infections, tumors and sarcoidosis (Leslie *et al*., 2007). On the other hand, since the distribution of the lesion cannot be perceived because of the sample size it is of no use in the diagnosis of IPF. The employment of cryobiopsy to the process is very favourable, but further studies are necessary to confirm its usefulness in DILD.

2.2.8.3 High Resolution Computed Axial Tomography

The greatest diagnostic advancement is probably represented by the HRCT in the previous two decades in the study of diffuse lung diseases. HRCT, either by sequential (slice-by-slice acquisition) or volumetric acquisition (continuous acquisition) is the unchallenged procedure in the diagnosis of IPF. Determining the radiation dose employed in HRCT is very crucial; the radiation dose used in volumetric HRCT is triple the values obtained employing sequential HRCT. The decision to employ one or other procedure will rely on the balance between the expected details and the individual risk due to the enhanced radiation experienced. Taking an account of the patient's age and sex are conclusive factors and following of traditional protocols is suggested (e.g. sequential HRCT, with 10 mm intervals, in the preliminary evaluation of patients under 40 years, and multi-detector computed tomography (MDCT) in patients aged 50 years or over) (Mayo *et al*., 2003).

The aim of this procedure is to recognize observations classical of the UIP pattern, and to differentiate them from the less particular patterns present in other idiopathic interstitial pneumonias. The radiological reading should employ descriptive terminology based on the radiological–pathological correlation to prevent descriptive and conceptual issues, as suggested by the Fleischner Society (Hansell *et al*., 2008).

It was determined by the official 2011 ATS/ERS/JRS/ALAT consensus (Raghu *et al*., 2011) that in HRCT, the conclusive diagnosis of UIP is based on the recognition of four "classical" observations: (1) lung collaboration should have subpleural and basal predominance, (2) existence of evident reticulation, (3) presence of honeycombing with/without traction bronchiectasis/bronchiolectasis and (4) describe the deprivation of observations contemplated to exclude a UIP pattern.

The occurrence of ground glass opacities should be nonexistent or least. Honeycombing, created by groups of thin-walled cysts, subpleural with a diameter between 3 and 10 mm, is a crucial observation for precisely diagnosing the UIP pattern. The diagnosis of a possible UIP pattern by HRCT in the absence of noticeable honeycombing; in such cases, the conclusive diagnosis of UIP should be done by biopsy. Lung biopsy can be ignored only when the HRCT exhibits a definitive pattern, classical of UIP. The positive prognostic value of HRCT in the diagnosis of UIP is 90%–100%. A UIP pattern can also be recognized in asbestosis, chronic hypersensitivity pneumonitis and few connective tissue diseases (Churg *et al*., 2006). HRCT also authorizes the existence of related comorbidities (pulmonary hypertension, emphysema, lung cancer), which may describe the clinical expansion of the disease, to be evaluated. Apart from idiopathic interstitial pneumonias, other diffuse lung diseases can also be determined by HRCT. It is suggested by the 2011 official ATS/ERS/JRS/ALAT consensus that the diagnosis of idiopathic interstitial pneumonias can be based on the consensus between the clinician, radiologist and pathologist (Raghu *et al*., 2011).

2.2.8.4 Histopathological Pattern

The surgical lung biopsy is done as the conclusive diagnosis in the case if the HRCT does not manifest a conclusive design of typical UIP. The sample for biopsy are acquired

from more than one lobe , and if it is possible the sample can be collected from the middle lobe and it is better to avoid the linguala, since they normally exhibit non- specific changes that do not give the diagnostic data. Atelectasia because of the extraction can be decreased by smoothly instilling formaldehyde by a needle, or by trembling the tissue with formaldehyde in the container after removing the suture. The histological pattern of UIP is explained by the four main condition: (a) Sign of marked fibrosis or deformation of lung architecture, related or not with honeycombing and generally subpleural and paraseptal; (b) Existence of patchy lesions in which the fibrotic region are combined with region of healthy lung; (c) existence of gibroblast loci in the region of meeting point of fibrosis and healthy parenchyma and (d) The histopathological findings unpredictable with UIP is not present.

Amidst the characteristics not affined with a UIP pattern are the existence of hyaline membranes, existence of foci with organizing pneumonia, granulomas, mainly airway centred changes, marked interstitial inflammatory cell infiltrate far from region of honeycombing or an alternative diagnosis can be characterized by the existence of other findings (Raghu *et al*., 2011). A histological pattern are almost identical from UIP can be spot in systemic diseases(For example .Scleroderma and rheumatoid arthritis), drug induced pneumonitis, chronic hypersensitivity pneumonitis , asbestoris and familial fibrosis, so during biopsy the existence of granulomas, asbestos bodies, particular infections or other exogenous agents should be removed. Due to the above reasons a UIP pattern must not illuminate straightly as an IPF pattern, without rejection of all these diseases. The amalgamation of the HRCT findings along with the histological pattern is used to create the diagnosis of IPf, eliminate it or , if the data are indeterminate, continue as feasible or most likely as result (Spagnolo *et al*., 2015).

2.2.8.5 Clinical Prediction Models in IPF

Clinical findings from history, physical examination, and/or test results are coalesced in clinical prediction models which are also considered as statistical models to evaluate the probability of the consequence, generally a diagnosis or prognosis (Toll *et al*., 2008). The thorough selection of indicator parameters rely on their success which are reproducibly and generally measured in present clinical practice, evolution through acquired statistical

procedures involving internal validation, and eventually execution of external validation and clinical influence analysis (Harrell *et al*., 1996; Laupacis, 1997; Toll *et al*., 2008).

A clinical prediction model, the CRP score has been evolved in IPF (King *et al*., 2001b). It includes age, smoking status, and profusion of fibrosis, clubbing and pulmonary hypertension on chest radiography, total lung capacity, and partial pressure of arterial oxygen during maximum exercise. A high anticipation of survival in the cohort from which it was obtained was exhibited by the CRP score, but has not been extensively embraced in clinical practice due to its deficient valid external validation and employs few parameters that are not regularly measured in present clinical practice (i.e., clubbing, profusion of fibrosis and pulmonary hypertension on chest radiography, and partial pressure of oxygen during maximum exercise).

Data employed from a study with large and well-identified population of patients with IPF exhibited that numerous variables were autonomous indicators of mortality, comprising: age (≥ 70 yr vs. < 60; HR, 2.2 [95% CI, 1.3–3.6]), history of respiratory hospitalization (HR, 4.0 [95% CI, 2.5–6.4]), 24-week alteration in percent predicted FVC (≤ −10 vs. > −5; HR, 8.3 [95% CI, 5.5–12.5]), percent predicted FVC (≤ 50 vs. ≥ 80; HR, 5.9 [95% CI, 2.6–13.3]), percent predicted DLco, 24-week alteration in Dl_{CO}, and 24-week alteration in health-associated quality of life (du Bois *et al*., 2011). A clinical pattern was described by the investigators comprising of only four indicators (age, history of respiratory hospitalization, percent predicted FVC, and 24-wk alteration in FVC) that anticipated the overall risk of 1-year mortality (du Bois *et al*., 2011). If substantiated, such a risk-scoring structure should be helpful in clinical practice.

2.2.9 Differential diagnosis

There are numerous significant clinical components that are considerate in differential diagnosis of interstitial lung diseases (ILD) and IPF which is the most general type of ILD.

Table 1: Clinical characteristics for differential diagnosis of IPF

Feature	Description
Age	Sarcoidosis, PSS, RA, SLE, Sjogren's syndrome general in young,

	IIPs (specifically UIP) in the older age groups
Gender	CVDs, Lofgren's syndrome in women
Tobacco smoking	DIP, respiratory bronchiolitis related IIP
Occupational exposure	Hypersensitivity pneumonitis, pneumoconiosis
Onset of symptoms	Acute, subacute or chronic
Drug intake	cytotoxics, amiodarone, NFT
Family history	sarcoidosis, UIP
Febrile illness	infections, SLE, vasculitis, sarcoidosis, TPE
Hemoptysis	vasculitis (WG), pulmonary haemorrhage, hemosiderosis, Goodpasture's
Athralgia/arthritis	sarcoidosis (ankle arthritis), RA(hands)
Skin lesions	Sarcoid lesions, EN, vasculitic ulcer, subungual infarct, heliotrope, PSS, rheumatoid nodule, butterfly rash
Eye involvement	Uveitis, conjunctivitis, scleritis, xerophthalmia in sarcoidosis, CVD, WG, Sjogren's
Peripheral lymphadenopathy	TB, sarcoid, fungal infection, HIV
Digital clubbing	UIP
Raynaud's phenomenon	PSS

Source: Source: Adopted from Pande (2013)

In view of the prognostic distinctions that prevail amongst the IIPs, precise diagnosis of IPF is crucial. Clinical diagnosis of IIPs presently is established on a comprehensive medical history along with a physical examination. Prior identification of IPF certainly usually begins with a high degree of clinical intuition and good clinical awareness accompanied by chest radiographs and lung function tests. In IIP presumed patients HRCT is conducted. HRCT is now an essential component of the diagnostic technique for IIPs (fig. 1), as explored below in detail, wherein a constant technique in which pulmonologists, radiologists, pathologists and thoracic surgeons are all involved in a significant role. The requirement for SLB in as many as 50% of patients with IIP may be abolished though by the

radiological diagnosis of HRCT (Raghu *et al*., 1999b; Hunninghake *et al*., 2001), the conclusive technique for eliminating other disease operations still continues to be the histological diagnosis by SLB that can imitate IPF, especially the hypersensitivity pneumonia (American Thoracic Society & European Respiratory Society, 2002). IPF is clinically a powerful accused in any patient aged o50 yrs representing with unidentified dyspnoea on strain that has been existing over a time of o3 months, and with affirmation of bibasilar, inspiratory ‘‘velcro-like’’ crackles on chest auscultation. Though the existence of at least three of these minor diagnostic specifications, patients must additionally me*et al*l four major specifications, which comprise: 1) the removal of other known reasons of ILD; 2) atypical pulmonary function tests with affirmation of diminished and limited gas exchange; 3) bibasilar reticular deformities with negligible ground-glass opacities on lung HRCT; and 4) bronchoalveolar lavage or transbronchial lung biopsy without characteristics to assist an auxiliary diagnosis (NCBI, 2000).

While the existence of IPF is not eliminated in a standard chest radiograph, radiographic affirmation of decreased lung volume and honeycombing and reticular opacities is extremely indicative. If there is radiographic affirmation of concurrent pleural disease, remarkable lymphadenopathy or alveolar opacities an auxiliary diagnosis to IPF is more probable.

The pulmonary fibrosis of asbestosis is interstitial and has basal subpleural diffusion, analogous to that observed in idiopathic pulmonary fibrosis, which is the crucial differential diagnosis. There are distinctions amongst the 2 diseases nevertheless independent from the existence or non-existence of asbestos. Firstly, the interstitial fibrosis of asbestosis though not clear is assisted by very less infection, which is better evolved in idiopathic pulmonary fibrosis. Secondly, by guarding with the unhurried pace of the disease, the fibroblastic foci that distinguish idiopathic pulmonary fibrosis are scarce in asbestosis. Thirdly, asbestosis is virtually constantly supplemented by mild fibrosis of the visceral pleura, which is a characteristic that is unusual in idiopathic pulmonary fibrosis (Roggli *et al*., 2010).

2.2.10 Prognosis

One of the most frequent interstitial lung diseases, IPF, has the worst prognosis, with a medial survival of two to three years (NCBI, 2000).As per the outcomes of studies on the prognosis of IPF, several components, like old age, male, smoking history, dyspnea, decreased pulmonary operation, enhanced eosinophils or neutrophils in the bronchoalveolar lavage, radiological abnormality, honeycombing opacity on HRCT and fibroblast foci on biopsy, were exhibited to be related with poor prognosis (Flaherty *et al*., 2003a; Nicholson *et al*., 2002; King *et al*., 2001a). It was analysed by Cano *et al*. (2004) that the BMI was one of the mortality indicators due to several reasons in 446 patients who had chronic respiratory failures, and that BMI was related with prognosis of patients with opposed pulmonary deterioration. Out of the aforesaid patients, 162 patients had opposed pulmonary deterioration33, but most of them were patients with chest wall abnormality or kyphoscoliosis. In this study, unluckily the outcome was acquired from patients who had chronic respiratory failure due to several reasons since the ratio of patients with interstitial lung disease or IPF was not exhibited, it was strenuous to precisely associate BMI with mortality risk which was caused by IPF (Cano *et al*., 2004). High BMI imparted to the enhancement of the survival time of patients with IPF34 was analysed and the malnutrition level caused thymic atrophy and decreased T-lymphocyte operation, thus enhancing inflammation risk and reducing the survival (Tilg & Moschen, 2006; Savino, 2002).

2.2.11 Predictors of Survival in IPF

The anticipated survival in IPF is exhibited by many discrete clinical variables. These may be further subdivided into clinical indicators derived from the history and physical examination, physiologic predictors, radiographic predictors, pathologic predictors, and biomarker predictors. Components that are related usually with reduced survival duration comprise: older age, history of smoking, more acute physiologic deterioration, lower body mass index (BMI), greater radiologic magnitude of disease, and the progression of other problems or situations, specifically, emphysema, pulmonary hypertension and bronchogenic cancer (Alakhras et al., 2007; Nadrous et al., 2005; Collard et al., 2003; King et al., 2001b).

2.2.11.1 Clinical Predictors

Age:

A clinical component of IPF is older age with a median age of 66 years during the period of diagnosis (NCBI, 2000; Raghu *et al*., 2006b). Older age additionally has been exhibited to bestow a poorer prognosis. It was exhibited in one study that a Hazard Ratio (HR) of 0.25 (Confidence Interval [CI], 0.125–0.5) for survival in patients younger than 50 years of age (Erbes *et al*., 1997). Median survival in another study for patients younger than 50 years of age was 116.4 months in contrast with 62.8 months for subjects aged 50–60 years, 27.2 months for subjects 60 to 70 years of age and 14.6 months for subjects older than 70 years of age (King *et al*., 2001b). A descriptive study of patients with IPF younger than 50 years of age although witnessed a median survival of only 2.1 years, in contrast to that witnessed in older patients with IPF (Nadrous *et al*., 2005). It was proposed by the authors of this study that earlier findings of younger age as a beneficial prognostic component may have been because of the inclusion of patients with nonspecific interstitial pneumonia in the previous studies and/or distinctions in the definition of disease onset. It was demonstrated currently by Fell and colleagues that age, in coalesces with the observations on HRCT is a significant diagnostic tool that recognizes patients with IPF (Fell *et al*., 2010). Emanating data additionally proposes that age-associated modifications in cellular activity may a play significant role in the pathogenesis of IPF (Collard, 2010).

Sex:

It is observed that IPF is more common in men, but sex distinctions in survival have been variable (Schwartz *et al*., 1994; King *et al*., 2001b; Erbes *et al*., 1997). According to a study that basically evaluated sex distinctions in IPF the female sex observed to bestow a remarkable survival benefit (HR, 0.63; CI, 0.41–0.97) after assimilating for age, smoking level and baseline physiologic variables (Han *et al*., 2008). This survival benefit prevailed remarkable even after modifying for 6-month alterations in 6-minute walk test (6MWT) desaturation and FVC % anticipated, proposing the survival benefit may not be completely described by distinctions in disease advancement. Mortality rates in women with pulmonary fibrosis although are rising more quickly as compared to men (Olson *et al*., 2007).

Ethnicity:

The role of ethnicity in the prognosis of IPF contains restricted data. Whites are more probable to be diagnosed with IPF than blacks (Olson *et al*., 2007). A previous study on the unison guidelines proposed higher mortality of whites in contrast to the blacks (Mannino *et al*., 1996), while two more current studies of patients recorded for lung transplantation observed that the survival among both blacks and Hispanics decreased in contrast to the whites that continued after assimilation of comorbidities and socioeconomic status (Lederer *et al*., 2006c, 2006a). It was exhibited by Olson and coworkers that age-assimilated mortality rates in Hispanics are lower than in white non-Hispanics (Olson *et al*., 2007).

Smoking status:

The smoking level consequence on the survival is also been inconsistent. It was observed in older studies that survival benefit in present smokers as compared to the past and never smokers (King *et al*., 2001b). The influence of smoking status on IPF in a study precisely exploring it, exhibited that the survival benefit in present smokers in contrast to the former smokers on univariate analysis, while after assimilation for disease severity, a "healthy smoker effect" was demonstrated since this consequence was no longer remarkable (Antoniou *et al*., 2008). A selection prejudice was noticed in the healthy smoker effect in studies of respiratory illnesses, since individuals most fragile to the irritating consequences of tobacco are more probable to quit smoking, thus focussing on individuals who are "resistant" to the short-term consequences into the present smokers "healthier" category from a respiratory point of view (Becklake & Lalloo, 1990). Nonsmokers had a higher survival rate generally than past smokers and all smokers (present and past).

Dyspnea:

To evaluate the quality of life, disease severity, and prognosis dyspnea scores are employed in diverse pulmonary diseases. The Medical Research Council chronic dyspnea score at baseline and the clinical-radiographic-physiologic (CRP) dyspnea score at baseline and change in score at 6 and 12 months in IPF have exhibited to be remarkable and autonomous indicators of survival after assimilation for disease seriousness by physiologic variables (Manali *et al*., 2008; Collard *et al*., 2003).

Physical findings:

The exhibited IPF related physical examination observations with prognosis are digital clubbing and BMI. A remarkable related decrease in survival was exhibited by digital clubbing after assimilation of age and smoking status with an HR of 2.5 that was extremely notable (King *et al*., 2001b). This relation although has not been distinctively studied in other cohorts. An inverse relation is exhibited by BMI with survival, with a median survival of 3.6 years for BMI less than 25, 3.8 years for BMI 25 to 30, and 5.8 years for BMI greater than 30 (Alakhras *et al*., 2007). Per 1-unit rise in BMI there was an HR of 0.93. The protective consequence of enhanced BMI cause in IPF is uncertain, but as hypothesized with other chronic lung diseases, it may be that reduced BMI is a marker of malnutrition and/or increased activity and basal energy dissipation (Alakhras *et al*., 2007).

Impact of comorbidities:

Pulmonary hypertension is frequent in IPF and related with lower diffusing capacity of carbon monoxide (DlCO), desaturation during exercise, shorter walk distances and enhanced risk of death in patients with IPF (Lettieri *et al*., 2006a; Hamada *et al*., 2007; Fell & Martinez, 2007; Nathan *et al*., 2007; Nadrous *et al*., 2005). In an IPF recorded study of patients for lung transplantation, 32% of patients had pulmonary hypertension by right-sided heart catheterization (Lettieri *et al*., 2006a). Pulmonary hypertension persistent patients had much greater mortality (1-yr mortality of 28% in contrast to 5.5% for patients without pulmonary hypertension), and the risk of mortality risk linearly associated with mean pulmonary artery pressure. According to another study on continuous right-sided heart catheterization in patients with IPF anticipating transplantation approximately all patients exhibited evolution of pulmonary hypertension subsequent in their path (38.6% at baseline and 86.4% at transplantation) (Nathan *et al*., 2008a).

Since there are restricted data substantiating successful particular therapies for pulmonary hypertension in patients with IPF and right-sided heart catheterization is invasive, its regular utilization for prognostic evaluation alone is inappropriate, and non-invasive procedures for screening would be advantageous. Transthoracic echocardiography as a non-invasive procedure of capturing pulmonary hypertension have been evaluated by various

studies and have exhibited that increased approximate pulmonary artery systolic pressure is related with decreased survival employing thresholds of 40 to 50 mm Hg (Song *et al*., 2009; Nadrous *et al*., 2005). Its test features are poor though, with an accuracy of only 40% in contrast to the right-sided heart catheterization (Nathan *et al*., 2008b). B-type natriuretic peptide extent may be more anticipating of mortality than pulmonary artery systolic pressure by transthoracic echocardiography since it is associated with pulmonary hypertension (Song *et al*., 2009). As measured by HRCT the main pulmonary artery diameter may be a questionable indicator of pulmonary hypertension in IPF (Zisman *et al*., 2007). In choosing patients with higher pretest probability for having pulmonary hypertension in IPF other clinical variables may be helpful, comprising reduced DlCO, poor performance on 6MWT and use of supplemental oxygen (Lettieri *et al*., 2006a). A prediction formula employing room air saturation, DlCO, and FVC indeed exhibited adequate accuracy and high sensitivity for drecognizing pulmonary hypertension in IPF, indicating the role in screening for pulmonary hypertension (Zisman *et al*., 2008).

The patients with IPF and emphysema are generally heavy cigarette-smoking men who exhibit comparatively reserved lung volumes related with irregular deterioration of gas exchange and encounter serious dyspnea on exertion (Grubstein *et al*., 2005; Mura *et al*., 2006; Jankowich *et al*., 2008; Casas *et al*., 2008; Silva *et al*., 2008; Akagi *et al*., 2009). The baseline pulmonary function tests are affected by emphysema by enhancing lung volumes and declining DlCO and FEV1/FVC, as well as modifying the conversion of these values over a period and hence modifying or concealing the evaluation of disease seriousness at baseline and advancement over a period (Cottin *et al*., 2005; Akagi *et al*., 2009). In these patients the early and severe pulmonary arterial hypertension originates and they have a critical survival in contrast to the patients with IPF without emphysema (Mejía *et al*., 2009; Cottin *et al*., 2010). It is observed by few professionals that the relation of IPF with emphysema is a discrete clinical structure (Millar & Denison, 1990; Wiggins *et al*., 1990; Hiwatari *et al*., 1993; Doherty *et al*., 1997; Silva *et al*., 2008; Cottin *et al*., 2005; Mejía *et al*., 2009; Cottin *et al*., 2010).

Subsequent research is necessary to ascertain that other comorbidities may also impact the outcome in IPF. Gastroesophageal reflux and IPF have a strong relation

(prevalence of nearly 90%) (Patti *et al*., 2005; Raghu *et al*., 2006a; Sweet *et al*., 2007; Tobin *et al*., 1998). Though a causal association is uncertain, additionally it has been postulated that gastroesophageal reflux may be a risk factor for microaspiration, and this may be significant in the aeitiology and pathogenesis of IPF (Lee *et al*., 2010). Patients with IPF have decreased survival with notable coronary artery disease in contrast with those with mild or no disease, an interesting observation given the prevalence of the disease and confirmation that few patients with IPF die due to cardiac reasons (Nathan *et al*., 2010). Bronchogenic carcinoma moreover happens with enhanced recurrence in IPF (9.8 to 38%) and has a considerable influence on prognosis (Bouros *et al*., 2002).

Radiographic Predictors:

The radiographic norm in the assessment of IPF is the HRCT of the chest, providing vital diagnostic and prognostic details. Numerous parenchymal deformities can be evaluated and determined, comprising consolidation, reticulation, extent of ground-glass opacities and honeycombing. Honeycombing and reticulation are usually merged to generate an overall degree of fibrosis score. The overall pattern can be additionally classified by its uniformity with the common interstitial pneumonia (UIP) pattern.

The overall degree of fibrosis out of these discrete CT observations has been constantly exhibited to associate with disease seriousness variables on pulmonary function tests and prognosis (Mogulkoc *et al*., 2001; Battista *et al*., 2003; Lynch *et al*., 2005; Shin *et al*., 2008; Best *et al*., 2008; Sumikawa *et al*., 2008). Quantification of fibrosis fascinatingly may be programmed by a computer system and speculate survival (Iwasawa *et al*., 2009).

The UIP pattern on HRCT (basically basilar and subpleural honeycombing) has also been exhibited to simulate a worse prognosis in patients with IPF in contrast with those having atypical HRCT observations, indicating that the HRCT pattern computes prognostic details to histopathologic diagnosis (Flaherty *et al*., 2003b). Other studies although exhibited that in patients with histologic UIP, the prognosis of patients with an atypical pattern and the UIP pattern on HRCT are alike (Lynch *et al*., 2005; Sumikawa *et al*., 2008).

Physiologic Predictors:

Numerous physiologic parameters like spirometry, lung volumes and gas exchange on pulmonary function testing have been employed to evaluate disease seriousness and anticipate survival in IPF. The ones most frequently related with prognosis are FVC, TLC, and DlCO (McLoud, 2005; King *et al*., 2001b; Erbes *et al*., 1997; Manali *et al*., 2008; Hamada *et al*., 2007; Mogulkoc *et al*., 2001; Shin *et al*., 2008). Confounding by obstructive lung disease is one of the disadvantages with executing these measures, particularly emphysema, which results in lesser decrease in lung volumes and a greater decrease in gas exchange (Akagi *et al*., 2009). To describe emphysema in IPF a composite physiologic index has been created integrating FVC, DlCO, and FEV1 into a formula that associates better with disease magnitude by CT than any discrete pulmonary function test and may be a more precise indicator of survival (Wells *et al*., 2003; Latsi *et al*., 2003).

The modifications over a period of time may refine predictive power although baseline pulmonary function tests are helpful for anticipating prognosis. 6- to 12-month alterations in FVC and DlCO are highly predictive of outcome as exhibited by various studies (Flaherty *et al*., 2006; Hanson *et al*., 1995; Collard *et al*., 2003) and over a period of time become more predictive of prognosis than most baseline features, comprising histopathologic diagnosis (Jegal *et al*., 2005; Latsi *et al*., 2003). Clinically notable modifications in FVC and DlCO have basically been contemplated to be greater than 10% and greater than 15%, respectively. Even marginal reductions in FVC at 6 months (Swigris *et al*., 2005; Bjoraker *et al*., 1998; Nagai *et al*., 1999; Nicholson *et al*., 2000; King *et al*., 2001a; Collard *et al*., 2003) nevertheless are related with higher risk for mortality (Zappala *et al*., 2010; Collard *et al*., 2003; du Bois *et al*., 2011). Modifications greater than 15% in DlCO only were anticipating the mortality risk (Zappala *et al*., 2010).

Exercise testing is another procedure to evaluate the physiologic seriousness of lung disease. Exercise testing is more delicate than resting physiological testing in the identification of deformities in oxygen transfer. Patients with IPF as a group, exhibit a restriction in exercise tolerance, with a reduced maximal work load (median, 50.4% indicated as percentage of anticipated), increased Vd/Vt, and abnormal gas exchange (reduced PaO2 and increased alveolar arterial Po2) (King *et al*., 2001b). Exercise gas exchange indeed has been exhibited to be a delicate variable for succeeding the clinical path of IPF (Fulmer *et*

al., 1979; Keogh & Crystal, 1980). Patients have an enhanced risk of death if the Vo2max less than 8.3 ml/kg/min at baseline (Fell *et al*., 2010). The 6MWT has become the most extensively employed exercise test in most of the lung diseases, including IPF, given its easy execution and reproducibility (Eaton *et al*., 2005; Kadikar *et al*., 1997). Distance walked (Lederer *et al*., 2006b; Caminati *et al*., 2009) and desaturation (Hallstrand *et al*., 2005; Flaherty *et al*., 2006) during the 6MWT both have been observed to anticipate mortality, and in one study a composite of the product of distance and desaturation anticipated mortality better than either of the measures alone (Lettieri *et al*., 2006b). Abnormal heart rate recovery after 1 minute of rest after the 6MWT also may be a unique and strong indicator of mortality (Lettieri *et al*., 2006b). Current data exhibits that a significant modification in 6MWD is extremely predictive of mortality (i.e., a decrease in 6MWD > 50 m over 24 wk is related with a fourfold enhancement in the risk of death at 1 year [P < 0.001]) (Bois *et al*., 2011). It has been recommended additionally that the least significant distinction for 6MWD is nearly 30 m (i.e, patients can distinguish the smallest modification in distance as distinct from the earlier test and that would authorize, an alteration in the management in the lacking of annoying side effects and lavish costs) (Swigris *et al*., 2010; Bois *et al*., 2011). The confirmation to the effectiveness of desaturation during exercise testing for anticipating mortality can be done by two other exercise tests, the 15-step and 4-minute step tests (Shitrit *et al*., 2009; Stephan *et al*., 2007).

Pathologic Predictors:

The histopathologic pattern is UIP that recognizes IPF, and it conveys the worst prognosis amongst the idiopathic interstitial pneumonias (American Thoracic Society & European Respiratory Society, 2002; Bjoraker *et al*., 1998; Nicholson *et al*., 2000). Biopsies from distinct lobar specimens in the same patient fascinatingly may exhibit histologic discordance, that is, nonspecific interstitial pneumonia in one area and patterns of UIP in another area (i.e., discordant UIP). Discordant UIP category patients exhibit survival, clinical and physiologic characteristics comparable to those observed in the concordant UIP category, and significantly, the prognosis in both concordant and discordant UIP categories was notably worse than that of the concordant nonspecific interstitial pneumonia category (Flaherty *et al*., 2001; Monaghan *et al*., 2004).

Dense fibrosis and honeycombing is identified in UIP with architectural deformation, fibroblastic foci (foci of multiplying fibroblasts), subpleural and paraseptal disposition and heterogeneous implication (American Thoracic Society. Idiopathic pulmonary fibrosis, 2000). As evaluated by both semi-quantitative and quantitative procedures, fibroblastic foci amongst these characteristics are postulated to play a significant role in the pathophysiology of IPF and their profusion, and have been exhibited, in some cohorts, to anticipate survival (Enomoto *et al*., 2006; Nicholson *et al*., 2002; King *et al*., 2001a). It has been exhibited that lymphoplasmacytic inflammation can anticipate response to immunomodulatory remedy in UIP, while the existence of organizing pneumonia anticipates a lack of response (Collard *et al*., 2007a). None of these characteristics although were observed to be anticipating of survival (Collard *et al*., 2007a). Stating the developing dependency significantly on the clinical and chest imaging criteria to diagnose IPF, the diagnosis remains uncertain on the clinical grounds alone wherein surgical lung biopsies are now commonly executed in atypical cases. This may thus restrict the role of pathology as a regular indicator of prognosis.

Biomarker Predictors:

The blood and bronchoalveolar lavage (BAL) fluid biomarkers have been exhibited to relate with the disease advancement and survival in IPF. Though most remain experimental and have not been extensively employed in clinical practice. A better indicator of survival was exhibited by B-type natriuretic peptide rather than echocardiographic evaluation of pulmonary hypertension (Song *et al*., 2009). Prognosis in most diseases is negatively associated with the albumin levels, and anticipates survival in patients with idiopathic interstitial pneumonias expecting transplantation (Zisman *et al*., 2009). A high molecular weight mucin-like glycoprotein (human MUC1 mucin), Krebs von den Lungen-6 (KL-6) is a delicate marker for interstitial lung diseases, and patients with IPF with higher KL-6 degrees may have decreased survival (Yokoyama *et al*., 2006). The alveolar type II pneumocytes secrete surfactant proteins A and D (SP-A and SP-D) and enhance in the blood in relation with breakdown of the alveolar epithelium (Greene *et al*., 1999). To anticipate survival in patients before present international consensus guidelines for IPF the levels in BAL fluid and blood were exhibited (McCormack *et al*., 1995; van den Blink *et al*., 2010). High serum levels of both SP-A and SP-D more currently were exhibited to be related with enhanced

mortality but not the magnitude of honeycombing on HRCT (Takahashi *et al*., 2000). SP-A and SP-D levels in serum seem to be autonomous indicators of mortality (Barlo *et al*., 2009; Kinder *et al*., 2009), and their inclusion to clinical indicators alone may enhance prediction of 1-year mortality (Kinder *et al*., 2009). Extracellular matrix remodelling is significant in matrix metalloproteinases (MMPs) and seems to be increased in both blood and BAL fluid in patients with IPF. In one study, MMP-3, -7, -8, and -9 levels in BAL fluid were enhanced in patients who died early in the follow-up (McKeown *et al*., 2009). As exhibited by another study the MMP-7 was negatively associated with FVC and DlCO, but a relation with prognosis was not basically studied (Rosas *et al*., 2008). A significant role in inflammatory cell migration was exhibited by CC-chemokines (CCLs), and several members are increased in IPF. CCL-18, a CC chemokine in serum, released by the alveolar macrophages, was currently exhibited to be a powerful and autonomous indicator of mortality (Prasse *et al*., 2009). Increased CCL-2, -17, and -22 in BAL fluids may anticipate poor outcome (Shinoda *et al*., 2009). Mesenchymal cell progenitors are fibrocytes that are involved in tissue repair and fibrosis, and the circulating levels are increased in IPF and enhance subsequently during acute aggravations (Moeller *et al*., 2009). Their levels do not associate with the disease seriousness by lung function or radiologic scores but seems to be an autonomous indicator of early mortality. BAL cell counts eventually may be helpful in anticipating mortality. The BAL neutrophil percentage at baseline has been exhibited to be autonomous to anticipate 1-year mortality, while the lymphocyte and eosinophil percentages had no relation with mortality (Kinder *et al*., 2008).

2.2.12 Management

The main cause for morality and illness is caused by IPF and so it reflects the huge not met up medical requirement (Spagnolo *et al*., 2015).Anyhow, over the previous five years, there is a remarkable strides to ameliorate the effect on IPF on patients by advanced and recent pharmaceutical treatments.

In spite of these advances, the surgical intervention by lung transfer (LTx) is left over as the sole therapy which can potentially remove the root cause of IPF related dyspnea (Yet the above treatment is used as a last option).

Pharmacological treatment:

Glucocorticoids or immunosuppressive drugs constitute the conventional method to treat patients since there was a thought that inflammation is associated to the development of IPF, mainly to the patients have milder case of disease (Bando, 2016). Nevertheless, in the year 2011 ATS/ERS/JRS/ALAT instruction advises that corticosteroid monotherapy, cyclosporine A therapy, or the combination of both corticosteroid and immune suppressant (azathioprine or cyclophosphamide) should be avoided for the treatment of IPF (Bando, 2016). The unrevealed expose of new thought was a study at 2012 states that a triple anti-inflammatory treatment combination using N-acetyl cysteine, prednisone, and azathioprine was notably harmful to patients with IPF. The trial was cosy away since they discovered the resulted in 10% enlargement in mortality-mainly because of respiratory causes-and a material (>300%) rise in hospitalization and unfavourable effects (Raghu *et al*., 2012).

Preferably than the immunosuppressant agents, from October 2014, on the two recently FDA approved oral antifibrotics named pirfenidone and nintedanib either of them was used to treat mild-tomoderate. But, the effectiveness of the drug on severe IPF and the optimal length of therapy was not known, since it was introduced comparatively recent times. Not either were approved in international IPF guidelines (Handa & Azuma, 2016).

Pirfenidone , a pyridine is to be trusted to act through anti-inflammatory and anti-fibrotic chemical pathway ,in fact the correct mechanism remains unknown (Karimi-Shah & Chowdhury, 2015).It is a belief to impair the TGF- β production and effect (Fernandez & Eickelberg, 2012).The meta- analysis of three European /Japanese trials of Pirfenidone appears a decrease in the proportion of patients undergo larger than 10% a forecast decline in FVC is close to 44% in the pirfenidone group compared with the placebo (Noble *et al*., 2016). Likewise the FDA- mandated study previous to U.S. approval found comparatively reduction of 50% in the proportion patient who undergoes a diminish in predicted FVC (Aravena *et al*., 2015).It has been noticed that pirfenidone in trial outcomes possess more complementary mortality rates compared to nintedanib, yet this may be result due to differently structured trials (Wells & Rosas, 2016).

In Japan, Nintedanib is a tyrosine kinase inhibitor is used first to treat IPF. It seems to appear that it have a wide inhibitory activity on the downstream signalling cascades on fibroblasts and myofibroblasts (Wollin *et al*., 2015). Nintedanib was discovered to decrease the decline in FVC and also detaining the onset of acute exacerbation (Richeldi *et al*., 2014).There is a steady rate in number of death in nintedanib group to those in the placebo group, yet the above study have not that much ability to demonstrate a mortality benefit.

The major antioxidant glutathione 's precursor molecule Acetylcystenine , daily dosage level of 1800 mg is given, has been exibit to replace depleted pulmonary glutathione levels (Behr *et al*., 1997, 2002) and as a result, the lung function shows statistically notable development in patients with fibrosing alveolitis after 12 weeks 18 weeks of treatment.

It is also illustrated that these newly-introduced oral therapies (pirfenidone and nintedanib) do not drive back the fibrosis, instead they just detain the patient's functional decline (O'Flaherty *et al*., 2015). Furthermore ,the result of latest study states that usage of both the above drugs in combination or utilized alone, reveals greater efficacy in decreasing in vitro proliferation of fibroblastic cells (Lehtonen *et al*., 2016).This was portend by a 2025 editorial that brief noted that " The IPF treatment of the future is based on the combination therapy (Wells, 2015).The main provocation in architecture of combined or best use of different treatment , Doctors. Kolb, Jenkins and Richeldi states that "IPF, we still do not know to explain the cause of treatment failure. The short fall of lung function on a definite period of time …has been largely used to assess disease progression and the risk of death in IPF, a question was raised on its value….and not significant to show the effect of therapy of an individual and so cant explain treatment failure" (Kolb *et al*., 2016).They proclaim that more controlled studies, and just not by retrospective data reviews, there should be chase in an attempt to balance on the combined use of both drugs" individual needs with group endurance" (Kolb *et al*., 2016).

The clinicaltrials.gov states that, many prospective therapies are under examination, including antiviral therapy focusing herpesvirus. As illustrated above ,a dormant connection between herpes virus and IPF has been recognised (Kropski *et al*., 2012).

Non-pharmacological treatment:

i. Oxygen Therapy and ventilation

It is predictable; that it is universal dyspnea is undergone by the patients with IPF, for the patients with hypoxemia because of IPF the ambulatory oxygen therapy are frequently used. Inspite the progress of time, as of 2013, no clinical trials have estimated the functional outcomes or endurance of patients with IPF hinge on either in term or long period oxygen therapy (Criner, 2013). In the middle-1990s ,a retrospective statistical research of patients was done by Mayoclinic come to an end that the patients with IPF treated with oxygen proceeded inadequate than those not obtained this treatment (Douglas *et al*., 2000). Nonetheless ,this research could not decide whether the use of oxygen therapy coordinates with severity of disease or actually reflects a lower occurrence of survival resulting from the oxygen therapy (Douglas *et al*., 2000).

Likewise, another research found, without additional comment, that the supportive use of oxygen was a remarkable risk factor for mortality of patients with IPF (Lynch *et al*., 2005). In spite of absence of clinical trials and the results of research connecting use and mortality, majority of physicians are treating patients with IPF apparently believed that the supplemental oxygen treatment is suitable for use while resting, exercise, or nocturnal peripheral oxygen saturation drop under 89% (Holland & Swigris, 2014). “This opinion is probably the guidance by clinicians disinclination to leave inaccurate something….that can be rectified when so many other feature of the diseases are incurable” (Holland & Swigris, 2014). Hence, oxygen therapy continued to be a main pallitative component in the administration of the patients with IPF , as it showed to upgrade symptoms and inclusive quality of life (Criner, 2013).

For the patients with IPF affected by acute exacerbation proceed to hospitalization, so sometimes mechanical ventilation is used for that patients. Only minor amount of patients with IPf are affected by acute exacerbation, yet it is connected with high mortality. An inclusive review of 17,000 patient’s medical record with IPF berwixt 2006 and 2012 reviewed the relative use of mechanically invasive ventilation (MV) (endotracheal and tracheostomy) and non-invasive mechanical ventilation (NIMV). The all-inclusive mortality for the whole cohort of patients with IPF was 11.3%. The patients with MV had undergone elevated mortality (51.6% vs. 30.9%), were young (66.3 years vs. 70.2 years), and finally

lengthy stay at the hospitals (13.3 days vs. 6.5 days) than the patients who receives NIMV (Rush *et al*., 2016). Possibly it confirms the harmless impact of patient's utilization of ambulatory oxygen therapy , in such a way that the research by those in the study has no effect on the mortality comparatively between MV and NIMV cohorts (Rush *et al*., 2016). It was illustrated that the extremity condition that might probably the use of MV over NIMV in the initial instances makes differentiation between the influences of these modalities of care to be tough.

ii. Pulmonary Rehabilitation

Number of research have found a welfare from pulmonary rehabilitation, though there is no agreeable quality on the type, potency or time duration of treatment (Puglisi *et al*., 2016). In a assessment of these studies ,pulmonary rehabilitation was present ,may be unsurprisingly, to ends in "development in exercise forbearance , especially a transient elevation in the distance travelled in the walktest or reduction in heart rate" (Puglisi *et al*., 2016).

But a doubt was raised concerning the long-duration welfare of such treatment. For a sample, a study in 2015 found that in comparing patients with IPF in Israel who went through a 12-week period of pulmonary rehabilitation with a control category did not, the outcome of the discovery to survival and cardio-respiratory associated hospitalization exibit no remarkable differences (Vainshelboim *et al*., 2015). In a manner, pulmonary rehabilitation perhaps observed akin to palliative care-permitting development in quality of life(or end of life) without conveying development in striking or reversing the latent condition. Nevertheless, there can be no hesitation that patients with IPF are in acute need of development of their emotional and psychological state.

iii. Lung Transplant

As a common rule, patients with IPF are eligible for LTx when post-transplant life anticipation run over their current life anticipation lacking the transplant (George, 2011). As a result of seriousness of the disease and the ability of the treatment , IPF is presently a usual sign for which United Network for Organ sharing assign lungs for transplant, having elevated from 15% in 2000 to 37% in 2009 (George, 2011).

Numerous patients with IPF acquiring a LTx can be anticipated to with stand for several years after the procedure. Lately, the outcome of a retrospective research on whole Dutch patients with IPF who were filed for LTx in between 1989 and 2001 were reported. Out of these 98 patients, 30% of patients lost their life while waiting for aLTx. Meanwhile 52 pateints got aLTx with a average survival post- surgery of 10 years. Among the number of patients died on the waiting list , 21.9% were esteemed highly necessary based on conquering European transplant standards, while 38.6% were able to chose patients (ten Klooster *et al*., 2015). In the final stages of IPF in the most senior patients, bilateral lung transplantation (BLT) is the favoured course to single lung transplantation, since it has notably increased survival rate (Gulack *et al*., 2015). However ,based on the Dutch study, those patients who critizise harshly for BLT seems to have an elevated risk of pre-transplant mortality (ten Klooster *et al*., 2015). Undoubtedly, they were judged correctly as having more acute need for LTx than others on the record, though the elevated mortality may directly be derivable to relative shortage of both lungs for transplant.

iv. Psychological

With the state of forecast as evenly grim as IPF, and in the persistent delay in its diagnosis from the outset of symptoms, and the doubt over the development of the disease in individual patients, it appears sensible to await many patients with IPF to fight emotionally and psychologically with their diagnoses. A qualitative study of a category of 17 patients in England between 2007 and 2012 established that the patients reported “Strive to get a diagnosis and manage with a life –limiting ,suddenly developing illness with not a proper treatment and less backing structures (Duck *et al*., 2015)”.

It is well known that throughout the pertinent period, both pirfenidone or nintedanib were not yet ready for the use. On the period of Eropean trials for pirfenidone, a qualitative study was initiated on 71 patients with IPF acquiring the drug. They also disclosed alike difficulties with diagnosis and the effect of the state on their quality of life (Russell *et al*., 2016). Although , they also associated that pirfenidone had accustomed them a measure of faith although involved over sideeffects (nausea and photosensitivity), lower hope was noted to those using supplemental oxygen, primarily due to its use defined their activities and recognize them in public as other than healthy (Russell *et al*., 2016). The PROMIS Petient-

Reported Outcomes Measurement Information System was used to conduct an internet – based survey, organized two times with the sample of 220 patients with IPF during not disclosed period of time (Thus creating delibration of the effect of pharmaceutical treatments not possible) found scores of the patients with IPF were proportionate to those seen in patients with major depressive disorder (Yount *et al*., 2016).This research also states that those acquiring supplemental oxygen therapy were more injured than non-users in fatigue, social role aid, and their physical function (Yount *et al*., 2016).

2.3 Previous studies

Myllärniemi and Kaarteenaho (2015) outlined the reported analysis on the preclinical studies of the three main IPF drugs includes piefenidone, nintedanib, and N-acetyl cysteine (NAC).The report examined the study protocols, dissimilarities , and principal findings in the latest trials of these pharmacological treatments. The schedule for drug development and the plan for findings to the clinical use have been very contrasting in these cadres. Most of the countries recently received approval for pirfenidone which was discovered in 1976, but still today the correct mechanism remains unclear. On the contrary, nintedanib (BIBF1120) was recognized in wide screening tests as an exact specific inhibitor of convinced tyrosine kinases, yet there was no availability of published data of preclinical test just before 2014. A mucolytic drug named NAC with an antioxidant mechanism of action is declared to hold defined anti-fibrotic characterisation in many experimental models but showed unsuccessful in a latest randomized placebo- controlled trial. Currently, no healing treatment is available for IPF. In order for superior comprehension of the molecular mechanism of IPF, relative preclinical tests inclusive animal models and in vitro experiments on human lung cells are required to assist the development of therapeutic drugs.

Rindone and Rosset (2014) inspect the spot on N-acetylcysteine in idiopathic pulmonary fibrosis treatment. Idiopathic pulmonary fibrosis (IPF) yet a untreatable disease. The recommended therapy contains of pirfenidone combined with other drugs named azathioprine and acetylcycteine. The New England journal of Medicine reported a new review that goes counter the regular use of N-acetylcycteine (NAC) to be used on patients with IPF. There are also other studies available in favour of N-acetylcycteine. The prior study reviews the whole developments and summarize the fact by confirming that new studies

should be undergone to reveal whether the NAC must be delivered in combination with pirfenidone or not.

Behr *et al*. (2016) investigated the safety and forbearance of acetylcycteine and pirfenidone combination treatment in idiopathic pulmonary fibrosis where in incidental, double-blind, placebo controlled and phase 2 trial was undergone. In Europe in order to treat idiopathic pulmonary fibrosis, pirfenidone is used with oral acetylcyctenine also known as N-acetylcyctenine. Nevertheless, no unplanned examination was done on the safety and tolerability of the combined formation of the drug.

The safety and tolerability of acetylcysteniene linked with pirfenidone in patients who had IPF was evaluated by the PANORAMA. They also determined the exploratory efficacy endpoints. And from the PANORAMA study recommended that the combination of acetlycyctenine with pirfenidone does not significantly modify the pirfenidone's tolerability profile and improbable to be favorable in IPF.

A double-Blinded randomized trial was done by Huang *et al*. (2015) of pirfenidone in the Chinese patients with Idiopathic Pulmonary Fibrosis. Idiopathic pulmonary fibrosis (IPF) possesses shortage of productive treatment. Pirfenidone was antiquated to treat the patients with IPF. The Antioxident and antifibrotic outcome on IPF cases were deployed by N-acetylcyctenine (NAC).This research is a double-blinded, improved placebo-controlled, arbitrary phase II trial of pirfenidone in Chinese patients with IPF. Chinese IPF patients with light to average deterioration of pulmonary function were allocated with either oral pirfenidone (1800 mg per day) and NAC (1800 mg per day) or placebo with NAC (1800 mg per day) for around 48 weeks. The primary endpoints were modified in forced vital capacity (FVC) and walking length and the minimum SPO_2 at the time of the 6-minute walk test (6MWT) at the week 48.The basic secondary endpoint was the advancement less survival time. On correlation, the placebo combined with high dose NAC, the pirfenidone combination with high-dose NAC extended the progression –free survival of Chinese patients with IPF from low to neutral destruction of pulmonary function.

2.4 Research Gap

The examination of previous researches conducted in the context of treating IPF with different pharmaceutical interventions revealed that the efficacies of the different drugs involved in the treatment of IPF were examined wherein individual efficacies were concentrated to a great extent. Secondly, extent literature focused more on the efficacies of combined treatment of pirfenidone with nintedanib and little focus is made on the efficacy of pirfenidone and N-acetylcysteine for the treatment of IPF. Finally, a pairwise meta-analysis on the efficacy of pirfenidone and N-acetylcysteine is still lacking which would provide better insights for the treatment of IPF. In this regard, the present research is a meta-analysis which assesses the efficacy of pirfenidone with N-acetylcysteine for the treatment of IPF.

CHAPTER III: RESEARCH METHODOLOGY

The present chapter elaborates on the type of methodology that is employed in the present research wherein the chapter further elucidates the design of the research which is used to examine the efficacy of the pharmacological intervention (pirfenidone with N-acetylcysteine) for idiopathic pulmonary fibrosis. In this regard, studies are selected and examined using meta-analysis. For the research objectives to be achieved, the present research considers meta-analysis as the method to satisfy the research questions. The various steps involved in conducting the meta-analysis are explained in the chapter and the justification for the choice of meta-analysis is also elaborated. The methodology is constructed on the basis of the different statements stated in the guidelines of PRISMA which aids reviewing the studies in a transparent manner and provide results that are consistent and provide assistance to future researches.

3.1 Research Paradigm

Howell (2013) states that a paradigm as the process which would ascertain on how knowledge could be analysed. A research paradigm is deemed to affect or regulate researches wherein Weaver and Olson (2006, p.460) defined the term as the belief practices and patterns which influences the research inquiry within an area of study by the provision of lenses, processes and frames which facilitates accomplishment of investigation. In any research, it is stated that two different paradigms exist and the selection is based on the type of research; they are positivist and interpretivist (Weaver & Olson, 2006). In the present research, the positivist paradigm is selected which is justified by its superiority over other paradigms and well suits the research context and could satisfy the research aims and objectives. Every research paradigm possesses its own methodology, ontology, epistemology, and associated methods (Bowling, 2009; Weaver & Olson, 2006). Ontology is defined as the study which is metaphysical in nature whereas an epistemological study mostly refers to theories and philosophies. The definition of Weaver and Olson (2006) for methodology states that methodology is the manner through which knowledge is manipulated wherein a research method involves the use of specific instruments which involves collection of data for the analysis of the same from which useful research inferences and insights could be acquired.

The selection of the positivist research paradigm is based on the reasons of the paradigm's origin which is rooted in physical science wherein the approaches are generally systematic and scientific. The knowledge that is acquired from such a research approach is normally an assemblage of facts which is observed through observations such as experiments (WOLF, Week 3). The selection of a methodology for a positivist paradigm generally involves a quantitative approach wherein the generation of a hypothesis is based on the existence of knowledge in the context selected for the research (Bahari, 2010). The derivation of knowledge is described in a statistical manner wherein a quantitative methodology could quantify and measure the phenomenon which is contrary to the qualitative research methodology that looks for describing experiences, meaning and useful insights through textual analysis (Coolican, 2004). A quantitative positivist research paradigm employs several kinds of research instruments such as surveys, questionnaires, structured observations and quasi experiments (Holloway & Wheeler, 2010). On the contrary, an interpretive approach takes into consideration the theoretical beliefs which is constructed on social values wherein the means to interact with such a construction would be the use of language, meanings and analysis of the acquired inferences (Myers, 2008, p.38). The interpretive approach further takes into consideration the use of qualitative research methods which allows the acquisition of detailed narrative description of the research context. The involvement of the researcher would be high in an interpretive approach wherein the entire research process is facilitated by the researcher. The several methods involved in an interpretive research approach are interviews, case studies, participant observations and life-studies (Holloway & Wheeler, 2010).

Several guidelines are available which necessitates the maintenance of conduct during the meta-analysis. For systematic reviews and meta-analyses, the most commonly used guidelines are Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) (Moher *et al*., 2009) and Meta – analysis of Observational Studies in Epidemiology (MOOSE) (Stroup *et al*., 2000). Though both guidelines are similar based on the framework, the PRISMA framework is used in the research.

3.2 Meta-analysis of Randomised Controlled Trials

On the basis of the aims and objectives of the present research, meta-analysis is selected which could answer the research questions. A meta-analysis is defined as the quantitative research method which is non-experimental and could collect data as a pool together from two or more experimental studies that possess similar hypothesis (Bruce *et al*., 2008; Anderson, 2010). For the present meta-analysis, Randomised Controlled Trial (RCT) studies are used. The definition for RCT is as follows: "An experiment which is epidemiological wherein the selected subjects in a population were allocated randomly into two different groups namely the study group and the control group wherein these groups were allocated with or without experimental preventive procedure or intervention". The assessment of the results of an RCT is based on the comparison of disease rates, death, recovery or other outcomes in both control and study groups (Rajagopalan *et al*., 2013). One alternative term for RCT is Randomised trial which is used as a synonym in many cases; however some researchers tend to use 'randomised trial' to compare multiple treatment groups with each other which is different from RCTs wherein comparison is made between treatment groups and control groups/ placebo groups (Ranjith, 2005). The publishing of first RCT is facilitated by Sir A. Bradford Hill (Anon, 1948) who served as an epidemiologist for the Medical Research Council of England. However, the development of randomisation as a principle experimental design method took place in the year 1920 (Armitage, 2003). However, in the recent years, RCTs have found a unique position in medical researches and have become an optimal method for rational therapeutics (Meldrum, 2000). The selection of RCTs for meta-analysis is based on the fact that RCTs yield important research information and an examination of research findings from several RCTs could provide further more insights on the research topic.

3.3 Research Procedure

As aforementioned, several approaches of research are available wherein for the aim of reporting and to examine the conduct of the research, the PRISMA guidelines is utilised in the present research.

3.4 Search strategy

In the present research, the search for articles was carried out through different medical databases wherein the selection criteria at first included the selection of articles which are conducted in the period of 2006-2016. The various medical databases include Science direct, Cochrane databases, PubMed, EMBASE, and Cinhal and Medline. The search for literature was carried out between the time frame of December 2006 and December 2016. The ten years literature was examined in the present research wherein screening was made for selecting only RCTs. All searches were conducted to acquire full text articles wherein the search for literature studies was based on the PICO terminology (Population/ patients, Interventions, Comparison and outcome). The PICO methodology identifies the specific criteria for inclusion/ criteria for choosing the studies for investigation.

Population or patient	RCT, Patients with Idiopathic Pulmonary Fibrosis (IPF)
Intervention	Pirfenidone with N-acetylcysteine
Comparison	Intervention with Control groups which would have been administered a placebo or a placebo and combination or single drug
Outcome	The efficacy of combined drug therapy (Pirfenidone with N-acetylcysteine) for the treatment of Idiopathic Pulmonary Fibrosis

There are several keywords which are used to search for previous literature and identify the required RCT studies for the meta-analysis. The keyword search included the following terms: “combined drug therapy for Idiopathic Pulmonary Fibrosis” OR “combined drug therapy for IPF”, “pirfenidone with N-acetylcysteine”, “Efficacy of pirfenidone with N-acetylcysteine” or “Efficacy of pirfenidone with NAC”, and “combined treatment using pirfenidone with NAC”. The search strategy even narrowed down to examine the different cross references used in the articles. Other mono-therapy related articles which examined the efficacy of pirfenidone or NAC were analysed for acquiring a better understanding of the topic selected and the individual characteristics of each drug. The eligibility criteria which are provided in the following sections were also scrutinised for the selection of studies for meta-analysis.

3.4.1 Inclusion criteria

The inclusion criteria set for the selection of studies are as follows:

- Randomised Controlled Trial (RCT) studies related to efficacy of Pirfenidone with N-acetylcysteine
- Studies wherein the population are defined with intervention and control groups both being patients with IPF
- Studies which assessed the efficacy of Pirfenidone with N-acetylcysteine as a combined drug therapy
- Studies in English language
- Studies within the time frame of 2006-2016
- Studies which assessed the efficacy of Pirfenidone with N-acetylcysteine as intervention and control groups which could be administered with any drug treatment modality such as single drug therapy, combination of placebo and a drug or only with a placebo

3.4.2 Exclusion criteria

The exclusion criteria set for the selection of studies are as follows:

- Studies which were not conducted within the selected time-frame (2006-2016)
- Studies which assessed the efficacy of more than two drugs and drug treatment other than the combination of pirfenidone and NAC were excluded
- Studies which were not in English language
- Studies which were not RCTs
- Studies which assessed the efficacy of Pirfenidone with N-acetylcysteine for some other diseases other than IPF

3.4.3 Assessment of bias risk and methodological quality

Any meta-analysis requires the assessment of quality of methodology used and bias risk as such analysis acts as a tool for determination of the weaknesses of the study which might affect the results of the analysis (Higgins & Altman, 2008). There are two different types of validity which include internal and external validity. The internal validity is used to

address the suitability and appropriateness of the research design whereas the external validity is used to address the appropriateness of the research questions considered. In this regard, the examination of internal and external validity reduces or eliminates the risks of bias. According to Leandro (2004), proper emphasis should be laid upon the assessment of risks so as to eliminate underestimation or overestimation of the size of the effects which leads to false negative or false positive conclusions. The risk of bias also aids in understanding the heterogeneity between the selected studies.

Several methods and tools are used to address the risks of bias in meta-analysis wherein the most commonly used instrument is the checklist which uses specific questions or scales. The summary of each question and the summative scores are acquired in the end after completing the checklist. The Review Manager software which is developed by the Cochrane collaboration is constructed for the examination of RCTs and is utilised for the present research.

3.5 Data Extraction

With the inclusion and exclusion criteria set, the researcher/ investigator collects the detailed data which is based on specific characteristics such as the country, the population of the study, the year of research, the efficacy of pirfenidone with NAC, the types of outcomes from combined therapy, the study design, age and so on. Relevant information associated with conducting the meta-analysis are acquired from the studies satisfying the inclusion and exclusion criteria.

3.6 Meta- analysis Using Review Manager (Rev Man 5.3)

From the studies selected, data were compiled together and examined using a statistical analysis software called Review Manager (Rev-Man 5.3) which was developed based on collaboration with Cochrane for the management of meta-analysis conducted with systematic review (Higgins & Green, 2011). Rev-Man 5.3 is further used for the research as a tool to examine and manage data with ease.

3.6.1 Dichotomous Comparisons

The various dichotomous comparisons were carried out for the different clinical outcomes and treatment for IPF using pirfenidone with NAC. In the present research, the conditions such as efficacy of pirfenidone with NAC, the selection of control with factors of adjustment such as age, gender, socioeconomic status and so on were grouped and compared. The collected data were input into the Rev-Man 5.3 software and statistical analysis was conducted using the collected data. Statistical analysis comprises of the following estimation-estimation of overall size effect measurement, effect size, sensitivity analysis, publication bias, and heterogeneity analysis (Leandro, 2004; Borenstein *et al*., 2009). The risks related to individual researches selected for meta-analysis were calculated and combined to provide the total estimation of risks. The present research was designed based on the determination of Efficacy of pharmacological intervention (pirfenidone with N-acetylcysteine) of idiopathic pulmonary fibrosis wherein a meta-analysis is deemed suitable for such a research.

3.6.2 Heterogeneity assessment

The assessment of heterogeneity is based on the determination of variation extend of the selected studies for meta-analysis. Heterogeneity assessment is one important component in meta-analysis wherein there are cases when included studies have variations which may mislead the research (Borenstein *et al*., 2009; Leandro, 2004). The assessment of heterogeneity could be performed based on several tests such as I^2 statistic, Cochran's Q test, H statistic or R statistic (Huedo-Medina *et al*., 2006). It is deemed that the Q statistic could not be used separately as such tends to possess low power heterogeneity determination and the value depends on the number of studies considered for the meta-analysis. In this regard, the I^2 statistic is computed which is claimed to possess better measure of heterogeneity. The Rev Man 5.3 software is used which reports both the I^2 and Q statistic and hence could be used for the assessment of heterogeneity.

3.6.3 Sensitivity analysis

Sensitivity analysis is performed so as to improve the robustness of the present meta-analysis. Furthermore, sensitivity analysis also tends to validate the result through the comparison of various results of the selected studies (Walker *et al*., 2008). In the present

research, the analysis of sensitivity was conducted based on the comparison of the results of the selected studies.

3.6.4 Assessment of publication bias

In many a meta-analysis, one important aspect is the assessment of publication bias wherein studies may tend to mislead with positive results only thereby neglecting the negative findings (Sutton, 2000; Haidich, 2010). Hence, there is a need to also assess the negative points of the research since neglecting the same would deliver to misleading conclusions. In this regard, the funnel plot test as stated in Sterne *et al*. (2011) is used to analyse publication bias.

3.7 Summary

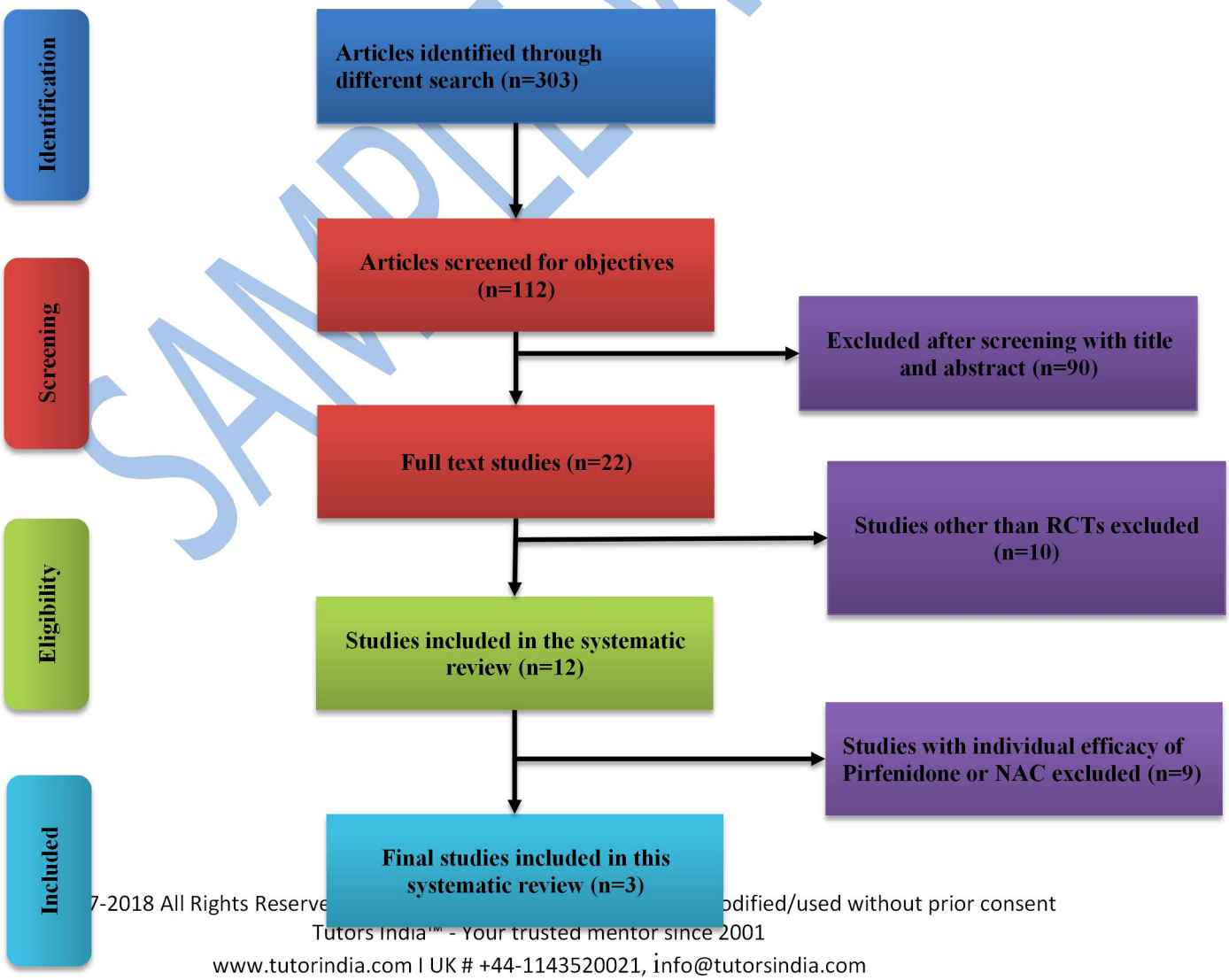
The present chapter focused on the design of the research and the different methods used in the present research. The present research justified the use of meta-analysis for the present research with the research purposefully focussing on the examination of efficacy of combined drug treatment therapy. The selection of RCTs was also justified with the fact that RCTs yield important research information which are factual, numerical and could be statistically analysed further. The different steps that are involved in the research were elucidated and the combined data were examined using the Rev-Man 5.3 software. Dichotomous variables' summative statistics are expressed using the Risk Ratio (RR) whereas the Mean Difference (MD) is used to summarise continuous data statistics. The combined estimates are presented with a Confidence Interval (CI) of 95 per cent and a p value less than 0.05 is considered to be of statistical significance. Statistical heterogeneity among the different researches selected is assessed using the I^2 value wherein an I^2 greater than 50 per cent is considered positive heterogeneity and the selection of Random- effect model will be facilitated. On the contrary, if the I^2 value is less than 50 per cent, then no heterogeneity prevails and a Fixed-effect model will be considered. The relative risk reduction (RRR) is computed using the formula "**(1-Relative Risk) x 100**".

CHAPTER IV: RESULTS

4.1 Introduction

Based on the inclusion and exclusion criteria set, the present research considered studies which were selected after in-depth analysis. The present research hence considered three studies for the systematic review wherein the filtering mechanism of the studies is purely based on the guidelines of the Preferred Items for Systematic Reviews and Meta–Analysis (PRISMA). According to Richards, (2015) the PRIMA guidelines aid the researcher to improve the reporting of both meta-analyses and systematic reviews. Following is the data extraction chart which summarises the search process and how studies are filtered and selected for the systematic review.

Figure 1: PRISMA Flow diagram depicting the selection of studies for systematic review on combined therapy of N-acetylcysteine (NAC) and pirfenidone



4.2 Selection of studies- PRISMA flowchart

The time period considered for the selection of studies for systematic review ranged from the period of 2006-2016 wherein the PRISMA guidelines and flowchart are used. However, with careful examination of previous researches pertaining to the topic led the researcher to identify researches from the year 2010 as other criteria were also set for inclusion. However, the studies which are considered eligible for the present research are found to be from the period of 2008 to 2016. Around 303 studies were identified to have relevance to the research topic wherein duplicate records were screened to further bring down the number to 112. Further screening revealed that only 22 researchers are related for the analysis in the systematic review as 90 records were screened based on their title and abstract. Furthermore, the criteria for filtering was set to include only Randomised Controlled trials (RCTs) and hence only 12 studies suited that specific criterion. Finally, as the present research necessitated the examination of the combined efficacy of NAC and Pirfenidone for the treatment of idiopathic pulmonary fibrosis, the number of studies further reduced and reached three. Hence with the final criterion, the present research which is a systematic review to examine the efficacy of pharmacological intervention (pirfenidone with N-acetylcysteine) of idiopathic pulmonary fibrosis considers only three studies for the systematic review.

4.3 Systematic assessment of review

The methodological assessment of the quality of review is performed using the Critical Appraisal Skills Programme (CASP) (CASP, 2013). For the evaluation of the studies considered in the present research, the Critical Appraisal Skills Programme (CASP) tool for RCTs is considered. 11 questions in the CASP tool which is purposefully designed for RCTs aids sensing of the trial in an appropriate manner. It covers three sections which include- Are the results of the study valid? (Section A) What are the results? (Section B) Will the results help locally? (Section C). All these sections aid the systematic analysis of the research article. For the initial screening, the answers of the first two questions should be ‘yes’. If the questions are yes, then the further questions could be answered (Casp, 2017).

Following are the questions of the CASP tool for RCTs (Table 1) and the answers to each question considering the research article for critical evaluation are also provided in Table 2.

Table 1- CASP for RCTs

Q. No	Question
	Are the results of the trial valid?
1	Did the trial address a clearly focused issue?
2	Was the assignment of patients to treatments randomised?
3	Were all of the patients who entered the trial properly accounted for at its conclusion?
	Is it worth continuing?
4	Were patients, health workers and study personnel 'blind' to treatment?
5	Were the groups similar at the start of the trial?
6	Aside from the experimental intervention were the groups treated equally?
	What are the results?
7	How large was the treatment effect? (Is the primary outcome clearly specified)
8	How precise was the estimate of the treatment effect?
9	Can the results be applied in your context? (or to the local population?)
10	Were all clinically important outcomes considered?
11	Are the benefits worth the harms and costs?

The assessment of the studies for the systematic review and the answers to the CASP tool are provided in Table 2.

Table 2- CASP assessment of included RCT studies

Study number	Author; year	Q. 1	Q. 2	Q. 3	Q. 4	Q. 5	Q. 6	Q. 7	Q. 8	Q. 9	Q. 10	Q. 11
1	Behr et al[1]	Yes	Yes	No. one patient in the intervention group withdrawn	Yes. Double blind	Yes	Can't tell. Information not available	**Yes.** Primary outcome: Assessment of safety and tolerability of acetylcysteine used in combination with pirfenidone in patients with IPF. **Result:** addition of acetylcysteine to pirfenidone does not substantially alter	90 per cent	Yes	Yes	Yes

[1] https://www.ncbi.nlm.nih.gov/pubmed/27161257

								the tolerability profi le of pirfenidone, although the incidence of photosensitivity should be closely monitored in patients receiving combination treatment				
2	Huang et al[2]	Yes	Yes	Yes	Yes. Double blind	Yes	Can't tell. Information not available	**Can't tell.** However, the lack of effective treatment for IPF led to this study wherein the	95 per cent	Yes	Yes	Yes

[2] https://www.ncbi.nlm.nih.gov/pubmed/26496265

								primary objective is to examined whether NAC+Pirfenidone is a good treatment drug combination for IPF **Result**: Compared with placebo combined with high-dose NAC, pirfenidone combined with high-dose NAC prolonged the progression-free survival of Chinese IPF				

								patients with mild to moderate impairment of pulmonary function.				
3	Sakamoto et al[3]	Yes	Yes	No. 7 patients in the intervention group excluded due to lung cancer, adverse effects, and poor adherence	Can't tell. Information not available	Yes	Can't tell. Information not available	**Yes**. Primary objective- to examined the effectiveness of combined therapy with pirfenidone and inhaled NAC for advanced IPF **Results:** Combination treatment with	95 per cent	Yes	Yes	Yes

[3] https://www.ncbi.nlm.nih.gov/pubmed/25639750

				to inhaled NAC				inhaled NAC and oral pirfenidone reduced the rate of annual FVC decline and improved PFS in patients with advanced IPF.				

The assessment of the included studies considered for the systematic review showed that all the studies that were included fall in the category of moderate to good quality. Hence, the studies are included further as they are deemed of value by this tool to support the findings of this research.

4.4 Summary of the included studies

As the present research considers the efficacy of NAC and Prifenidone as a combination therapy for the treatment of idiopathic pulmonary fibrosis, an in-depth examination revealed that only few researches were conducted in this context in the study period wherein the selected studies (n=3) were published only in the period of 2014-2016. One study by Behr et al[4] was published in the year 2016 whereas the other studies (Huang et al[5], Sakamoto et al[6]) were published in the year 2015. Based on the objectives of the research which include- 'evaluation of the efficacy of pirfenidone with NAC', 'Assessment of pirfenidone with NAC', and "deriving a management framework for IPF from the above and make recommendations for effective treatment" the studies are examined whereas the results are displayed based on these objectives. All the studies are RCTs and hence the results might provide generalised findings.

[4] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[5] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[6] https://www.ncbi.nlm.nih.gov/pubmed/25639750

S. no	Author; Year	Country	Design	Age group	Sample size		Study Duration	Outcome	Adverse event report
					Intervention	Control			
1	Behr et al[7]	Eight nations (Austria, Belgium, Denmark, France, Germany, Italy, Sweden, and the UK)	Randomized Controlled Trial	40-80 years	60	62	24 weeks	Clinical benefit from addition of acetylcysteine to pirfenidone is unlikely	There were nine serious adverse events reported by seven patients in the study which include: dyspnoea, headache, hypertension, intervertebral disc protrusion, and malignant lung neoplasm in the acetylcysteine

[7] https://www.ncbi.nlm.nih.gov/pubmed/27161257

									group, and aortic aneurysm, contusion, forearm fracture, and worsening IPF in the placebo group. However, the most common events were nasopharyngitis, cough and diarrhoea
2	Huang et al[8]	China	Randomized Controlled Trial	18-75 years	38	38	48 weeks	Compared with placebo combined with high-dose NAC,	In the intervention group, the adverse event (AE) rate was higher than that in the control group. Rash was

[8] https://www.ncbi.nlm.nih.gov/pubmed/26496265

								pirfenidone combined with high-dose NAC prolonged the progression-free survival of Chinese IPF patients with mild to moderate impairment of pulmonary function	more common in the pirfenidone group.
3	Sakamoto	Japan	Randomized	59-82 years	17	10	48 weeks	Combinatio	Only one patient

	et al[9]		Controlled Trial					n treatment with inhaled NAC and oral Pirfenidone reduced the rate of annual FVC decline and improved PFS in patients with advanced IPF.	developed photosensitivity but improved after treatment with steroid ointment and UV care and did not withdraw. Four patients discontinued therapy due to gastrointestinal discomfort, such as nausea and/or anorexia. However, most adverse events resolved after a decrease in dose

[9] https://www.ncbi.nlm.nih.gov/pubmed/25639750

									or temporary cessation of pirfenidone treatment.

The general characteristics of the studies included in the present research are elaborated as follows:

Behr et al[10] conducted a research to examine the tolerability and safety towards the use of acetylcysteine and pirfenidone as a combination therapy for the treatment of idiopathic pulmonary fibrosis wherein the study is a randomised placebo-controlled phase 2 trial. The previous research performed a double-blind randomised trial in eight nations of the world (Austria, Belgium, Denmark, France, Germany, Italy, Sweden, and the UK) wherein the research was conducted in 48 sites. The number of patients considered for the research on the whole is 123 (Intervention- 61 and control- 62) and belonged to the age group of 40- 80 years. The entire study duration considered is 24 weeks.

Huang et al[11] conducted a similar research as a double-Blind Randomized Trial of Pirfenidone wherein the research was conducted to assess the progression-free survival of IPF patients in China. The age group considered for the research ranged from 18-75 years and a total of 76 patiens were considered for the research wherein equal number of patients were recruited for both intervention and control groups. The research was performed as a randomised control double-blind multicenter trial in China and was conducted at 5 different sites in Northern China which include Beijing (3 sites), Tianjin (1 site) and Shenyang (1 site). The entire study duration considered is 48 weeks.

Sakamoto et al[12] conducted a case control study to examine the effectiveness of the combined usage of pirfenidone and inhaled N-acetylcysteine for the treatment of advanced Idiopathic Pulmonary Fibrosis wherein the study was conducted in Japan. The study is a randomised controlled trial which is conducted with patients falling within the age group of 59-82 wherein 34 patients were recruited for the research. Among the 34 patients, 24 patients were considered for the intervention group and 10 patients were recruited for the control group. The entire research was conducted for a period of 48 weeks and patients were considered from the University Hospital Medical Information Network under registration number UMIN000016045 (Japan).

[10] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[11] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[12] https://www.ncbi.nlm.nih.gov/pubmed/25639750

4.5 Patient characteristics, intervention and control details of the included studies

S. No	Author; year	Title	Patient characteristics	Is double blinded?	Intervention	Control
1	Behr et al[13]	Safety and tolerability of acetylcysteine and pirfenidone combination therapy in idiopathic pulmonary fi brosis: a randomised, double-blind, placebo-controlled, phase 2 trial	FVC of 50–90%, carbon monoxide diffusing capacity of the lungs (DLCO) of 30–90% (DLCO 35–90% in Italy), and had been receiving pirfenidone 1602 mg/day or higher	Yes	Patients were randomised to receive pirfenidone and acetylcysteine	Patients were randomised to receive pirfenidone and placebo

[13] https://www.ncbi.nlm.nih.gov/pubmed/27161257

			for at least 8 weeks before randomisation			
2	Huang et al[14]	Double-Blind Randomized Trial of Pirfenidone in Chinese Idiopathic Pulmonary Fibrosis Patients	percentage of predicted forced vital capacity (FVC) of at least 45%, percentage of predicted carbon monoxide diffusing capacity (DLCO) of at least 30%, and PaO2 of at least 50 mmHg when the patient is at rest and breathing	Yes	Patients were randomised to receive oral pirfenidone and acetylcysteine	Patients were randomised to receive placebo and acetylcysteine

[14] https://www.ncbi.nlm.nih.gov/pubmed/26496265

			room air			
3	Sakamoto et al[15]	Effectiveness of combined therapy with pirfenidone and inhaled N-acetylcysteine for advanced idiopathic pulmonary fibrosis: A case–control study	Patients with a diagnosis of advanced IPF (Japanese Respiratory Society stage III/IV IPF) and a relative decline in forced vital capacity (FVC) of ≥10% within the previous 6 (±2) months	Not specified	Patients were randomised to inhale N-acetylcysteine and pirfenidone	Patients were randomised to receive pirfenidone alone

[15] https://www.ncbi.nlm.nih.gov/pubmed/25639750

Of the studies considered for the systematic review, two studies are specified as 'double blind' RCTs whereas only one study has not provided any such information regarding blinding (Behr et al[16], Huang et al[17]). There were specific patient characteristics which were used in the previous researches to recruit patients. In the study by Behr et al[18], patients with an forced vital capacity (FVC) of 50–90 per cent is considered for the research wherein the diffusing capacity for carbon monoxide of the lungs, represented as 'DLCO' should be around 30-90 per cent. However, as the study also recruited patients from Italy, the DLCO for Italian patients was considered to be around 35-90 per cent. Furthermore, these patients should have been receiving pirfenidone to at least 1602 mg/day or even higher amounts for at least 8 weeks prior randomisation. However, the study by Huang et al[19] recruited patients with IFP at mild to moderate levels of impairment in the pulmonary functions wherein the percentage of FVC should be at least 45 per cent and the percentage of the predicted DLCO was considered to be at least 30 per cent and PaO_2 of at least 50 mmHg when the patient rests and breathes room air. The study by Sakamoto et al[20] considered patients diagnosed with advanced Idiopathic Pulmonary Fibrosis wherein the stages considered are Japanese Respiratory Society stage III/IV IPF; furthermore, patients with relative decline in the values of FVC of greater than or equal to 10 per cent within the 6 months (±2 months) prior randomisation are also considered in the previous research by Sakamoto et al[21].

[16] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[17] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[18] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[19] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[20] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[21] https://www.ncbi.nlm.nih.gov/pubmed/25639750

4.6 Evaluation of Efficacy of Prifenidone with NAC

S. No	Author; Year	Number of participants	Intervention		Control		Adverse events (based on medication)	Severe adverse events	Efficacy end-points	Outcomes of the research
			Male	Female	Male	Female				
1	Behr et al[22]	122	53	7	51	11	(Intervention= 17; Control= 16)	(Intervention=6; Control= 2)	- Exploratory efficacy measurements included forced vital capacity (FVC), carbon monoxide diff using capacity, and	patients treated with acetylcysteine experienced a greater decline in FVC than those treated with placebo suggest that acetylcysteine is unlikely to have a benefi cial role in IPF when combined with pirfenidone and raise

[22] https://www.ncbi.nlm.nih.gov/pubmed/27161257

									6 min walk distance; - Primary endpoint: 28 days after last drug dose	the distinct possibility that the combination might be harmful in patients with IPF
2	Huang et al[23]	76	33	5	38	0	52.63 per cent high in Intervention than in control grou	-	- The primary endpoints were defined as the change in FVC from baseline to week 48, and the change in the maximal distance on the 6MWT and the	PFD combined with highdose NAC compared to placebo combined with high-dose NAC prolonged the Progression Free Survival time in Chinese IPF patients with mild to moderate impairment of pulmonary function

[23] https://www.ncbi.nlm.nih.gov/pubmed/26496265

									change in the lowest SPO2 during the 6MWT from baseline to week 48. - The secondary endpoints were defined as the change in the result on the resting PFT, including the percentage predicted FVC, FEV1 and the	

									percentage predicted FEV1, total lung capacity (TLC) and the percentage predicted TLC, DLCO and the percentage predicted DLCO, DLCO/VA from baseline to week 48; the change in ABGs including PaCO2,	

									PaO2, and SaO2; episodes of AE-IPF	
3	Sakamoto et al[24]	27	14	3	9	1	No adverse events due to inhaled NAC; 4 patients discontinued the study due to gastrointestinal discomfort	-	- lower 48-week declines in FVC in a subset of patients with a mean baseline vital capacity (VC) of almost 80% and a carbon monoxide diffusing capacity	Combined treatment with NAC and pirfenidone might improve the poor prognosis of patients with advanced IPF

[24] https://www.ncbi.nlm.nih.gov/pubmed/25639750

									(DLco) of almost 43% of the predicted value	

The efficacy of using NAC in combination with Prifenidone is examined wherein the selected studies are explored. The study by Behr et al[25] which examined the safety and tolerability of using the combination of Pirfenidone with NAC had exploratory efficacy measurements which included forced vital capacity (FVC), the diffusing capacity if carbon monoxide and a 6 min walk distance. The examination of the efficacy was performed in the modified intention to treat population wherein all patients included in the research were randomised and received one dose of the medication specified in the study. According to the previous research, the need for examining the efficacy of the drug combination stems from various researches which examined the combined therapy of acetylcysteine with prednisone and azathioprine versus placebo[26]. However, Behr et al[27] revealed the fact those patients that were treated with NAC as a combination with pirfenidone experience high level of decline in the FVC values than those that are treated with a placebo. However, the study also reveals the likeliness to play a beneficial role in the treatment of IPF provided that the combined efficacy might also trigger harmful effects in patients. Huang et al[28] however examined whether the combination of pirfenidone to N-acetylcysteine group affects the treatment of IPF. The previous research revealed that compared with the control group which utilised a placebo with the high dosage of NAC, the intervention group which included pirfenidone with NAC showed prolonged PFS of chinese patients with IP; however, these patients witnessed mild to moderate levels of impairment in the pulmonary function. However, in the study by Sakamoto et al[29], it is revealed that patients that received pirfenidone with NAC had better median survival and more stable FVC compared with patients in the control group.

[25] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[26] Raghu G, Anstrom KJ, King Jr TE, Lasky JA, Martinez FJ, for the Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fi brosis. N Engl J Med 2012; 366: 1968–77.
[27] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[28] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[29] https://www.ncbi.nlm.nih.gov/pubmed/25639750

4.7 Assessment of likelihood of combination therapy towards decreasing IPF based mortality rate

In all the studies considered for the systematic review, there were no information regarding the likelihood of combination therapy towards decreasing IPF based mortality rate. However, there were results which revealed whether the combination treatment had delivered better outcomes. In the study by Behr et al[30], it is discerned that among the 123 patients considered for the study (60 in the intervention group and 62 assigned to the control group), there was an occurrence of at least one adverse event wherein it is stated that 46 out of 60 patients in the intervention group and 50 out of 62 patients in the control group witnessed one adverse event. 17 out of 60 patients in the intervention group and 16 out of 62 patients in the control group witnessed adverse event related to the treatment considered in the study wherein the number of patients which experienced severe adverse event was three in the intervention group and two in the control group. Life-threatening events were witnessed in one patient in the intervention group and one patient in the control group wherein death was witnessed in one patient in the intervention group and three in the control group. Though there is large outcomes in terms of death in the intervention group when compared to the control group, there were serious adverse events reported by patients in the control group. Patients in the placebo group witnessed serious events such as aortic aneurysm, contusion, forearm fracture, and worsening IPF in the placebo group whereas patients in the intervention group witnessed serious events such as dyspnoea, headache, hypertension, intervertebral disc protrusion, and malignant lung neoplasm. However, it is photosensitivity which occurred most frequently in the intervention group treated with combined acetylcysteine and pirfenidone. On the whole, the study by Behr et al[31] reveals that there are no likely clinical benefits from the addition of acetylcysteine to pirfenidone; however, there are evidences of harmful effect in patients with IPF and hence the likelihood of combination therapy towards decreasing IPF based mortality rate is unknown in the previous research.

In the research by Huang et al[32], among the 89 patients screened only 78 were recruited for the study wherein equal number of cases were registered in both placebo and intervention

[30] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[31] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[32] https://www.ncbi.nlm.nih.gov/pubmed/26496265

group. It is revealed that at the 24 the week of the study, there were significant outcomes in the intervention group treated with NAC and pirfenidone; however the same did not persist till the 48th week which is the entire study period. During the 24th week of the treatment, there was a mean decline in the DSPO2 and FVC per cent during the 6MWT in the pirfenidone group which was low in the control group. However, there were no significant differences witnessed between both the groups at the 48th week wherein the pirfenidone treatment group did not achieve the maximal distance difference on the 6MWT at either the 24th or the 48th week. The only significant finding in the pirfenidone group (intervention) is the prolonged progression-free survival time in the IPF patients with hazard ratio equal to 1.88, 95% confidence interval: 1.092–3.242, with P value equal to 0.02. However, in the pirfenidone group it is evident that the rate of adverse event is higher than the control group. In addition, four cases died with two in the intervention group and two in the control group. The only significance of the study with respect to the intervention group is the ability of the combination therapy to prolong progression-free survival time which might have an impact on the IPF based mortality rate.

In the study by Sakamoto et al[33], patients diagnosed with advanced IPF and with relatively lowered levels of FVS were recruited. A 12-month follow-up with the evaluation of the pulmonary function revealed that 8 of the 17 patients in the intervention group found the treatment effective whereas only 2 out of 10 patients in the control group found the treatment to be effective. There was no information pertaining to the death of patients and hence information with respect to mortality rate could not be discerned in the previous study.

4.8 Summary

The present chapter is the "Results" chapter which pertained to the examination of the studies included for the systematic review wherein the present research examined the combined efficacy of Pirfenidone and acetylcysteine for the treatment of IPF. Only three studies were enrolled in the present research wherein two studies- Huang et al[34] and Sakamoto et al[35] examined the efficacy of the drug combination in specific nations such as China and Japan

[33] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[34] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[35] https://www.ncbi.nlm.nih.gov/pubmed/25639750

respectively. However, one study by Behr et al[36] attempted to cover the efficacy of the combined drug treatment in eight nations which include Austria, Belgium, Denmark, France, Germany, Italy, Sweden, and the UK. The inclusion of these studies was based on crucial examination of the inclusion and exclusion criteria set wherein the PRISMA guidelines and flowchart are used. The CASP tool is then used for the assessment of the RCTs considered in the present research wherein all the studies are of moderate to good quality and hence the studies are reliable to be utilised for the systematic review. All studies considered for the research are RCTs wherein they all fall under the period of 2015-2016. Almost all studies revealed adverse effects with respect to the administration of combined therapy; however there were reduction in the PFS and FVC in the intervention group.

[36] https://www.ncbi.nlm.nih.gov/pubmed/27161257

CHAPTER V: DISCUSSION AND CONCLUSION

The present study is the systematic review concerned with the examination of the efficacy of the Pirfenidone and NAC for the treatment of IPF. An examination of previous literature pertaining to the topic revealed various results which all pertained to the individual efficacy of pirfenidone and acetylcysteine. Furthermore, there are other drugs which are also found to have better effects and are beneficial for the treatment of IPF. One such drug is nintedanib. There are several recommended treatment for IPF wherein the most common are pirfenidone and nintedanib[37] which is also a licensed combination for the treatment of IPF in the year 2011 and 2015 by the EMA[38] [39] wherein the US Food and Drug administration (FDA) has also licensed the same for the treatment of IPF in the year 2014[40]. There are immense recommendations for using Pirfenidone and nintedanib for the treatment of IPF wherein regulatory bodies such as National Institute for Health and Care Excellence (NICE) in England[41] and the Scottish Medicines Consortium (SMC)[42] have also recommended these drugs. However, the use of N-acetylcysteine as a combined mode of treatment with prednisolone, and azathioprine[43] is generally not recommended but is still in clinical practice[44]. While these researches depict the beginning of novel drug therapy for the treatment of IPF, more examination is required for the assessment of the drug efficacy and

[37] Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis: an update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med. 2015;192(2):e3-19. CrossRef, Medline

[38] European Medicines Agency. Public summary of opinion on orphan designation: pirfenidone for the treatment of idiopathic pulmonary fibrosis. March 12, 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500006133.pdf. Accessed February 9, 2017.

[39] European Medicines Agency. EU/3/13/1123: Public summary of opinion on orphan designation: nintedanib for the treatment of idiopathic pulmonary fibrosis. March 3, 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2013/05/WC500143247.pdf. Accessed February 9, 2017.

[40] U.S. Food and Drug Administration. News release. FDA approves Ofev to treat idiopathic pulmonary fibrosis. October 15, 2014. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418994.htm. Accessed February 9, 2017.

[41] National Clinical Guideline Centre (UK). Diagnosis and management of suspected idiopathic pulmonary fibrosis: idiopathic pulmonary fibrosis. 2013. National Institute for Health and Care Excellence: Clinical Guidelines, No. 163. Available at: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0068972/. Accessed February 9, 2017.

[42] Scottish Medicines Consortium. Nintedanib (Ofev). October 12, 2015. Available at: https://www.scottishmedicines.org.uk/SMC_Advice/Advice/1076_15_nintedanib_Ofev. Accessed February 9, 2017.

[43] https://www.ncbi.nlm.nih.gov/pubmed/27937011

[44] http://www.jmcp.org/doi/10.18553/jmcp.2017.23.3-b.s5

the combined effects of these drugs. As there are strong evidences to prove the combined efficacy of pirfenidone and nintedanib, researching further on the same drug combination will add up an additional research to the literature. However, it is evident that the combined efficacy of pirfenidone and nintedanib is yet to research as studies in this context are rare. In this context, the present study aimed to assess the present evidence on the efficacy of combination therapy of pirfenidone with NAC.

For the systematic review, the researcher searched different scholarly websites and PubMed for reports that are published in the same context in any language before 2017 using the terms such as "combined drug therapy for Idiopathic Pulmonary Fibrosis" OR "combined drug therapy for IPF", "pirfenidone with N-acetylcysteine", "Efficacy of pirfenidone with N-acetylcysteine" or "Efficacy of pirfenidone with NAC", and "combined treatment using pirfenidone with NAC". This search revealed several results wherein the articles such as review papers, pre-clinical studies, and reports which investigated on the disease rather than the drug combination were excluded from the inclusion into the research (systematic review). At the end, there were three RCTs which investigated the combination of pirfenidone and acetylcysteine as a viable treatment for IPF which are the researches by Behr et al[45], Huang et al[46] and Sakamoto et al[47].

5.1 Efficacy of Pirfenidone with NAC

Pirfenidone (PFD), whose chemical name is 5-methyl-1-phenyl-2-[1H]-pyridone, is a drug agent that is developed for the treatment of IPF wherein the drug and its metabolite substances such as 5-carboxypirfenidone (PFD-COOH) and 5-hydroxypirfenidone (PFD-OH) are known for their anti-oxidant and anti-fibrotic effects[48] [49]. After clinical phase II and phase III trials, Pirfenidone is used for the treatment of IPF in patients in Europe, India and Japan. However, the case of N-acetylcysteine is a different scenario. There are several researches which evaluated the anti-oxidant properties of *N*-acetylcysteine for IPF treatment wherein there is never a general result to prove the efficacy of the drug; mostly there had been

[45] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[46] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[47] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[48] Carter NJ. Pirfenidone: in idiopathic pulmonary fibrosis. Drugs. 2011;71:1721–1732
[49] Togami K, Kanehira Y, Tada H. Possible involvement of pirfenidone metabolites in the antifibrotic action of a therapy for idiopathic pulmonary fibrosis. Biol Pharm Bull. 2013;36:1525–1527.

contradicting results[50] [51]. A research by Bando et al[52] revealed that there were no significant differences in the curves of survival between patients treated with *N*-acetylcysteine and in patients that received no treatment. However, as the study was an open case-control study with small sample size, the results of the research were not so generalised. However, it was Demedts et al[53] who revealed that *N*-acetylcysteine which when consumed thrice a day at 600mg dosage with the standard therapy for IPF and with the combination of azathioprine and prednisone improves the functioning of lungs in patients with IPF. In addition, Homma et al[54] revealed that the use of *N*-acetylcysteine as a monotherapy might have better effects in patients diagnosed with early stages of IPF whereas Tomioka et al[55] state that *N*-acetylcysteine delays the progression of the disease. Combining the better benefits of both pirfenidone and NAC for the treatment of IPF, the present research attempted to examined the combined efficacy of both these drugs which after serious processes of screening based on inclusion and exclusion criteria revealed three studies by Behr et al[56], Huang et al[57] and Sakamoto et al[58].

Similar to the first objective of the present research which attempted to examine the efficacy of the drug combination (Pirfenidone + NAC), the previous researches by Behr et al[59], Huang et al[60] and Sakamoto et al[61] also had the same objective. Firstly, the study by Sakamoto et al[62] is examined which is the first study to examine the effectiveness of the combined therapy with pirfenidone and inhaled N-acetylcysteine for the treatment of patients with advanced IPF.

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[50] Bando M, Hosono T, Mato N, et al. Long-term efficacy of inhaled N-acetylcysteine in patients with idiopathic pulmonary fibrosis. *Intern Med* 2010; 49:2289–2296. [PubMed]
[51] Martinez FJ, de Andrade JA, Anstrom KJ, et al. Idiopathic Pulmonary Fibrosis Clinical Research Network. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 2014; 370:2093–2101. [PMC free article] [PubMed]
[52] Bando M, Hosono T, Mato N, et al. Long-term efficacy of inhaled N-acetylcysteine in patients with idiopathic pulmonary fibrosis. Intern Med 2010; 49:2289–2296. [PubMed]
[53] Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 2005; 353:2229–2242. [PubMed]
[54] Homma S, Azuma A, Taniguchi H, et al. Efficacy of inhaled N-acetylcysteine monotherapy in patients with early stage idiopathic pulmonary fibrosis. Respirology 2012; 17:467–477. [PubMed]
[55] Tomioka H, Kuwata Y, Imanaka K, et al. A pilot study of aerosolized N-acetylcysteine for idiopathic pulmonary fibrosis. Respirology 2005; 10:449–455. [PubMed]
[56] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[57] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[58] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[59] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[60] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[61] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[62] https://www.ncbi.nlm.nih.gov/pubmed/25639750

Pirfenidone, which is a proven therapy for the treatment of IPF is considered and has better effects in the treatment of patients with mild to moderate levels of IPF, the effects of the drug are not examined to a great extent among patients who have developed advanced IPF (such as Stage III or Stage IV IPF)[63]. In this backdrop, it is evident for the treatment of IPF, the need for drug combination with therapeutic modalities persists thereby targeting several pathways involved in fibroproliferation[64]. In this backdrop, Sakamoto et al[65] examined the safety and efficacy of pirfenidone monotherapy versus combination therapy involving pirfenidone with inhaled NAC for patients with advanced stages of IPF.

However, the second research considered for the systematic review is conducted by Huang et al[66] who conducted a double blind RCT in the Chinese IPF patients wherein research is in specific is to examine whether a combined therapy of high dosage NAC and pirfenidone can aid patients recuperate from IPF. The use of high dose NAC is not commonly recommended for patients with IPF though the drug has anti-fibrotic and anti-oxidant effects. According to the IPF guidelines, the use of high dose NAC is not recommended[67]. Furthermore, a clinical trial by [68] also discerned the fact that for the treatment of IPF, NAC with high dose did not deliver better effects. However, ATS recommends administering patients with high dose of NAC if they have better tolerating levels to such drug dosages. In this context, Huang et al[69] conducted a clinical trial to use NAC and pirfenidone as a combination therapy for IPF.

Following the footsteps of Sakamoto et al[70] and Huang et al[71], Behr et al[72] conducted a double blind, placebo controlled phase 2 RCT wherein the research examined the

[63] Homma S, Sugino K, Sakamoto S. The usefulness of a disease severity staging classification system for IPF in Japan: 20 years of experience from empirical evidence to randomized control trial enrollment. Respir. Investig. 2015; 53: 7–12. doi: http:// dx.doi.org/10.1016/j.resinv.2014.08.003.
[64] Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA et al. ATS/ERS/JRS/ ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am. J. Respir. Crit. Care Med. 2011; 183: 788–824.
[65] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[66] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[67] Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med. 2005;353:2229–2242
[68] Idiopathic Pulmonary Fibrosis Clinical Research NetworkMartinez FJ, de Andrade JA, et al. . Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2093–2101.
[69] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[70] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[71] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[72] https://www.ncbi.nlm.nih.gov/pubmed/27161257

tolerability and safety of pirfenidone and acetylcysteine combination therapy in IPF. The research considered several researches wherein the research by Sakamoto et al[73] was also taken into account by Behr et al[74]. It is revealed that in European nations, according to [75] and [76], more than one third of patients were reported to have received both acetylcysteine and pirfenidone. After the PANTHER study[77], there is a decline in the use of acetylcysteine; however, only two researches by Sakamoto et al[78] and Oltmanns et al[79] have examined the combined efficacy of pirfenidone and acetylcysteine. In this context, Behr et al[80] conducted a PANORAMA study to investigate the tolerability and safety of oral acetylcysteine with pirfenidone for the treatment of IPF.

The examination of all the studies revealed contrasting information regarding the efficacy of the combined drug therapy. Though it is revealed that several clinical trials have been conducted for treating IPF, the disease still remains to be a fatal and a progressive disease[81] [82]. However, with the aim to provide a novel combination that could effectively treat IPF, the study by Sakamoto et al[83] examined the combination therapy of pirfenidone and inhaled NAC which revealed that the treatment improved the values of FVC in more than 45 per cent of patients with advanced IPF. It is further revealed that in the intervention group receiving combined treatment, the value of PFS was better than those in the control group receiving Pirfenidone alone. The results of the research further reveal the fact that in patients with advanced IPF, inhaled NAC and pirfenidone decreased the risks of poor outcomes. However,

[73] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[74] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[75] Behr J, Kreuter M, Hoeper MM, et al. Management of patients with idiopathic pulmonary fi brosis in clinical practice: the INSIGHTS-IPF registry. Eur Respir J 2015; 46: 186–96
[76] Oltmanns U, Kahn N, Palmowski K, et al. Pirfenidone in idiopathic pulmonary fi brosis: real-life experience from a German tertiary referral center for interstitial lung diseases. Respiration 2014; 88: 199–207
[77] Martinez FJ, de Andrade JA, Anstrom KJ, King Jr TE, Raghu G, for the Idiopathic Pulmonary Fibrosis Clinical Research Network. Randomized trial of acetylcysteine in idiopathic pulmonary fi brosis. N Engl J Med 2014; 370: 2093–101.
[78] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[79] Oltmanns U, Kahn N, Palmowski K, et al. Pirfenidone in idiopathic pulmonary fi brosis: real-life experience from a German tertiary referral center for interstitial lung diseases. Respiration 2014; 88: 199–207
[80] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[81] King TE Jr, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, Noble PW, Sahn SA, Szwarcberg J, Thomeer M et al. INSPIRE Study Group. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. Lancet 2009; 374: 222–8.
[82] King TE Jr, Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stähler G, Leconte I, Roux S, Raghu G. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am. J.Respir.Crit.Care Med. 2008; 177: 75–81.
[83] https://www.ncbi.nlm.nih.gov/pubmed/25639750

with respect to background factors such as age, gender, history of smoking, DLco and FVC, there were no great differences witnessed between the intervention and the control group. Furthermore, the rate of change in FVC on an annual basis was −610 mL in the intervention group whereas the same is −1320 mL in the control group with P-value less than 0.01. The data further reveals that the combination therapy decreases FVC compared to the control group with rapidly progressive IPF in its advanced stages.

However, in the study by Huang et al[84] it is revealed that there was no significant difference in the primary endpoints that was observed between the control and the intervention groups. However, there was a significant decline in the values of FVC in the 24th week of the research in both the intervention and the control groups. It is also revealed that the combined treatment method led to the prolonged PFS duration in patients with IPF. This is similar to the result of Sakamoto et al[85] which also revealed the prolonged PFS in patients in the intervention group. A further analysis was performed by the researcher wherein it was revealed that in 4 cases (1 in the control group and 3 in the intervention group) there is a substantial decline in the parameters of Pulmonary Function Tests (PFT) such as TLC, FVC, and DLCO since the adverse events which were evident within the 4 weeks of the end-of-treatment timepoint. Further re-evaluation of the data with these 4 cases excluded revealed that the combined treatment had effects on FVC which was observed in both 24 and 48 weeks. However, the research warrants large sample size to verify the results obtained which was further examined by Behr et al[86].

With the need to evaluate the efficacy of the drug combination within a large sample size, Behr et al[87] conducted an RCT for which 121 patients were recruited. The examination of the previous study revealed that this research is the first RCT to investigate the tolerability and safety of the combined treatment method (Oral Acetylcysteine and Pirfenidone) wherein the efficacy of the drug combination was compared with pirfenidone alone as the control in IPF patients. It is revealed that there are no significant alterations in the safety and tolerability of using the combined drug treatment method; however, adverse events such as photosensitivity are evident in the intervention group which the researchers state that further analysis is

[84] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[85] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[86] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[87] https://www.ncbi.nlm.nih.gov/pubmed/27161257

required. An exploratory efficacy analyses is performed which revealed that patients which received combination therapy has experienced a decline in the functioning of their lungs than patients in the control. In the PANORAMA study, the exploratory endpoints revealed no evidences of the benefits of using oral acetylcysteine and prifenidone as a combined treatment method for IPF.

5.2 Assessment of the likelihood of combination therapy towards reducing mortality rate

For all the studies considered for the systematic review, it is evident that no specific information regarding the likelihood of reducing the mortality rate in IPF patients is present in the researches. However, with respect to the adverse events all studies revealed better outcomes. In the research by Sakamoto et al[88], it is revealed that patients diagnosed with advanced IPF and with relatively lowered levels of FVS during the 12-month follow-up with the evaluation of the pulmonary function had 8 of the 17 patients in the intervention group to have stated the treatment to be effective; however only 2 out of 10 patients in the control group found the treatment as effective for advanced IPF. Furthermore, there is no specific information pertaining to the death of patients revealed in the study by Sakamoto et al[89].

However, in the study by Huang et al[90] which recruited 78 patients for the research revealed that at the 24 the week, significant outcomes were seen in the intervention group which is treated with pirfenidone and NAC. Though the outcomes were significant in the 24th week, the same did not persist till the 48th week. Furthermore, in the intervention group there is high rate of adverse events than the control group. Additionally, four cases died wherein two belonged to the intervention group and two belonged to the control group. However, the prolonged PFS which is evident in the research might reveal that the combined treatment can to some level decrease the rate of mortality in IPF patients.

Behr et al[91] discerned the fact that life-threatening events were witnessed in one patient in the intervention group and one patient in the control group wherein death was witnessed in one

[88] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[89] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[90] https://www.ncbi.nlm.nih.gov/pubmed/26496265
[91] https://www.ncbi.nlm.nih.gov/pubmed/27161257

patient in the intervention group and three in the control group. This might relate the likeliness of the combined treatment which reduces mortality rate to some extent in the intervention group. In all these studies, there is no evidences of reducing the rate of mortality; however, with the reduction of adverse effects of IPF all studies warrant that the combined treatment, to some extent aid reduction of rate of mortality in patients with IPF.

5.3 Management framework for IPF

There have been significant advances in the management of IPF clinically since the development of the evidence-based guidelines in 2011[92]. Several weak and conditional recommendations have been received with respect to the treatment of IPF wherein the guidelines developed in the year 2011 has been reviewed with recommendations provided[93]. However, there are no interventions till date which could act as recommendations for the treatment. Till date several recommendations have been made with respect to the treatment of IPF with novel agents such as nintedanib and pirfenidone. However, there are chances for future researches to open the venues for the developing Pirfenidone and N-acetylcysteine as a combined drug treatment for IPF. However, these researches are still in its infancy and hence medical practitioners should look into other management of IPF appropriately.

The results of the study by Behr et al[94] revealed that though there are safety constraints with respect to the use of N-acetylcysteine with pirfenidone in patiens with IPF, the findings of the research should be considered with caution as the sample size is relatively less. Furthermore, this is applicable for all the researches considered for the systematic review as the sample sizes of all these studies are relatively less in number. However, to reveal a more clear evidence on the examination of efficacy of N-acetylcysteine and pirfenidone a four armed study as specified by Raghu[95] needs to be performed which should comprise of the following- control group; pirfenidone monotherapy; NAC monotherapy; and combination therapy. In addition, the present research suggests the use of high sample size so

[92] https://www.thoracic.org/statements/resources/interstitial-lung-disease/IPF-Full-length.pdf
[93] https://www.thoracic.org/statements/resources/interstitial-lung-disease/IPF-Full-length.pdf
[94] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[95] http://www.thelancet.com/pdfs/journals/lanres/PIIS2213-2600(16)30327-7.pdf

as to verify the results and acquire more indepth insights on the combine drug treatment mechanism.

Clinicians are confronting towards treating IPF patients wherein the decisions of treatment should involve individualising the decision with that of patients; however, this requires considering the conditional recommendations and hence should be more cautious towards comparing the benefits of one intervention with another. The factors which need to be examined before deciding the treatment procedures for IPF include anatomic and physiologic variables and the level of confidence of the overall certainty. In addition, the studies considered for the systematic review revealed that for the combined treatment using acetylcysteine with pirfenidone, there is no clear consensus regarding the duration of benefit and hence future researches are required for optimal therapy and its duration.

5.4 Conclusion

IPF is a condition with unknown aetiology but with high rate of mortality which is associated with the lack of treatment modalities. Pharmacological interventions are the only manner through which IPF can be treated effectively. However, the use of anti-inflammatory combinations with corticosteroids which is the mainstay treatment modality has not delivered good results and hence other novel drugs need to be developed. Over the years, with the development of drugs such as pirfenidone, nintenadib and N-acetylcysteine, researchers are attempting to examine the efficacy of these novel drugs and examine whether the combine use of these drugs might render better treatment effects on patients with IPF. In this context, the present research considered the utilisation of both pirfenidone and N-acetylcysteine as the combined drug treatment for patients with IPF wherein a systematic review and a meta-analysis is conducted.

The examination of previous researches revealed only three studies to fall under the inclusion and exclusion criteria set for the research which includes Behr et al[96], Sakamoto et al[97] and Huang et al[98]. All these studies are examined based on the objectives set wherein the exploration of the results and findings of the previous researches revealed that Pirfenidone

[96] https://www.ncbi.nlm.nih.gov/pubmed/27161257
[97] https://www.ncbi.nlm.nih.gov/pubmed/25639750
[98] https://www.ncbi.nlm.nih.gov/pubmed/26496265

and N-acetylcysteine when combined together decreases FVC decline and some studies even represent the prolonged PFS in the intervention group. However, the studies revealed adverse events to have caused in the intervention group more which is associated with the fact that patients in the intervention group received high dose of combined drug and prolonged use of the same. Furthermore, these researches further revealed that the combined treatment method is suggested for patients with mild, moderate and intense levels of IPF; however the interpretation lacks generalisation due to low sample size. In addition, the assessment of likelihood of combination therapy towards decreasing IPF based mortality rate revealed reduction of adverse effects of IPF in all studies which warrant that the combined treatment, to some extent aid reduction of rate of mortality in patients with IPF. For the management of IPF, careful examination of the individual patient characteristics and factors such as anatomic and physiologic variables is required so as to decide whether individual or combined treatment modality could be used in the case of IPF.

5.5 Recommendations

All the previous researches considered for the systematic review and meta-analyses possess limitations which affect concluding the benefits of the combined drug treatment. As a common limitation, all studies lack generalisation of results as the sample size is relatively low. Furthermore, this might affect the use of pirfenidone and N-acetylcysteine as a combined drug treatment for IPF. Secondly, the duration for research is less which further affects the findings of each study. Hence, the study recommends future researches to consider a sample size which can effectively validate the outcomes of all the previous researches.

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