Derleme|Review

İnterstisyel Akciğer Hastalığında Gelecek

The Future in Interstitial Lung Disease

Katerina ANTONIOU MD PhD[1], Elyse E. LOWER MD[2], George MARGARITOPOULOS MD, PhD[3], Eleni BIBAKI MD[1], Maria BOLAKI, MD[1], Robert P. BAUGHMAN MD[2]

[1] Department of Respiratory Medicine & Laboratory of Molecular and Cellular Pneumonology, Faculty of Medicine, University of Crete, Greece

[2] Department of Medicine, University of Cincinnati Medical Center, Cincinnati, OH, 45267, USA

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

SUMMARY

The traditional method to diagnose idiopathic interstitial lung disease has relied on high resolution CT scan (HRCT) and surgical lung biopsy. More recently, recognition patterns and detailed algorithms have been developed to analyze HRCT in interstitial lung disease. Cryobiopsy has been found the procedure to be a cost effective alternative to open lung biopsy in diagnosing interstitial lung disease. Clinical observations led the scientists into the theory that genetic factors are involved actively in the pathogenesis of IPF. Cutting edge research methods such as genome-wide association studies and whole-genome sequencing revealed several genetic loci associated with IPF susceptibility. Genetic testing will be used in the future for further characterize patients with pulmonary fibrosis in order to provide personalized management. The diagnosis of interstitial lung disease is often made at a multi-disciplinary conference. In the future, one can anticipate the attendance by others such as an interventional pulmonologist to help decide on the best approach to diagnosis. The radiologist will be aided by a computer analysis which will provide a numerical score regarding HRCT texture. The pathologist will be provided a detailed gene signature of the tissue, a statistician may also be required to interpret the probability of a specific diagnosis. In the future, management of interstitial lung disease will be quite different. However, with stabilization of the pulmonary fibrosis, other problems will arise.

Keywords: *Interstitial lung disease, diagnosis, genetics, treatment, future.*

Yazışma Adresi / Address for Correspondence

Robert P. Baughman, MD
Department of Medicine, University of Cincinnati Medical Center, Cincinnati, OH, 45267, USA
e-posta: baughmrp@ucmail.uc.edu
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ÖZET

İdiyopatik interstisyel akciğer hastalıklarının tanısında geleneksel yöntemler; yüksek çözünürlüklü bilgisayarlı tomografi (YRBT) ve cerrahi akciğer biyopsisidir. Son zamanlarda, interstisyel akciğer hastalığının (İAH) YRBT bulgularını analiz etmek için tanıma paternleri ve detaylı algoritmalar geliştirilmiştir. İAH tanısında açık akciğer biyopsisine alternatif olarak önerilen cost-efektif yöntem kriyobiyopsidir. Klinik çalışmaların sonuçları, bilim adamlarına İPF patogenezinde genetik faktörlerin aktif rol oynadığını düşündürmüştür. Genome-wide ve tümgenom sekans çalışmaları İPF duyarlılığı ile ilgili bazı genetik lokusların belirlenmesini sağlamıştır. Gelecekte genetik araştırmalar ile fibrozisli hastaların tanımlanması sağlanabilecek ve bireysel tedaviler planlanabilecektir. İAH tanısı sıklıkla multidisipliner olarak konur. Gelecekte, girişimsel pulmonolojist gibi bir hekimin bu ekibe eklenmesi ile tanı için en iyi yaklaşım belirlenebilir. Bilgisayar analizi yardımı ile radyolog YRBT'de sayısal skorlamalar yapabilir. Patolog dokunun detaylı gen profilini çıkarabilir, ayrıca istatistikçi spesifik tanı olasılığını hesaplamak için gerekebilir. Gelecekte, İAH tedavisi çok farklı olabilir. Ancak pulmoner fibrozisin stabil hale getirilmesi başka sorunların ortaya çıkmasına neden olacaktır.

Anahtar Kelimeler: *İnterstisyel akciğer hastalığı, tanı, genetik, tedavi, gelecek.*

INTRODUCTION

Diagnosis

The traditional method to diagnose idiopathic interstitial lung disease has relied on high resolution CT scan (HRCT) and surgical lung biopsy[1]. This approach is discussed elsewhere in this book. In the future, both of these techniques will be changing.

Radiologic evaluation current depends on pattern recognition by the radiologist. The emphasis has been on training radiologist to appreciate certain features on HRCT. In particular, the presence of subpleural honeycombing and traction bronchiectasis have been found to be reliable indicators of a usual interstial pneumonia (UIP) pattern[2]. The role of HRCT also depends on other factors which will influence the likelihood of a correct assignment of the HRCT pattern to a particular diagnosis[3].

Early studies of automated readings of HRCT scans found six independent texture features: honeycombing, ground glass, bronchovascular, nodular, emphysema like, and normal[4]. More recently, recognition patterns and detailed algorithms have been developed to analyze HRCT in interstitial lung disease[5,6]. These automated systems have shown good correlation with physiologic measurements[5,7]. They have also been shown to have prognostic value[8]. Automated HRCT readings will lead to more reproducible readings. One can hope that this will lead to better identification and classification of various interstitial lung diseases.

One aspect of computerized HRCT reading is the use of detailed formatting to detail different patterns within the HRCT. For example, the presence of loss of lung tissue seen with emphysema mixed with increased reticular thickening seen with IPF. The combination of pulmonary fibrosis with emphysema (CPFE) has been described as a distinct clinical entity[9,10]. Patients with CPFE have an overall worse outcome than IPF[11]. There is in part due to the higher rate of pulmonary hypertension[12].

To date, the diagnosis of CPFE relies on radiologic assessment of the degree of emphysema seen on HRCT[9,10]. This is at best a qualitative assessment. Automated HRCT interpretation has been shown to improve the quantification of HRCT findings and therefore lead to more precise quantification[13]. One of the areas of future research in pulmonary fibrosis is how to classify and treat CPFE. With a more accurate method for quantification of both the emphysema and fibrosis, research into that area should be easier to perform.

In addition to radiology, tissue analysis is important in providing the correct diagnosis for various interstitial lung diseases. The surgical lung biopsy has been the method of choice for tissue confirmation in most cases[1]. This is because the size of a transbronchial lung biopsy is usually too small to characterize the pattern of fibrosis. The recent introduction of cryobiopsy to evaluate interstitial lung diseases has led to availability of larger tissue obtained via a bronchoscopy and has a higher yield than traditional transbronchial biopsy [14].

There have been several series documenting the value of cryobiopsy in evaluating interstitial lung disease. The reported diagnostic yield is around 70% of most large studies [14-18]. In most of these studies, the results of the biopsy were used with other clinical information, including results of HRCT, to arrive at a specific diagnosis.

Because the cryo sample is usually too large to withdraw through the channel of the bronchoscope, the standard procedure is to withdraw the entire bronchoscope to retrieve the sample. However, this may lead to unmonitored bleeding, which can be severe. There have been several different methods proposed to control bleeding. One technique is to place a balloon tip catheter in the airway and tamponade the bleeding locally immediately after the biopsy 18. Another approach to remove the initial bronchoscope with the cryo sample. A second bronchoscope is then immediately placed in airway to control the bleeding[15].

Overall, the use of cryobiopsy was associated with increased risk over the risk of traditional transbronchial lung biopsy[19]. The major problem was bleeding, which can be life threatening at times. While most centers have reported a low rate of severe bleeding[15,16,18], some groups have encountered significant problems with bleeding. However, the cryobiopsy was safer than a surgical lung biopsy[17]. An analysis of yield and cost of the cryobiopsy has found the procedure to be a cost effective alternative to open lung biopsy in diagnosing interstitial lung disease.

Genetic Studies

IPF is a chronic, progressive lung disease that is characterized by the devastating effects of irreversible scarring of lung parenchyma caused by extracellular matrix deposition, myofibroblast foci formation and alveolar epithelial cell hyperplasia. There are cumulative data supporting the idea that it results from alveolar epithelial cell injury and subsequent dysregulated repair as well as enhanced epithelial apoptosis[20]. The underlying disease process is variable and unpredictable, with many different molecular processes being involved. An increase in the incidence and prevalence of IPF has been documented and the prognosis remain poor despite the widespread use of the new antifibrotic drugs.

Nowadays, the pathogenesis of IPF is undergoing extensive research. The interaction of both genetic and environmental factors has been incriminated. Cigarette smoking and exposure to several environment/occupational agents are the most important environmental risk factors for IPF, while comorbid conditions, such as emphysema, gastroesophageal reflux, viral or bacterial lung infections, and radiotherapy, has also been observed to increase the risk of IPF[21].

Clinical observations such as the heterogenous nature of the disease's course, it's occurrence among relatives or in the context of rare genetic diseases, and the widely different response to experimentally induced fibrosis in mice, led the scientists into the theory that genetic factors are involved actively in the pathogenesis of IPF[22]. Cutting edge research methods such as genome-wide association studies and whole-genome sequencing revealed several genetic loci associated with IPF susceptibility and opened up new horizons in the diagnosis, prognosis, and management of IPF[22].

The vast majority of cases of idiopathic pulmonary fibrosis occur in people with no family history of the disease (sporadic form). However, recent data supports the existence of familial form of the disease in about 2-20% of the cases. Familial pulmonary fibrosis (FPF) is defined as the presence of at least two cases of pulmonary fibrosis in the same family and is characterized chiefly by autosomal dominant trait of inheritance. Clinical features such as age of onset and radiological patterns have different clinical phenotypes caused by interactions among genetic and non-genetic factors[23].

Several gene variants and the consequent malfunctional proteins were discovered to be associated with the familial pulmonary fibrosis. These genes are clustered according to the pathophysiological pathways involved. One group are genes related to alveolar stability (surfactant protein C, SFTPC, surfactant protein A2, SFTPA2 and ATP-binding cassette member A3, ABCA3). Another group, genes related to telomerase dysfunction and telomere length, have been extensively studied and have been detected in ten percent of FPF cases and one to three percent of sporadic IPF patients. Since telomere length is related to aging, this is in line with the observations that IPF is often a disease of elderly. The MUC5B gene expresses major gel-forming proteins in human airway secretions that have a decisive impact on viscoelastic properties of airways. Some MUC5B variations have an increased risk of pulmonary fibrosis[20]. Finally, recent data have revealed that specific genes with known role in inflammation and immunity, such as TOLLIP,

ELMOD2, major histocompatibility complex (MHC), interleukins, tumor necrosis factor [TNF], and transforming growth factor β [TGF-β] have genetic susceptibility loci for pulmonary fibrosis[21,22].

Surfactant proteins are responsible for alveolar stability. Surfactant protein C (SFTPC) gene is located on the short arm of chromosome 8 and encodes surfactant protein C (SP-C), a hydrophobic protein responsible for lung homeostasis. A breakthrough occurred in 2001 when Nogee and colleagues identified a mutation in SFTPC, the gene encoding surfactant protein C (SPC), in a mother and child with ILD. In both cases the mutation was recognized on one allele, implying the autosomal dominant pattern of inheritance[24]. Later two further mutations were identified (L188Q and Ile)73 in SFTPC gene and so far more than 40 pathogenic mutations have been discovered[25,26]. These variants lead to an excessive accumulation of prosurfactant protein C in the endoplasmic reticulum (ER) provoking further ER stress which fatally drives to the activation of unfolded protein response (UPR) which contribute to alveolar epithelial cell apoptosis. In other words, prosurfactant protein C does not succeed to mature and to maintain alveolar stability interacting with surfactant phospholipids and other surfactant proteins. Interestingly, L188Q mutation was found to be implicated in the enhancement of EMT in alveolar epithelial cell in response to endoplasmic reticulum stress[27]. SFTPA2 encodes surfactant protein SP-A which belongs to the family of collectin proteins and is involved in the innate defense system and pulmonary immune response. A mutant protein of SP-A2 is assumed to cause disease through ER stress and a change in the secretion of TGF-β. There are also data supporting the role of abnormal SP-A in the co-existence of lung cancer and pulmonary fibrosis[28]. ATP-binding Cassette member A3(ABCA3), a transporter protein expressed in the AECII plays role in surfactant metabolism and transport. Mutations in this gene have been mostly identified in neonatal respiratory distress syndrome or ILDs of childhood[25].

Telomerase complex genes constitute another important group of genes involved in pulmonary fibrosis. They maintain telomere integrity by adding sequences to the ends of chromosomes[29]. Telomerase reverse transcriptase component (TERT) and the RNA template component (TERC) encode the two key components of telomerase complex. Telomerase mutations cause short telomeres and are detected in 8-15% of FPF and 1-3% of sporadic pulmonary fibrosis cases[30]. Telomere length is correlated with abnormal tissue renewal capacity, a key feature of an age-related disease. In addition to the genes mentioned above, variants in DKC1[31], which encodes the telomerase complex component dyskerin, RTEL1 which encodes a regulator of telomere elongation and PARN, involved in m RNA processing have been reported only in FIP cases. Collectively, variants in telomere-related genes are identified in 15-20% of FIP cases[32,33].

MUC5B gene encodes a member of the mucin family proteins, is expressed by bronchiolar epithelial cells, and contributes to the normal viscoelastic properties of lung mucus. Seibold et al identified a single polymorphism in the promoter of MUC5B (rs35705950) in 38% of IIPs cases and 34% of FIP. Heterozygous subjects had a 7-fold increased risk for fibrosis, while homozygous subjects had a 20-fold increased risk for developing fibrosis[34]. The rs35705950 variant of MUC5B is the most strongly linked genetic risk factor of developing IPF to date. Increased expression of MUC5B in the peripheral airspaces causes lung injury by slowing lung clearance of inhaled toxins and microorganisms, promotes alveolar collapse and contribute to honeycomb cysts formation[22]. Despite the grand genetic effect of MUC5B rs35705950, there is a significant proportion of carriers that will never develop the disease, pinpointing the theory that genetic prepossession alone is sufficient enough to develop the clinical entity of lung fibrosis. Notably, there are elements supporting the more favorable prognosis in the carriers of MUC5B rs35705950 allele[35].

Among genes related to immunity and inflammation are Toll-like receptors (TLRs).They are expressed by immune-related cells and have been implicated in the pathogenesis of IPF. The TLR3 is a contributor of innate antiviral immunity[36]. A TLR3 polymorphism (L412F) associated with reduced TLR3 function was detected in an increased proportion of IPF patients[37]. It was also found that fibroblast with this variant have functional dysregulation. TOLLIP is a protein also involved in innate immune responses through its interaction with TLR and TGF-b. So far three SNPs have been identified in TOLLIP and clinical correlations have been conducted. The allele of rs5743890 was associated with IPF mortality[38].

Occasional reports have shown that variants also in other genes involved in major cellular processes such as ELMOD2, expressed in alveolar macrophages

and AECII, major histocompatibility complex genes, interleukins, tumor necrosis factor, transforming growth factor β and PTEN-induced putative kinase 1 (PINK1), involved in mitochondrial dysfunction, can be rarely found in some cases of IPF patients[39].

Genetic testing will be used in the future for further characterize patients with pulmonary fibrosis in order to provide personalized management. At present, genetic testing is recommended only in cases with interstitial lung disease and either familial interstitial pneumonia, onset of disease before 50 years, bone marrow failure, thrombocytopenia, myelodysplastic syndromes, dyskeratosis congenital or cryptogenic cirrhosis[23].

While several genetic abnormalities have been described, no single gene abnormality is universally found for any of the idiopathic interstitial lung diseases. The lack of a single gene does not mean that genetic information is not useful in diagnosing interstitial lung diseases. However, a combination of genes must be assessed. These gene signatures may prove useful in diagnosis.

An early study of gene expression in lung tissue demonstrated a striking difference in the gene pattern between IPF and chronic hypersensitivity pneumonitis[40]. Differences in gene signatures of various interstitial lung diseases have been noted over the years[41,42]. These observations led to clinical trial evaluating gene signatures of lung tissue, including transbronchial biopsy samples. A preliminary presentation of the trial reported that a genomic classifier of usual interstitial pneumonia had a specificity of 88% and sensitivity of 67% (Brown K et al Presented at American Thoracic Society May 2017). Gene signatures from peripheral blood have also been shown to be different in IPF versus other conditions[43].

The diagnosis of interstitial lung disease is often made at a multi-disciplinary conference[44]. The usual participants are the clinician, the radiologist, and the pathologist. In the future, one can anticipate the attendance by others such as an interventional pulmonologist to help decide on the best approach to diagnosis. The radiologist will be aided by a computer analysis which will provide a numerical score regarding HRCT texture. The pathologist will be provided a detailed gene signature of the tissue, similar to what is being increasingly used in evaluating cancers. A statistician may also be required to interpret the probability of a specific diagnosis (Table 1).

Table 1. Future directions in diagnosis.

Automated Computer Analysis of HRCT
Use of cryobiopsy to replace surgical lung biopsy
Gene signature analysis of lung tissue
Combination methods to enhance diagnostic accuracy

Therapy

Despite an exponential increase in the number of idiopathic pulmonary fibrosis (IPF) treatment trials, until recently, no pharmacological treatment had altered natural history, as judged by a reduction in the rate of lung function decline[45]. In 2014, the long waiting came to an end with the widespread commercial availability of the two anti-fibrotic compounds, pirfenidone and nintedanib. Different factors contributed to this achievement.

Our understanding regarding the pathogenesis of IPF has changed. Initially, it was believed that fibrosis was the result of chronic inflammation. According to the current paradigm, IPF is the result of an epithelial-driven and fibroblast-activated process in which inflammation may have only an ancillary role[46]. Along the same line, anti-inflammatory treatment had proved ineffective in IPF. In previous trials, compounds that inhibit individual mediators or signaling pathways were tested. However, the knowledge that multiple pathways are simultaneously activated in IPF led to the choice of compounds that act through pleiotropic effects, modulating multiple biological pathways[47].

The design of the clinical trials has improved. The inclusion criteria were more precise in the recent successful trials. The diagnosis of IPF was confirmed after central review of high resolution computed tomography (HRCT) scans and, when available, surgical lung biopsy samples by radiologists and pathologists with experience in IPF. This allowed the inclusion of well-defined patients in the study cohorts. The choice of the end-point has changed. In the past, different end points were used making it difficult to compare the results obtained from different trials. The current consensus favours serial forced vital capacity (FVC) as the primary end point that best captures chronic disease progression, although this choice was not unanimous[48,49]. FVC was used as the primary end point for both of the pivotal pirfenidone and nintedanib trials.

Pirfenidone

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is an orally administered drug with anti-fibrotic, anti-inflammatory, and anti-oxidant activities. Encouraging results observed in phase II and phase III trials[50-53] led to the design of the two CAPACITY trials (studies 004 and 006) which were conducted in North America, Australia, and Europe[54]. Patients with mild-to-moderate IPF defined as an FVC ≥ 50% predicted, diffusion capacity for carbon monoxide (DLco) ≥ 35% predicted, and 6MWT distance ≥ 150 m were included. In study 004, 435 patients were assigned to receive either high-dose pirfenidone (2,403 mg/day) or low-dose pirfenidone (1,197 mg/day) or placebo in a 2:1:2 dosing ratio; in study 006, 344 patients were assigned to receive high-dose pirfenidone (2,403 mg/day) or placebo. In both studies, the primary end point was the change of FVC percentage predicted from baseline to week 72. Only the study 004 met the primary end point. High-dose pirfenidone (2,403 mg/day) was associated with significantly reduced mean decline in percentage predicted FVC compared with placebo (-8 and -12.4%, respectively) and a lower prevalence of declines in FVC of 10% or greater at 72 weeks. The European Medicines Agency (EMA) licensed pirfenidone for use in mild to moderate IPF based on evaluation of the these results. However, the U.S. Food and Drug Administration (FDA) based on the conflicting results from the CAPACITY trials, required the performance of an additional study, the ASCEND trial[55].

The same rigorous criteria for the diagnosis of IPF applied in CAPACITY trials were also applied in ASCEND. Severity exclusion criteria consisted of FVC < 50% predicted (as in the CAPACITY studies) and DLCO < 30% predicted (compared with < 35% in the CAPACITY studies). This multi-center study randomized patients to either pirfenidone 2403 mg/day (278 patients) or placebo (277 patients). The study met the primary end point which was the change from baseline in FVC over 52 weeks, quantified as a continuous variable, and evaluated non-parametrically. The mean decline from baseline in FVC was 235 mL in the pirfenidone group and 428 mL in the placebo group (absolute difference 193 mL, relative difference 45.1%; P<0.001). Moreover, pirfenidone also significantly reduced the proportion of patients who had a decline of ≥ 10% in the percentage of the predicted FVC or who died, and increased the proportion of patients who had no decline in the percentage of the predicted FVC as compared with placebo (16.5% vs 31.8% [p< 0.001] and 22.7% vs. 9.7% [p< 0.001], respectively). Pre-specified pooling of three studies (CAPACITY and ASCEND) showed that pirfenidone therapy was associated with a reduced risk of death at 1 year (hazard ratio, 0.52; 95% confidence interval, 0.31-0.87; p= 0.01). The positive results from the ASCEND study have led to the licensing of Pirfenidone by the FDA on October 2014 for treatment of IPF regardless of the severity of the disease.

Several important observations have emerged from pooled analyses of these studies. A decline in FVC of > 10% in the first 6 months of treatment was associated with a much lower risk of a further 10% FVC decline or death compared with placebo in patients who continued the treatment[55]. Therefore, an initial decline should not be viewed as treatment failure because it was not predictive of the future behavior of the disease.

Recent analyses post-hoc analyses of the CAPACITY and ASCEND have showed that treatment benefits of pirfenidone on serial FVC trends are virtually identical in patients with a baseline FVC above or below 80%[56]. This means that institution of treatment is equally important in symptomatic patients with a more preserved lung function and that the natural course of the disease is independent on the baseline disease severity.

Pooled data also indicated that pirfenidone reduces the risk of hospitalization from respiratory causes. Although the reason is not clear, the authors hypothesized that this could be the result of a decrease of the rate of acute exacerbations and of the activity of the disease[57].

Acknowledging the difficulties to design pharmaceutical trials using all-cause mortality as a primary end-point as well as the limitations of pooled data analysis and meta-analysis, Nathan and colleagues have recently shown that the use of pirfenidone was associated with a reduced relative risk of death compared with placebo[58].

The survival benefit in patients with IPF receiving pirfenidone or best supportive care (BSC) in a population that met the inclusion criteria of patients enrolled in the ASCEND and CAPACITY trials was recently studied[59]. Interestingly, mean survival was estimated to be 8.72 years with pirfenidone and 6.24 years with BSC providing a survival benefit of an average of 2.47 years compared with BSC. Sensitivity analyses found that pirfenidone was associated with

a consistent improvement in life expectancy compared with BSC.

Clinical trial data, single-centre experience, and real-life registries[60-63] consistently showed that the most frequent adverse events are gastrointestinal and skin-related. Importantly, they tend to occur early, usually 3-6 months after the beginning of the treatment. Prevention is vital, but in case they develop, they often resolve with dose reduction. In some cases, temporary withdrawal with subsequent cautious re-introduction of the reduced dosage pirfenidone tolerated.

Nintedanib

Nintedanib is a potent intracellular inhibitor of the receptor tyrosine kinases, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGFR), and non-receptor tyrosine kinases of the Src family[64,65]. Similar to pirfenidone, nintedanib has anti-fibrotic and anti-inflammatory activities.

The efficacy of nintedanib 150 mg twice daily has been demonstrated in three randomized placebo-controlled clinical trials. The TOMORROW trial was a phase IIb dose-finding trial. 432 patients received nintedanib 50 mg once daily, 50 mg twice daily, 100 mg twice daily, 150 mg twice daily, or placebo for 52 weeks[66]. It was noted that 150 mg twice daily reduced the decline in FVC at 52 weeks by 68.4% (60 mL/year compared with 190 mL/year). Moreover, a reduced incidence of acute exacerbations and a preservation of health-related quality of life were observed with nintedanib versus placebo. Subsequently, the dose of 150 mg twice daily was tested in two duplicate phase III trials.

In INPULSIS I and II trials, 1066 patients were randomized in a 3:2 ratio to receive nintedanib 150 mg twice daily or placebo for 52 weeks[64]. The novelty in the inclusion criteria was that patients with "possible" usual interstitial pneumonia pattern (UIP) on HRCT (i.e., reticulation in a subpleural, predominantly basal distribution without honeycombing, but with an additional requirement that traction bronchiectasis be present) were included. Severity inclusion criteria consisted of FVC ≥ 50% predicted and DLCO 30 to 79% predicted. Change of FVC in 52 weeks was the primary end-point in both trials. In INPULSIS-1, the annual rate of decline in FVC was 114.7 mL/year in the nintedanib group versus 239.8 ml/year with placebo. In INPULSIS-2, the annual rate of decline in FVC was 113.6 mL/year in the nintedanib group versus 207.3 mL/year with placebo. The positive results of the INPULSIS study have led to the licensing of Nintedanib by the FDA on October 2014 for treatment of IPF regardless of the severity of the disease.

Several important findings emerged from the pooled analyses of the data from TOMORROW and INPULSIS trials. A benefit regarding the reduction of acute exacerbation was observed[67].

The magnitude of treatment benefit with nintedanib was similar in patients with an FVC greater or less than 70% and 90% 68. In the placebo arms. the same rate of FVC decline was observed regardless the fact that baseline FVC was reduced or preserved. These results indicate that many patients with marginally impaired lung function are likely to benefit from early treatment.

According to the recent guideline document, the diagnosis of IPF requires the presence of a "definite" UIP pattern on HRCT. In any other case, the performance of a surgical lung biopsy is warranted 69. The performance of the biopsy is not always possible because of the severity of the disease, comorbidities, or patient preference. The INPULSIS trials showed that patients with a "possible" UIP pattern and without lung biopsy confirmation of the diagnosis had the same rate of FVC decline and the same response to treatment to those with a "definite" UIP pattern on HRCT or with a biopsy proven IPF[70].

Clinical trial pooled data showed that the most frequent adverse event is diarrhea, which was reported in 62.4% of patients in the nintedanib group versus 18.4% in the placebo group. However, only 4.4% of patients discontinued nintedanib prematurely due to diarrhea[64,71]. In a year, open label extension trial, no new safety and tolerability issues were observed. INPULSIS-ON is an ongoing open-label extension trial in which patients who completed an INPULSIS trial in either the nintedanib or placebo group had receive open-label nintedanib 150 mg twice daily, with dose reductions or interruptions recommended to manage adverse events. An interim analysis of data from INPULSIS-ON showed that patients who continued nintedanib had the same rate of decline with patients included in the INPULSIS trial. This finding suggests that the efficacy of nintedanib is maintained for up to 3 years[71]. Another aspect of the INPULSIS-ON trial is that patients with an FVC < 50% predicted were included. These patients were excluded from the INPULSIS trial. It was observed that the absolute changes in FVC

from baseline to week 48 were similar in patients with FVC ≤ 50% and > 50% predicted at baseline[72]. This suggests that nintedanib may be efficacious in advanced disease. However, the results should be interpreted with caution because only 24 patients with FVC ≤ 50% predicted were included in this analysis.

Treatment of Associated Problems

Most of treatment trials in IPF and other fibrotic lung diseases have focused on dealing with the parenchymal fibrosis. There are other aspects of care of IPF patients that are increasingly being recognized. As we move forward in the management of these patients, there are other issues will need to be addressed[73]. Among these issues are pulmonary hypertension, co-morbidities, fatigue, and the need for palliative care (Table 2). The diagnosis and treatment of pulmonary hypertension in pulmonary fibrosis is discussed elsewhere in this book.

Patients with IPF admitted to the hospital often have significant co-morbidities[74,75]. Diabetes is a commonly observed comorbidity[73,74]. Its presence is associated with an increased risk for death 76. An often cited reason for diabetes is the use of glucocorticoids for treatment, including acute exacerbations[74]. Another commonly noted comorbidity is gastro esophageal reflux (GERD)[73,75]. While GERD may not contribute to increased mortality, it has been found that treatment for GERD may improve survival[77], although not all studies reported that GERD treatment was associated with improved survival[75]. Coronary artery disease is another significant comorbidity encountered in IPF patients[73,76]. Using multi-variate analysis, CAD remains an independent risk factor for death[78]. Since treatment for hypertension and hyperlipidemia are effective risk reduction strategies in the general population, these comorbidities should be actively sought and treated. Future strategies in IPF will need to address the role of these comorbidities.

Patients with IPF have an increased risk for lung cancer[79]. This combination is associated with an increased mortality[75]. The identification of earlier cases of IPF likely will lead to identifying co-existing lung cancer and interstitial lung disease. Future studies will need to determine how best to handle these cases. For example, what are the limits of radiation therapy for local control? Also, are certain chemotherapies likely to enhance or worsen the patient's prognosis?

Table 2. Pulmonary fibrosis associated medical issues.

Pulmonary hypertension
Co morbidities
Fatigue
Palliative care

Unfortunately, most patients with interstitial lung disease die as a consequence of progressive fibrosis. The role of end of life planning and palliative care are just beginning to be explored. This is important, since recent studies have identified that there is a gap in understanding of the clinical course and outcome of advanced interstitial lung disease, such as IPF. In one study of two London hospitals, IPF patients had a good understanding of terminal status of their disease[80]. However, they had a poor understanding of prognosis and how the disease would evolve. This included lack of understanding of the causes of death from IPF. The patients and care givers wanted more information. Interviews of the health professionals taking care of these patients found that they struggled with the balance of information and hopelessness. Interestingly, no participants were aware of palliative care resources. This observation led to the development of an intervention using a communicating case conference. In a randomized trial, those randomized to a communicating case conference had significantly better outcome[81].

There have been several studies which examined interventions to improve quality of life for IPF patients. In a systematic review, Bajwah et al identified 19 interventions in 3635 patients[82]. These interventions included 17 randomized clinical trials. In a meta-analysis, the authors broke down interventions into those with weak or no evidence versus those with moderate to strong evidence (Table 3). The strongest evidence was for either pulmonary rehabilitation or pirfinedone to improve 6 minute walk distance (6MWD). Interestingly, oxygen supplementation itself was not associated with improvement in 6MWD in studies reported to date.

Several interventions have been proposed to relieve breathlessness in advanced lung disease including pulmonary fibrosis. The most widely used drugs are opioids. A Cochrane report found of the 26 studies reported, that there was an overall small improvement in level of breathlessness[83]. Major complications included nausea, vomiting, constipation, and sedation. Another Cochrane report evaluated the use of benzodiazepines for breathlessness[84]. Of the eight papers

Table 3. Interventions to improve quality of life in progressive fibrotic lung disease.

Weak evidence

- Prednisone, morphine, penicillamine, colchicine on dyspnea
- Thalidomide and interferon gamma on cough
- Morphine sulfate on anxiety
- Rehab on fatigue
- Thalidomide and doxycycline on QOL

Moderate to strong evidence

- Moderate evidence for sildenafil to improve quality of life
- Moderate evidence for pulmonary rehabilitation to improve quality of life
- Strong evidence for pirfenidone to improve 6MWD
- Strong evidence for pulmonary rehabilitation to iomprove 6MWD

reviewed, they could not demonstrate any benefit for benzodiazepine treatment. However, there were increased side effects with use, mostly sedation.

Cough is another major problem for pulmonary fibrosis patients. In a double blind, placebo controlled, cross over trial, thalidomide was found to improve cough symptoms and quality of life[85]. The drug is expensive sedating, and can lead to significant constipation. In addition, it has been found to increase the risk for deep vein thrombosis and pulmonary emboli in some conditions[86].

For advanced pulmonary fibrosis, respiratory failure requiring mechanical ventilation is associated with a poor outcome. In a study of 27 pulmonary fibrosis patients requiring mechanical ventilation, only four patients were discharged from hospital alive without lung transplant and only one was alive one year later[87]. Use of non-invasive ventilation (NIV) was associated with better short term outcome. Of 18 patients in one study on NIV, eight were alive 90 days later[88]. This same group reported a successful case of respiratory failure managed with extra corporeal membrane oxygenation (ECMO)[89]. However, this resuscitation seems most useful for those patients who were eventually able to undergo lung transplant[90].

In one large US study of end stage IPF patients, over half of the patients died in hospital without palliative care referral[91]. Most of these patients had been diagnosed as IPF more than three years before their death. In this study, those patients referred to palliative care were more likely to die at home or in a hospice setting. In another study, only 4% of IPF patients were referred for palliative care before ICU admission[92].

A systematic review identified over twenty randomized trials evaluating early palliative care referral[93]. Some, but not all, studies demonstrated improved quality of life, directiveness, and care giver satisfaction. In addition, there was a reduction in aggressive care, hospitalizations, and length of stay in hospitals. However the methodology of these studies was inconsistent with various definitions for early referral and usual care for the patient.

To improve this situation, a needs assessment tool for progressive disease in interstitial lung disease (NAT:PD-ILD) has been developed[94]. This was adapted from a needs assessment toll for cancer patients. The NAT:PD-ILD instrument reflects patient/caregivers experiences. It identified that patients focus on physical symptoms (cough, sexual issues) and isolation, caregivers worry about loss of input and future, and clinicians worry about balancing information and hope. The widespread use of the NAT: PD-ILD may improve communication between the three major participants of the end of life of the pulmonary fibrosis patient.

In the future, diagnosis and management of interstitial lung disease will be quite different. As new techniques and treatments are adapted to these patients, better outcomes should be encountered. However, with stabilization of the pulmonary fibrosis, other problems will arise. With the rise in the number of successful treatments for IPF, new information will be gleaned.

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