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Review Article

A Review of Idiopathic Pulmonary Fibrosis

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Abstract

stitial lung diseases are a heterogeneous group of disease processes that result in damage to the lung parenchyma through inflammation and fibrosis. This review focuses on idiopathic pulmonary fibrosis (IPF), the most common idiopathic interstitial pneumonia. IPF is an irreversible disease and patients typically present with chronic, progressive shortness of breath that may be accompanied by a cough, bibasilar crackles on auscultation, and finger clubbing on inspection. Although the exact mechanism of IPF remains unknown, it is believed to be the result of an aberrant wound healing process following repetitive injury to alveolar epithelial cells. The diagnosis of IPF requires clinical, radiologic, and histopathologic correlation through a multidisciplinary discussion. High resolution computed tomography (HRCT) plays an important role in diagnosis. The clinical course of IPF is variable, often complicated by acute exacerbations. Pirfenidone is the only drug approved for use in mild to moderate IPF and treatment should also focus on non-pharmacologic therapies. Supplemental oxygen use and pulmonary rehabilitation have been shown to improve exercise tolerance and quality of life. Treatment of comorbid conditions including gastro esophageal reflux disease, pulmonary arterial hypertension, depression and anxiety is increasingly being recognized as an important component of therapy. A multidisciplinary model of care can help to provide symptom-centered management, education and self-management. Given the poor prognosis, guidelines recommend that palliative care in IPF should be started early as an adjunct to disease-specific therapy.

Keywords: Idiopathic pulmonary fibrosis; Interstitial lung disease; Fibrotic lung disease; Multidisciplinary care

Abbreviations

6MWD: 6-Minute Walk Distance; AE: Acute Exacerbation; AEC: Alveolar Epithelial Cell; ATS: American Thoracic Society; BAL: Bronchoalveolar Lavage; CCL18; Chemokine Ligand 18; COPD: Chronic Obstructive Pulmonary Disease; CTD-ILD: Connective Tissue Disease-Associated Interstitial Lung Diseases; DLCO: Diffusing Capacity; EMT: Epithelial to Mesenchymal Transition; ERS: European Respiratory Society; FLD: Fibrotic Lung Disease; FVC: Forced Vital Capacity; GERD: Gastroesophageal Reflux Disease; HRCT: High Resolution Computed Tomography; ICU: Intensive Care Unit; IIP: Idiopathic Interstitial Pneumonia; IL-8: Interleukin 8; ILD: Interstitial Lung Disease; IP: Interstitial Pneumonia; IPF: Idiopathic Pulmonary Fibrosis; KL-6: Krebs Von Den Lungen 6 Antigen; MRC: Medical Research Council; NAC: N-Acetylcysteine; NICE: National Institute of Clinical Excellence; NSIP: Nonspecific Interstitial Pneumonia; OSA: Obstructive Sleep Apnea; PAH: Pulmonary Arterial Hypertension; PPI: Proton Pump Inhibitor; PR: Pulmonary Rehabilitation; QOL: Quality Of Life; SP-A: Surfactant Protein A; SP-D: Surfactant Protein D; UIP: Usual Interstitial Pneumonia

Introduction

Interstitial lung diseases (ILDs) are a diverse group of disease processes that result in damage to the lung parenchyma through varying degrees of inflammation and fibrosis [1-5]. They are generally categorized into 4 groups: (1) those of known cause or association, (2) the idiopathic interstitial pneumonias (IIPs), (3) the granulomatous ILDs, and (4) other forms of ILD. While far greater than 100 entities have been identified as causing ILD, the most commonly encountered conditions include idiopathic pulmonary fibrosis (IPF), sarcoidosis, connective tissue disease-associated interstitial lung diseases (CTD-ILD) and hypersensitivity pneumonitis [4-6]. Identifying the underlying etiology is often essential as it drastically alters discussions surrounding prevention, treatment and prognosis.

The IIPs are differentiated by the fact that they have no known underlying etiology. These distinct clinic opathological entities were initially classified by the American Thoracic Society (ATS) and European Respiratory Society (ERS) in a joint statement published in 2002 [1]. Therein they described 7 different entities including IPF and nonspecific interstitial pneumonia (NSIP). A 2013 update of this statement revised its classification to differentiate between the major, rare and unclassifiable IIPs, while further separating the major IIPs into chronic fibrosing, smoking-related, and acute/subacute interstitial pneumonias (IPs) [7]. Furthermore, the update provided a different classification scheme based on disease course, ranging from reversible and self-limited to progressive and irreversible despite therapy. This scheme places more emphasis on identifying treatment, appropriate monitoring, and prognosis, and is especially helpful in cases of unclassifiable IPs and certain IIPs such as NSIP (Figure 1)

This review will focus on recent developments in IPF, the most common of the IIPs, including addressing an increasing shift towards a more multidisciplinary management approach as well as the

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importance of effective palliative care.

Idiopathic Pulmonary Fibrosis

IPF is a specific form of fibrotic interstitial pneumonia that is chronic, progressive, irreversible, and often deadly [6, 8,9]. The most common of the IIPs, IPF usually presents in older adults with its effects limited to the lungs. Patients with IPF typically complain of a chronic exertional dyspnea that may be accompanied by a cough, bibasilar crackles on auscultation, and finger clubbing on inspection. IPF is a diagnosis of exclusion and requires a histopathologic and/or radiologic demonstration of a usual interstitial pneumonia (UIP) pattern, which is defined below.

The incidence of IPF is quoted as 4.6 to 16.3 cases per 100 000 per year and is thought to be rising, with a prevalence ranging from 14 to 63 cases per 100 000 per year depending on the specific case definition or criteria used [10]. The disease is found to be more common in men and increases in frequency with advancing age – most diagnoses of IPF are made in the 6th and 7th decade of life.

Although IPF is considered to be idiopathic, it has been associated with a number of potential risk factors including cigarette smoking, exposure to metal dusts and wood dust, and the presence of chronic viral infections [8,9]. Most cases of IPF are sporadic in nature but familial associations are recognized, accounting for less than 5% of all IPF diagnoses. The role of other medical comorbidities, including gastroesophageal reflux disease (GERD), pulmonary hypertension, obstructive sleep apnea (OSA), and chronic obstructive pulmonary disease (COPD), remain unclear in the diagnosis, treatment and progression of IPF [9].

The rising incidence of IPF along with its progressive, irreversible presentation and numerous associated comorbidities is placing an increasing burden on health care systems. IPF patients are twofold more likely to utilize inpatient and outpatient medical services when compared to matched controls, with an inpatient mortality rate that is three times higher than age matched controls [11]. Hospital admission rates for IPF in England increased by, approximately 5% per year between 1998 and 2010 [12]. In the US, hospitalization costs for IPF increased by fourfold between 1993 and 2008, and doubled between 2007 and 2008 to approximately $1.5 billion [13]. The annual aggregate incremental cost due to IPF in the United States is likely over $1 billion [11]. Addressing this increasing burden requires not only further research in the pathogenesis of IPF to identify more effective therapeutic interventions, but also the development of improved management plans. This should be done through a multidisciplinary approach to optimize symptom control, develop patient centered plans and eventually, palliation.

Pathogenesis

The exact mechanisms of the development of IPF remain largely unknown. It has long been believed that a chronic inflammatory process injures the lung and modulates fibro genesis, leading to end-stage fibrotic scarring and pulmonary fibrosis. This model of inflammation-driven fibro genesis has been questioned. Inflammation is not a prominent histopathological finding in usual interstitial pneumonia (UIP), and there is little evidence of prominent inflammation in early disease. In 2001, Selman et al. proposed that IPF is the result of an aberrant wound healing process following repetitive epithelial injury [14]. Targeted injury of alveolar epithelial cells (AECs) consistently induces pulmonary fibrosis in experimental models. Pathologic examination of UIP tissues reveals diagnostic lesions known as 'fibroblastic foci' (dense collections of my fibroblasts and scar tissue).The AECs adjacent to these fibroblastic foci often remain hyper plastic and abnormal rather than undergoing appropriate repair [15]. Several animal models have demonstrated similar defects [16-19].

Lung fibroblasts from patients with fibrotic lung diseases differ from normal lung fibroblasts regarding proliferation, rate of collagen production and differentiation into my fibroblasts [20,21]. Several pathways result in accumulation of fibroblasts and my fibroblasts within fibrotic lungs including expansion of resident Mesenchymal cells, epithelial to mesenchymal transition (EMT), and differentiation of circulating precursors called fibrocytes [22,23]. Myofibroblasts cause basement membrane disruption and promote AEC apoptosis, eventually resulting in excessive deposition of extracellular matrix, destruction of alveolar-capillary units and formation of cystic fibrotic spaces [24]. This is one proposed mechanisms of IPF pathogenesis derived from animal models although there is no animal model that resembles the pathologic changes seen in human IPF.

Diagnosis

According to the most recent international guidelines the diagnostic criteria for IPF require the exclusion of other known causes of ILD as well as the presence of a UIP pattern on high-resolution computerized tomography (HRCT) or specific combinations of HRCT and surgical lung biopsy patterns [8]. A careful exclusion of known etiologies of ILD should be considered in all patients, including a detailed domestic and occupational exposure history, a medication review to identify any drugs associated with lung toxicity and serologic testing to assess for connective tissue diseases.

The UIP pattern is defined by specific histopathological and HRCT criteria [8]. On pathology, it requires evidence of marked architectural distortion in a predominantly sub pleural or paraseptal distribution, patchy lung involvement, and the presence of fibroblast foci. On HRCT, the focus is on reticular abnormalities, honeycombing, and traction bronchiectasis in a predominantly basal or sub pleural distribution. Given the high quality evidence demonstrating good HRCT specificity in the recognition of the histopathologic UIP pattern [26-29] (Figures 2-3) surgical lung biopsy is not always essential for the diagnosis of IPF. In the appropriate clinical setting the presence of a UIP pattern on HRCT is sufficient for the diagnosis of IPF [8]. In instances where patients have more physiologic impairment and co-morbidities, surgical lung biopsy carries a higher risk and may outweigh the benefits of establishing a definitive diagnosis of IPF [30].

While some cases are clear, the diagnosis of IPF often requires clinical, radiologic, and histopathologic correlation. It has been shown that improved diagnostic accuracy can be accomplished through a multidisciplinary discussion among clinicians, radiologists, and pathologists [25]. In situations where multidisciplinary discussion is not feasible it is recommended that patients be referred to experienced ILD centers for consultation [8].

Clinical Course

IPF is a universally fatal disease with a median survival after

diagnosis that ranges from 2 to 3.5 years [8,9]. The natural history of IPF has traditionally been defined as a slow progressive decline in lung function over time ultimately leading to death from respiratory compromise or a complicating comorbidity. However, there does in fact appear to be significant heterogeneity in the possible natural histories of IPF. The majority of patients experience a stable or slowly progressive course, with gradual symptom onset over months to years. A subset of patients may demonstrate a markedly accelerated clinical course with shortened survival and this appears to be more common in male cigarette smokers [9]. It is unclear whether these variations in natural history are primarily due to different phenotypes of IPF or varying epidemiologic factors.

Each clinical course, whether slow or accelerated, can be further complicated by episodes of acute worsening or exacerbation. An acute exacerbation (AE) of IPF has traditionally been identified as a combination of new or worsening dyspnea within days to weeks, significant gas exchange abnormalities on arterial blood gas, and new ground-glass opacities seen on chest imaging in the absence of an identifiable cause such as infection, heart failure or pulmonary embolism [8,9]. Only recently has a formal definition and diagnostic criteria been proposed by Collard et al [32]. Episodes of AE may be accompanied by symptoms of worsening cough, fever, and increased sputum production. While histology is not frequently sought it often demonstrates a pattern of diffuse alveolar damage; in some cases an organizing pneumonia pattern may be seen instead. AEs are not uncommon, affecting up to 20% of IPF patients, with multiple exacerbations possible [33]. AEs are a poor prognostic indicator with in-hospital and 90-day mortality of 50% and 60%, respectively.

Biomarkers

At present biomarkers are rarely used in the clinical management of pulmonary fibrotic diseases. Most of the previous studies evaluate the utility of biomarkers in the diagnosis of ILD. However, given the widely available use of HRCT, the need for biomarkers to diagnose ILD has become much less essential than finding a biomarker to predict survival and disease progression. For example, the allocation of donor lungs in the pre-transplant population could be improved by using a biomarker that predicts short-term survival.

Biomarkers derived from AECs and those produced by alveolar macrophages have been examined. Surfactant proteins A (SP-A) and D (SP-D) are exclusively produced in the lung by AEC bronchial epithelial cells and Clara cells [34,35]. Elevated SP-A and SP-D serum levels in pulmonary fibrosis are thought to be secondary to the increase in type II AECs due to hyperplasia and epithelial injury and basal membrane leakage causing spillover into the circulation [37]. In addition, serum SP-A and SP-D levels increase with exacerbations in IPF [36]. Takahashi et al. showed that there was considerable overlap in the serum protein concentrations between ILD survivors and non-survivors [38]. This decreases the utility of SP-A and SP-D serum levels in clinical practice.

Krebs von den Lungen 6 Antigen (KL-6) is a much in-like, high-molecular weight glycoprotein expressed on the surface membrane of type II AECs and bronchiolar epithelial cells [39]. When these cells are proliferating, stimulated or injured KL-6 is released making it a good marker of AEC injury. The median KL-6 serum concentration in healthy volunteers is 306 U/ml and none of the healthy volunteers had a KL-6 concentration >500 U/ml. Multiple studies have shown that KL-6 serum concentrations are elevated in various ILDs associated with pulmonary fibrosis and connective tissue diseases, on average >1000 U/ml [40-43]. Satoh et al. defined a cut-off value of 1000 U/ml as the most suitable to predict survival [44].

Spontaneous chemokine ligand 18(CCL18) production by alveolar macrophages from patients with IPF is up to 100-fold higher than CCL18 production by alveolar macrophages from controls [45]. In patients with fibrotic lung diseases, changes in CCL18 serum concentrations closely correlated with changes in pulmonary function data at follow up [46,47].

Evidence indicates a close correlation between pulmonary interleukin 8 (IL-8) production and Broncho alveolar lavage (BAL) neutrophils. Previous studies showed that BAL neutrophil counts correlate with disease severity and have a prognostic role in pulmonary fibrosis. However, neither cut-off values nor odds ratios have been estimated for IL-8.

Despite this evidence, no biomarkers have been established for clinical use thus far, largely due to a lack of prospective data demonstrating its utility in diagnosis or prognosis. Furthermore, the various studies are confounded by the by the fact that fibrotic lung diseases are uncommon and variable in nature, making it difficult to implement biomarkers in a clinical setting.

Treatment

Pharmacologic therapies

The clinical management of IPF remains a major challenge. There is currently no curative drug therapy for IPF. The goals of treatment should include improvement of quality of life through symptom relief, disease specific education, support and early discussion of palliative care. Although new drugs that may slow disease progression are being tested in clinical trials, they should be approached with caution inpatients due to limited evidence. Pirfenidone is an orally active drug that exhibits anti-inflammatory and anti-fibrotic properties. It is the only drug that has been approved for use in mild-to-moderate IPF in the European Union, Japan, UK, China, India and Canada. The National Institute of Clinical Excellence (NICE) recently recommended pirfenidone as a first-choice therapeutic agent in IPF patients with mild-to-moderate disease, defined as FVC > 50% of predicted [48]. The approval of pirfenidone was based on the pooled results of the CAPACITY Phase III trials, which consisted of two concurrent multinational, randomized, double-blind, placebo-controlled trials conducted over 72 weeks in patients with mild-to-moderate disease [49,50]. A phase III trial (ASCEND) has recently been completed in the US where 555 patients with IPF were randomly assigned to receive either oral pirfenidone (2403 mg per day) or placebo for 52 weeks [51]. In the pirfenidone group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died.

Interim results of an ongoing open-label extension study (RECAP), evaluating the long-term safety of pirfenidone showed that the majority of patients experienced only mild-to moderate adverse events and relatively few patients discontinued treatment due to an

adverse event [52]. A meta-analysis to analyze the safety profile of pirfenidone revealed that the pirfenidone group had a significantly higher rate of gastrointestinal, neurological and dermatological adverse events [53]. These side effects may worsen quality of life in patients with IPF and given that there is no data for longer overall survival in patients treated with pirfenidone, discontinuation of treatment should be considered if dose reduction does not help with symptom control.

The 2011 ATS/ERS guidelines were published before several important trials results, now considered as pivotal IPF studies, were known. These guidelines made recommendations for or against the use of many pharmacologic agents [16] (Table1). Combination corticosteroid, azathioprine and N-acetylcysteine (NAC) therapy has been the conventional approach for the treatment of IPF. The PANTHER-IPF study, a randomized, double-blind, placebo-controlled trial assigned patients with IPF who had mild-to-moderate lung-function impairment to one of three groups – receiving a combination of prednisone, azathioprine, and NAC (combination therapy), NAC alone, or placebo. After 50% of data had been collected, a planned interim analysis revealed that patients in the combination-therapy group had an increased rate of death and hospitalization, leading to a press release announcing the discontinuation of the triple therapy arm [54]. This combination should not be used to treat IPF. The PANTHER-IPF trial continued as a two-group study (acetylcysteine vs. placebo) without other changes, and at 60 weeks, there was no significant difference in the change in FVC, death or exacerbations between the acetylcysteine group and the placebo group [55].

ACE-IPF, a double-blind, randomized, placebo-controlled trial was designed to study the effect of warfarin on lung function in patients with progressive IPF (defined as a history of worsening dyspnea, absolute decline of either FVC >10% or DLCO > 15%, a reduction in arterial oxygen saturation > 5% or progression of radiographic findings) [56]. This study did not show a benefit for treatment with warfarin and furthermore, warfarin was associated with an increased risk of mortality in an IPF population who lacked other indications for anticoagulation. Given the lack of evidence showing any benefit, anticoagulation should not be used as a treatment for IPF.

In 2013, a double blind study (TIPAC) showed that use of Co-trimoxazole treatment resulted in a significant improvement of overall health-related quality of life and a reduction in all-cause mortality (HR, 0.21; 95% CI, 0.06–0.78; p=0.02) compared with placebo [57]. This was associated with a reduction in frequency of respiratory tract infections. Co-trimoxazole had no effect on FVC, the primary end point. Currently, a clinical trial is underway to evaluate decline in FVC ≥ 5% at 24 weeks and/or hospitalization for respiratory causes in patients with IPF assigned to oral cotrimoxazole versus placebo [58].

Nintedanib is an antagonist that inhibits a number of key tyrosine kinase receptors involved in the pathogenesis of fibrosis. Based on results from the phase IIb TOMORROW trial, which showed a trend toward a reduction in the decline in lung function, fewer acute exacerbations and preserved quality of life in IPF patients treated with Nintedanib [59], two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) were carried out to evaluate the efficacy and safety of 150 mg of Nintedanib twice daily

Table 1: Recommendations and evidence of pharmacologic treatments based on 2011 ATS/ERS guidelines.

Pharmacologic Treatment	Recommendation	Evidence
Corticosteroid monotherapy	Strong recommendation against	Very low quality
Colchicine	Strong recommendation against	Very low quality
Cyclosporin A	Strong recommendation against	Very low quality
Combination corticosteroid and immunomodulator (i.e. azathioprine or cyclophosphamide)	Strong recommendation against	Low quality
Combination corticosteroid, azathioprine, and acetylcysteine therapy	Weak recommendation against	Low quality
Acetylcysteine monotherapy	Weak recommendation against	Low quality
Interferon-γ1b	Strong recommendation against	High quality
Bosentan	Strong recommendation against	Moderate quality
Etanercept	Strong recommendation against	Moderate quality
Anticoagulants	Weak recommendation against	Very low quality
Pirfenidone	Weak recommendation against	Low to moderate quality evidence
Oxygen Therapy Pulmonary Rehabilitation	Strong recommendation for Weak recommendation for	Very low quality Low quality
Lung Transplantation GERD Treatment	Strong recommendation for Weak recommendation for	Low quality Very low quality
PH Treatment Mechanical Ventilation	Weak recommendation against Weak recommendation against	Very low quality Low quality

as compared with placebo in patients with IPF. Nintedanib reduced the decline in FVC in INPULSIS-1 and INPULSIS-2 [60]. Other drugs, like Sildenafil and Bosentan, agents commonly used to treat pulmonary arterial hypertension (PAH) were also tested in clinical trials where primary endpoints were not met [61-63]. Thalidomide was effective in the treatment of cough in a single center study that needs further validation in a larger trial [64]. Patients should be encouraged to enroll in clinical trials of new drugs whenever possible.

While there is a lack of controlled trials commenting on efficacy, dosing, and route of administration, acute exacerbations of IPF are generally treated with a course of corticosteroids as recommended by current international guidelines [8].

Smoking cessation and vaccinations are essential components of preventive care, especially in the elderly population and those with chronic medical conditions. As such, in addition to smoking cessation, all IPF patients may be considered for yearly influenza vaccinations as well as pneumococcal vaccinations every five years [65].

Non pharmacologic therapies

Oxygen therapy has long been felt to be beneficial in hypoxemic lung diseases [66] – early studies focusing on obstructive lung diseases showed a significant survival benefit in patients receiving long-term oxygen therapy [67, 68]. In IPF, nocturnal hypoxemia is common and has been shown to have a negative impact on health-related quality of life [69]. Daytime oxygen levels are the best predictor of nocturnal hypoxemia. Thus it is likely beneficial to initiate supplemental oxygen therapy in IPF patients experiencing resting hypoxemia or significant desaturation with physical activity. Although good evidence is still lacking, oxygen therapy in IPF can lead to a significant improvement in symptoms, quality of life, and endurance during pulmonary rehabilitation and is strongly recommended in the current international guidelines [8,70].

Pulmonary rehabilitation (PR) is a multi disciplinary, and comprehensive intervention for patients with chronic respiratory diseases that uses a combination of patient assessments, exercise training, education, and psychosocial support to reduce symptoms, optimize functional status and improve quality of life [70]. While much of the evidence for PR is in patients with COPD, many of these principles are being increasingly applied to IPF patients with mixed results. Multiple studies, including two randomized controlled trials, have demonstrated significant reduction in dyspnea, increase in 6 minute walk distance (6MWD), as well as improvement in quality of life outcome measures immediately following 8 to 10 week exercise-focused PR programs [71-74]. Unfortunately, by six months, patients who completed IPF PR programs showed a significant reduction or even complete loss of clinically important changes in dyspnea and 6MWD initially obtained. Early PR intervention also appears to be relevant. A study looking at 65 patients with stable IPF demonstrated that patients with a lower baseline Medical Research Council (MRC) dyspnea score, which was presumed to correlate with earlier course of disease, had greater improvements in 6MWD and overall health status after completion of a PR program [75]. In IPF patients where fatigue and de conditioning may be the dominant symptoms early referral to PR likely will be of benefit in order to prevent a continuous cycle of progressive deterioration [65]. Furthermore, IPF patients likely need PR programs tailored to their specific needs, an area that is still actively undergoing research [76].

As described above, the clinical course of IPF may include acute deteriorations that often lead to discussions around the option of mechanical ventilatory support. Unfortunately, the overall prognosis of IPF patients requiring ventilation is known to be very poor [77,78]. Data from 9 studies looking at 135 IPF patients mechanically ventilated in the ICU setting identified an aggregated mortality of 87% and long-term mortality (within 3 months of hospital discharge) of 94% [79]. As such, the use of mechanical ventilation in the acutely deteriorated IPF patient is generally discouraged [8]. Special considerations where mechanical ventilation might be more seriously considered include ventilating as a bridge to transplant.

Lung transplantation is the only "curative therapy" for IPF; it is the second most common condition for which transplantation is performed and has demonstrated survival benefit when compared to best medical therapy [80]. With wait times for lung transplantation equivalent to median survival times in IPF, patients with a confirmed UIP pattern on HRCT or lung biopsy should be referred for transplant assessment early in their disease course [81]. The guidelines for transplantation include a diffusion capacity <39% of predicted, ≥10% decline in FVC during 6 months of follow up, decrease in pulse oximetry to <88% during a 6-MWT or honeycombing on HRCT (fibrosis score of > 2) [82]. For unclear reasons, lung transplantation in IPF is associated with worse survival when compared to other lung diseases [80]. There is an ongoing debate regarding single versus double lung transplant in these patients, weighing the availability of transplantable lungs with short term and long term mortality [81,83].

Participation in local patient support groups should be encouraged in all patients with IPF, allowing for the ongoing provision of education and a sense of community [65]. Along with patients, support groups also offer excellent support to families by addressing their unmet psychosocial needs [84].

Comorbid conditions in IPF

The recognition of comorbid conditions associated with IPF has become increasingly common as the medical community continues to looks for effective therapies against this yet incurable disease [10]. GERD, often associated with respiratory disorders, is known to be highly prevalent in IPF with recent studies suggesting its presence in greater than 87% of IPF patients [85,86]. Its presentation in IPF is frequently atypical, with less than 50% of patients admitting to classic symptoms of heartburn and regurgitation. GERD has long been implicated as a possible underlying mechanism in the pathogenesis of IPF – it is suggested that GERD-related micro aspiration leads to slowly progressive lung injury and fibrosis [87]. Small studies looking at the treatment of GERD in IPF, either through proton pump inhibitor (PPI) therapy or Nissen fundoplication, have demonstrated stabilization of lung function and oxygen requirements as well as a decrease in IPF exacerbations [88,89]. Furthermore, a recent retrospective study by Lee et al demonstrated a possible survival benefit when medically treating GERD in IPF patients [90]. It is still unclear whether GERD is an initiating event or secondary phenomenon when it comes to IPF. Lung fibrosis can lead to increased diaphragmatic pressures, changes in lung mechanics, and exposure to certain medications all of which can increase the propensity towards

gastroesophageal reflux [85]. Nevertheless, current guidelines suggest that asymptomatic GERD should be treated in the majority of IPF patients [8].

Pulmonary arterial hypertension (PAH), defined as having a mean pulmonary arterial pressure greater than 25mmHg on right heart catheterization, has become increasingly recognized as a possible contributor to the manifestations and clinical course of IPF [8]. PAH is common in IPF, with a prevalence ranging anywhere from 32 to 85% depending on the timing of diagnosis and definition of clinically significant manifestations, and has been shown to have a negative effect on outcomes and prognosis in these patients [91]. Along with progressive dyspnea, patients often experience pedal edema, chest pain, as well as symptoms of dizziness and exertional syncope. In terms of treating the underlying PAH with PAH-specific therapies, some early studies have shown mild improvements in pulmonary hemodynamics and 6MWD suggesting possible benefits in small minority of IPF patients. However, current guidelines advise against treating the majority of IPF patients with any PAH-specific therapies [8,92-95].

Other comorbid conditions, including emphysema and OSA, continue to be increasingly recognized in IPF and research is ongoing as to the clinical implications of their investigation and treatment [96]. Finally, depression and anxiety are common in the IPF population due to ongoing chronic dyspnea, fatigue and de conditioning [65]. As such, appropriate screening for mood disturbances can be considered in all IPF patients as appropriate.

Multidisciplinary Model f Care

There has been increasing recognition that, in the absence of curative therapy, a more comprehensive approach should be applied when caring for the IPF patient [97]. Lee et al. have proposed three pillars of care in the management of IPF: disease-centered management (including pharmacologic and non-pharmacologic therapies, management of comorbidities and complications, and preventive care), symptom-centered management and education and self-management (including advanced care planning) [95].

It has been suggested that a multidisciplinary model specializing in IPF can be used to effectively deliver this form of comprehensive care [97]. This has already been initiated in the US through the Pulmonary Fibrosis Foundation Care Center Network (http://www.pulmonary fibrosis.org/CCN). In addition to the respiratory physicians and nurses, such a multidisciplinary model could include social workers, respiratory, physical, and occupational therapists as well as other medical and surgical specialists in order to provide comprehensive assessments and treatments in a single setting [97]. Evidence suggests that multidisciplinary clinics dedicated to ILD and specifically, IPF may confer improved outcomes including a possible survival advantage [98].

Palliative Care in IPF

Palliative care essentially aims to improve quality of life for patients and caregivers faced with life-threatening illness through the prevention, identification, assessment and treatment of physical, psychological, emotional and spiritual distress [99]. A recent ATS policy statement focusing on palliative care in respiratory diseases and critical illnesses proposes an individualized integrated approach. Palliative care should be initiated as soon as a patient becomes symptomatic and in conjunction with disease-specific therapy, with integration into all aspects of patient care in order to maintain an emphasis on good quality of life. Each approach needs to be individualized to meet the changing needs and preferences of the patient and caregivers, continually adjusting the balance between curative/restorative and palliative care. For example, patients with a chronic and debilitating cough can be taught proper coughing and airway clearance techniques. For dyspnea, pacing and energy conservation techniques will be unique to each patient depending on their circumstances and opioid dose and route of administration will depend on the severity of dyspnea with day-to-day activities. Breathing retraining will need to be tailored towards the patient's dysfunctional pattern; rapid breathing versus breath holding.

While guidelines recommend that palliative care in IPF should be started early as an adjunct to disease-specific therapy, IPF patients and their caregivers still often experience unmet end-of-life planning needs, poor coordination of care and dissatisfaction with communication [8,84,99]. Immediate and long term goals of care, including advanced directives, should be reviewed regularly due to the progressive and unpredictable nature of IPF. An effort must be made to better appreciate both the physical and psychological burden of disease on the patient and caregivers, taking advantage of patient "illness narratives" to allow for a more complete understanding of a specific clinical problem [84]. An interdisciplinary approach is often required, made up of physicians, nurses, social workers, as well as spiritual advisors and counsellors depending on the circumstances [99]. As such, referral to palliative care specialist should always be considered, especially if physicians are not well versed with the use of medications for palliation or do not have the necessary clinic or community support infrastructure.

Symptom management is a fundamental part of palliative care and continues to be a challenge in IPF patients. Dyspnea, a near-universal complaint in the IPF population, directly correlates with health status in IPF patients with higher dyspnea scores predictive of shortened survival, poor QOL and increased utilization of acute care resources [99-101]. A combination of patient education, behavior modification, appropriate oxygen titration and use of opioids has shown to be successful in managing dyspnea [102]. While concerns always linger, the use of low dose opioids and benzodiazepines in dyspnea management is known tobe both safe and efficacious [103]. Chronic cough, another common debilitating complaint, may be effectively treated with opiates with recent studies suggesting the possible role of thalidomide [8,65]. Corticosteroids can be considered in refractory cases [104]. Fatigue is another dominant symptom in the IPF population and may be effectively addressed through early pulmonary rehabilitation and oxygen therapy if the patient is hypoxemic [65]. Finally, the possibility for underlying depression or anxiety as described above may be managed through appropriate psychosocial supports and pharmacotherapy as needed. All these measures can be employed as an adjunct to routine medical care [99]. Along with improving quality of life, the institution of appropriate palliative care may even improve survival as was demonstrated in a study looking at patients with metastatic non-small cell lung cancer [105].

Conclusion

In summary, fibrotic lung diseases including idiopathic pulmonary fibrosis present a major therapeutic challenge to clinicians. Given the lack of clinically available biomarkers for diagnosis, a high index of suspicion must be maintained in patients presenting with chronic, progressive shortness of breath. All patients do not require surgical lung biopsy for diagnosis and HRCT may be sufficient. Patients should be referred to an ILD center for expert opinion. Currently, Pirfenidone is the only pharmacologic treatment with proven benefit. Further care of patients with IPF should focus on improvement of quality of life through symptom relief, disease specific education, support and early discussion of palliative care.

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