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Review Article

Idiopathic Pulmonary Fibrosis Management Review

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Abstract

Idiopathic Pulmonary Fibrosis (IPF) is a progressive and often fatal disease that usually manifests with dyspnea, cough and/or fatigue. The diagnosis of IPF requires the exclusion of known causes of pulmonary fibrosis. The diagnosis and management of patients with IPF ideally should be done in specialized interstitial lung disease centers in order to provide patients with the best possible care; this includes pharmacological and non-pharmacological therapeutic options to slow down the progression of the disease, to manage symptoms and to improve the quality of life of patients with IPF. The main treatment options include antifibrotic drugs, opioids, supplementary oxygen, pulmonary rehabilitation and lung transplantation. This review summarizes the guidelines and scientific evidence that support the various therapeutic options currently used in the management of patients with IPF. We also summarize the evidence on the therapeutic options for pulmonary hypertension and acute exacerbations of IPF, two complications associated with increased risk of death in IPF patients.

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is one of the most common Interstitial Lung Diseases (ILDs) and the most common idiopathic interstitial pneumonia. It is a chronic, progressive disease characterized by scarring of the lung and progressive loss of function [1,2]. Occurs primarily in older adults, it is limited to the lungs and, is associated with a radiological and/or histopathologic pattern of Usual Interstitial Pneumonia (UIP) [1]. A UIP pattern on High-Resolution Computed Tomography (HRCT) of the chest typically presents with reticulations (reticular pattern), traction bronchiectasis and subpleural cystic spaces (honeycombing) with a basal and peripheral predominance in the lungs [3]. The UIP pattern however, is not unique to IPF, and can be found in other ILDs, including those associated with connective tissue diseases, drugs, inhalation of organic dusts -called Hypersensitivity Pneumonitis (HP)-, or inhalation of asbestos -called asbestosis. A UIP pattern has been also associated to a rare congenital disorder called Hermansky-Pudlak syndrome.

Thus, the diagnosis of IPF requires the exclusion of all above mentioned causes of a histological or radiological pattern of UIP [1]. Most cases of IPF occur in isolation, but there is a familial form of pulmonary fibrosis in which several members of a family are affected and genetic abnormalities have been reported [4,5].

IPF is often a fatal disease, but the progression of IPF is highly unpredictable, and could have periods of relative stability that may be interrupted by episodes of accelerated decline, resulting in respiratory failure and death [6,7]. The incidence of IPF, is estimated at 3-9 cases per 100,000 per year in Europe and North America, and is increasing worldwide [8]. The trigger of the fibrotic process in IPF is still not fully known, and several factors have been associated with the development of IPF, including cigarette smoking, environmental pollutants, microbial agents, chronic microaspiration secondary to gastroesophageal reflux, and genetic abnormalities [9,10]. The goals of treatment in IPF are essentially to stop disease progression, reduce symptoms, prevent acute exacerbations and prolong survival [11,12].

Although the year 2000 guideline on diagnosis and management of IPF was based on the consensus of a group of international experts [13], the 2011 guideline represented a joint effort of several international respiratory societies: the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT). These guidelines reviewed all available evidence, clarified the definition of IPF, provided diagnostic criteria and provided recommendations for treatment [1]. Since the publication of the 2011 IPF guidelines, new evidence has become available for the treatment of IPF, which have been included in the 2015 ATS/ERS/JRS/ALAT guidelines on treatment of IPF as shown in table 1 [14].

The objective of this article is to review the existing evidence for the pharmacological and non-pharmacological therapeutic options currently available for the management of IPF, and its associated complications: Pulmonary hypertension and acute IPF exacerbations.

Table 1: Comparison of Recommendations in the 2015 and 2011 Idiopathic Pulmonary Fibrosis Guidelines.

Agent	2015 Guideline	2011 Guideline
New and revised recommendations		
Anticoagulation (warfarin)	Strong recommendation against use*	Conditional recommendation against use‡
Combination prednisone + azathioprine + *N*-acetylcysteine	Strong recommendation against use†	Conditional recommendation against use†
Selective endothelin receptor antagonist (ambarisentan)	Strong recommendation against use†	Not addressed
Imatinib, a tyrosine kinase inhibitor with one target	Strong recommendation against use*	Not addressed
Nintedanib, a tyrosine kinase inhibitor with multiple targets	Conditional recommendation for use*	Not addressed
Pirfenidone	Conditional recommendation for use*	Conditional recommendation against use†
Dual endothelin receptor antagonists (macitentan, bosentan)	Conditional recommendation against use†	Strong recommendation against use*
Phosphodiesterase-5 inhibitor (Sildenafil)	Conditional recommendation against use*	Not addressed
Unchanged recommendations		
Antiacid therapy	Conditional recommendation for use‡	Conditional recommendation for use‡
N-acetylcysteine monotherapy	Conditional recommendation against use†	Conditional recommendation against use†
Antipulmonary hypertension therapy for idiopathic pulmonary fibrosis-associated pulmonary hypertension	Reassessment of the previous recommendation was deferred	Conditional recommendation against use‡
Lung transplantation: single *vs*. bilateral lung transplantation	Formulation of a recommendation for single *vs*. bilateral lung transplantation was deferred	Not addressed

*Moderate confidence in effect estimates.
†Low confidence in effect estimates.
‡Very low confidence in effect estimates.

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Pharmacological Therapies

In 2012 a landmark randomized, double blind, placebo controlled trial (PANTHER-IPF) [15], changed radically the way we treat IPF. Traditionally, pulmonary fibrosis in IPF was thought to be the result of chronic inflammation triggered by an idiopathic autoimmune process. As such, corticosteroids and immunosuppressants were used as the main treatment of IPF, based on limited evidence.

In the PANTHER-IPF study patients were assigned to receive prednisone, N-Acetylcysteine (NAC) and azathioprine (combination therapy), NAC alone, or placebo. A pre-specified interim analysis of efficacy and safety planned at approximately 50% of data collection showed that the combination therapy, as compared with placebo, was associated with a significant increase in all-cause mortality, all-cause hospitalizations, and treatment-related severe adverse events.

Based on the results of PANTHER-IPF study and other negative clinical trials with immunosuppressants/anti-inflammatory drugs [16-18], as well as on evidence stemming from the basic sciences, the focus of treatment has now largely changed from anti-inflammatory drugs to anti-fibrotic drugs. Currently there are two anti-fibrotic drugs used in the clinical setting for the treatment of IPF: Pirfenidone and Nintedanib.

Before the studies on anti-fibrotic therapies, many other drugs had previously been assessed with the aim of reducing the progression of IPF, including Colchicine [19], Cyclosporine A [17,18], Cyclophosphamide [16], Interferon-γ 1b [20], Bosentan [21] and Etanercept [22]. All of the trials assessing these drugs were either negative or showed worse outcomes in the treatment than the control groups.

Antacids and N-Acetylcysteine are used in some centers with the aim of reducing IPF progression, but the evidence supporting their use is limited or controversial, as presented below.

Opioids are used for the management of the two main disabling or bothersome symptoms of IPF: dyspnea and cough. A common clinical observation is that breathlessness is acutely amplified during paroxysms of coughing and associated worsening hypoxemia in patients with IPF. Breathlessness has been shown to correlate with patient's Quality of Life (QoL) and survival. As the disease progresses, breathlessness can cause patients to become functionally impaired, which severely limits their activities [23].

We provide a summary of the evidence currently available on the therapeutic options mentioned above, which are used by clinicians in the management of patients with IPF.

Anti-fibrotic drugs

Pirfenidone: Pirfenidone is an oral medication that has anti-inflammatory and anti-fibrotic effects. In animal models it results in dose-related reductions in fibrosis through modulation of cytokines and growth factors, including transforming growth factor-β and tumour necrosis factor-α [24,25]. The 2015 guideline on IPF treatment provide a conditional recommendation for the use of pirfenidone in patients with IPF [14].The efficacy of pirfenidone in patients with IPF has been evaluated in four randomized, double-blind, placebo-controlled, phase 3 clinical trials, one conducted in Japan [26] and three multinational [27,28].

The Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes,

(CAPACITY) consisted of two phase III studies (006/Capacity 1 and 004/Capacity 2) and enrolled IPF patients aged 40-80 years with mild-to-moderate functional impairment, defined as Forced Vital Capacity (FVC) ≥50% predicted and Carbon Monoxide Diffusing Capacity (D_{LCO}) ≥35% predicted). Study 004, included 435 patients that were assigned to either pirfenidone 2,403 mg/day, pirfenidone 1,197 mg/day, or placebo; whereas study 006, enrolled 344 patients that were assigned to pirfenidone 2,403 mg/day or placebo. The primary endpoint of change in percent predicted FVC from baseline to week 72 was met in study 004. Study 006 did not show a benefit in the same primary outcome during the same period.

The CAPACITY trials provided also mixed results for the secondary endpoints: Pirfenidone significantly reduced the proportion of patients with an FVC decline ≥10% compared with placebo in study 004, but not in study 006. Conversely, pirfenidone significantly reduced the decline in 6-Minute Walk Test (6MWT) distance compared with placebo in study 006, but not in study 004.

Based on the CAPACITY trials pirfenidone was approved in Japan in 2008 and in Europe in 2011. The US Food and Drug Administration (FDA) requested an additional phase 3 study to prove its efficacy. The "Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis" (ASCEND) trial was then conducted. In this trial, 555 patients with definite UIP pattern on High Resolution Chest Computed Tomography (HRCT) or histology were randomized to pirfenidone 2,403 mg/day (n=278) or placebo (n=277) [27]. The study met its primary outcome of significant reduction in the decline in the percentage of predicted FVC from baseline to week 52. In addition, pirfenidone reduced by 47.9% the proportion of patients with a decline of ≥10% in percentage predicted FVC or who died; and increased the proportion of patients who had no decline in the percentage predicted FVC compared with placebo.

Additionally, pirfenidone reduced the decline of the 6MWT distance (p=0.036). A prespecified pooled analysis including data from ASCEND and the two CAPACITY trials showed that at 52 weeks, pirfenidone significantly reduced both all-cause mortality compared with placebo (3.5% vs. 6.7%; hazard ratio 0.52; p=0.01) and IPF-related mortality (1.1% vs. 3.5%; hazard ratio 0.32; p=0.006).

The 2015 guidelines on IPF treatment gave a conditional recommendation to pirfenidone, and put a high value on the potential benefit of the drug on patient-important outcomes such as disease progression as measured by rate of FVC decline and mortality and a lower value on potentially significant adverse effects and the cost of treatment. It is important to mention that, shared decision making with the patient is important; also, that patients must be educated on all potential adverse effects, because some patients may not be willing to tolerate adverse effects, especially if they are asymptomatic, as it frequently occurs in the initial phase of the disease.

Commonly reported side effects included photosensitivity, skin rash, nausea, vomiting, dyspepsia, dizziness, anorexia, fatigue and insomnia. Less than 5% of patients may develop drug induced elevation of liver enzymes and monitoring of liver function is recommended on monthly bases in patients on pirfenidone. All these side effects are reversible upon discontinuation of therapy.

Nintedanib: Nintedanib is a multiple tyrosine kinase inhibitor originally developed as an anticancer drug. It targets receptors of vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor, all thought to be involved in the pathogenesis of IPF [29]. An earlier Phase IIb study (TOMORROW) of 432 patients with mild to moderate IPF (FVC >50%) reported that treatment with 150 mg of nintedanib twice daily was effective in reducing FVC decline and preventing acute exacerbations, while preserving quality of life [30]. Following these results, investigators conducted two replicate phase 3 studies (INPULSIS-1 and INPULSIS-2) that randomized 1,061 IPF patients to receive either nintedanib (150 mg twice daily) or placebo [31]. Inclusion criteria included age ≥40 years, diagnosis of IPF made within the previous 5 years, FVC of ≥50% of predicted value, D_{LCO} of 30-79% of predicted value and HRCT performed within the previous 12 months. Notably, in the absence of a confirmatory surgical lung biopsy, the INPULSIS trials allowed the enrolment of patients with a radiological pattern of possible UIP on HRCT [32]. Both trials met their primary endpoint, with a statistically significant lower rate of decline in FVC in the nintedanib group compared to placebo in both INPULSIS 1 and INPULSIS 2 (~110 ml/year lower decline; p<0.001).

Nintedanib was also associated with a significant delay in time to first exacerbation in INPULSIS-2 but not in INPULSIS-1. There was a non-significant trend towards reduced mortality in patients treated with nintedanib compared to those in the placebo group (5.5% vs. 7.8 % one year mortality respectively; hazard ratio 0.70; p=0.14).

The most common drug-related side effects of nintedanib were diarrhea, nausea, and vomiting. Among nintedanib and placebo recipients, diarrhea was reported by 61.5% and 18.6% of patients in INPULSIS-1 and 63.2% and 18.3% of patients in INPULSIS-2, respectively. Most of the diarrhea cases were mild-to-moderate. Again, patients must be informed of the side effects of this treatment.

The 2015 guideline gave a conditional recommendation to nintedanib for patients with IPF.

Given the largest trials on the currently used anti-fibrotic drugs -pirfenidone and nintedanib- were published in 2014; their long term efficacy and the optimal duration of anti-fibrotic therapy in patients with IPF are still unknown.

N-acetylcysteine: N-acetylcysteine, a precursor of the endogenous antioxidant glutathione, has been used in IPF based on the assumption that an oxidant-antioxidant imbalance plays a role in the pathogenesis of the disease [33]. N-acetylcysteine is a precursor of the antioxidant molecule glutathione and normalizes its levels when they have been reduced by a continuous oxidizing action in the respiratory system. In a small pilot study, Tomioka and colleagues randomized 30 patients with IPF to either aerosolized NAC or bromhexine hydrochloride for 12 months [34]. They observed that NAC treatment significantly reduced the extent of ground glass opacities on HRCT, as well as the serum KL-6 levels, a serological marker for ILD. No differences in physiologic measurements or walk distance were found. The largest clinical trial assessing the effect of NAC was the PANTHER-IPF, a placebo-controlled, randomized, three-arm trial [15]. Patients with IPF were assigned to prednisone (A synthetic anti-inflammatory glucocorticoid derived from cortisone that inhibits many pro-inflammatory molecules such as cytokines, chemokines, arachidonic acid metabolites, and adhesion molecules), azathioprine (a long-lived prodrug of 6-mercaptopurine, that suppresses the proliferation of T and B lymphocytes), and NAC (combination therapy), NAC alone,

or placebo. A prespecified interim analysis of efficacy and safety showed that the combination therapy, as compared with placebo, was associated with a significant increase in all-cause mortality, all-cause hospitalizations, and treatment-related severe adverse events. Therefore, the three-drug regimen arm was stopped and PANTHER was continued as a double-blind, two-group study (NAC vs. placebo). Results of this study showed no significant difference in FVC change with NAC monotherapy compared to placebo. Also, there were no differences seen in the rates of death or acute exacerbations. A more recent phase 2 randomized placebo-controlled trial (PANORAMA study) concluded that the addition of oral NAC to pirfenidone does not substantially alter the tolerability profile of pirfenidone, but that it was unlikely to be beneficial in patients with IPF [35]. Of note, in the PANTHER-IPF study, patients treated with NAC, carrying the *TOLLIP* TT genotype, had a significant reduction in the composite endpoint of death, transplantation, hospitalization or decline of ≥10% in FVC; whereas those with the *TOLLIP* CC genotype were more susceptible to treatment-related harm [36]. Future Randomized Controlled Trials (RCTs) of NAC stratifying by *TOLLIP* genotypes would be needed to clarify the role of NAC in patients with IPF.

The 2015 guideline suggest that clinicians not use NAC monotherapy in patients with IPF (conditional recommendation, low confidence in estimates of effect). Because no evidence of significant harm was found, the guidelines committee made no suggestion related to discontinuation in patients already receiving NAC monotherapy.

Antacid therapy: It is suggested that the increased negative intrathoracic pressure associated with diseases that reduce lung compliance -like IPF-, may predispose to gastro-esophageal reflux [37]. In a prospective study of 17 consecutive IPF patients, using ambulatory pH monitoring, Tobin and colleagues compared the prevalence of Gastro-Esophageal Acid Reflux (GERD) in patients with IPF and patients with other ILDs (control group). They documented that 94% of patients with IPF had GERD compared to 50% in the control group [38]. Interestingly, 75% of patients with IPF and GERD did not have typical esophageal reflux symptoms such as heartburn or regurgitation.

A retrospective study of 204 IPF patients found that antacid treatment was associated with reduced fibrosis on chest imaging studies and longer survival time [39]. In a more recent analysis of patients assigned to the placebo arm in three RCTs of different pharmacological interventions (n=242), patients taking antacid treatment at baseline either Proton-Pump Inhibitors (PPIs) or Histamine 2 receptor blockers had a smaller decrease in FVC at 30 weeks compared with those not taking antacid treatment (p=0.05). This study however, showed no benefit of antacid therapy on all-cause mortality or all-cause hospitalization [40].

Based on the available evidence, the 2015 IPF guidelines gave a conditional recommendation for use of antacid therapy in patients with IPF (conditional recommendation, very low confidence in estimates of effect). The safety of PPI therapy was also considered in this recommendation, as well as the potential drug interaction of PPIs with other IPF medications and it was recognized that the long-term effects of GERD treatment in patients with IPF are unknown.

Opioids: Morphine has been used for many years to reduce dyspnea in patients at end of life. It has become increasingly used in the setting of IPF to manage cough and dyspnea, the two most common and disabling symptoms in IPF patients in addition to fatigue. Dyspnea impacts quality of life and life expectancy in patients with IPF, regardless of the pulmonary function status [41,42]. Morphine, one of the most commonly prescribed opioids to relieve pain, can be used to reduce the perception of breathlessness. It may act locally on opiate receptors in the lungs or centrally to reduce afferent breathlessness sensation [43]. Neuroimaging studies have demonstrated that dyspnea and pain activate common centers in the brain.

There are very little data from randomized controlled trials on the effectiveness of opioids in the management of breathlessness in IPF.

A recent review by Kohberg and colleagues of the use of morphine in the management of dyspnea in respiratory conditions, found only 14 small controlled trials totaling 311 patients looking at opiates to reduce dyspnea. The quality of the studies was highly variable, using different doses of medications and most studies were performed in patients with COPD. Half of the trials included in the review used systemic morphine and the other half inhaled morphine. Four of the fourteen studies found a clear benefit. Two found improved exercise tolerance. Another found benefit when combined with promethazine. The remaining studies found no effect, including all the studies that used inhaled morphine [43]. The benefit of morphine for the treatment of dyspnea in IPF remains unclear as studies to date are mostly not randomized, have small sample sizes (<100 patients), and include patients with other forms of lung disease (e.g., chronic obstructive pulmonary disease); therefore, this intervention needs to be further explored with large-scale studies in patients with IPF [23].

However, until more evidence is available, it is reasonable to offer a trial of opioids in patients with significant dyspnea (British medical research council dyspnea score ≥4/5), with close monitoring of potential side effects of opioids: constipation, nausea, vomit, confusion, decreased level of consciousness, hypotension and respiratory depression. Medications for nausea and constipation are usually prescribed concomitantly with opioids, and adjusted as required to manage these common side effects.

Non-Pharmacological Therapy

Lung transplant

For patients with IPF who fail medical treatment with antifibrotic drugs or those with advanced disease, lung transplant is the only therapeutic option that can be offered, but only a subgroup of patients with IPF qualify for lung transplant, as age >70 years, cancer, significant comorbidities or obesity (BMI>35 Kg/m^2) are contraindications for lung transplantation [44]. Nonetheless, for IPF patients who are appropriate candidates, lung transplant is the only "curative" treatment currently available and early referral is recommended, given the unpredictable course of the disease.

Over 36,000 patients received lung transplantation from 2004-2015, of whom 9,655 had IPF [45]. Double and single lung transplant can be performed, but the survival is not significantly different between the two options [46]. The current five year survival after lung transplantation for patients with IPF is ~50% [46]. Patients with single lung transplants have a higher incidence of cancer while those with double lung transplants have a higher incidence of graft failure [47].

Cell-based transplantation

Currently the only "curative" treatment available for IPF is lung transplantation, but many patients are not candidates for it given their age, weight or comorbidities. In addition, patients who receive a lung transplant must be on immunosuppressants for the rest of their life to prevent rejection, and these medications have many potential side effects, especially the risk of life threatening infections and malignancies. Because of this, alternative curative treatments are being investigated and "transplantation" of different types of cells with the ability to proliferate and/or differentiate into alveolar cells -such as stem cells and alveolar type II cells [48,49], that intend to repair damaged alveolar tissue are still in the experimental phase, but are promising therapeutic options in the future.

Oxygen therapy

Benefits: In IPF, hypoxia causes breathlessness through (1) increased respiratory rate to compensate for the hypoxia and (2) increased drive to breath (to induce a respiratory alkalosis) to counteract the exercise induced metabolic acidosis from the peripheral hypoxia. Oxygen therapy at rest and during exercise has been demonstrated to improve pulmonary hemodynamics and likely improve exercise capacity and prognosis in patients with IPF [13,23].

Supplemental O_2 would be expected to reduce central neural drive (and associated breathlessness) primarily by reducing breathing frequency and improved O_2 delivery to the peripheral muscles during exercise, which delays metabolic acidosis and the rise of ventilation [50].

The ATS 2011 IPF guidelines give a strong recommendation for long term oxygen therapy in patients with resting hypoxia. There actually is surprising little evidence supporting this recommendation in patients with IPF; the strong recommendation comes from expert opinion, pathophysiological knowledge, and extrapolation from studies of supplementary oxygen in patients with Chronic Obstructive Pulmonary Disease (COPD).

Two randomized controlled trials in the 1980's demonstrated a clear survival benefit with long-term oxygen therapy in patients with COPD and resting hypoxemia (NOTT, Report of Medical Research council working Party) [51]. The NOTT trial defined hypoxemia as PaO_2 ≤55 mmHg on room air or ≤59 mmHg for patients with cor pulmonale.

There is no evidence however that oxygen therapy improves survival or exercise tolerance in patients with exertional hypoxemia but normal resting oxygen levels. A randomized control trial on IPF patients by Nishiyma, et al in 2013 supported this conclusion [52]. A meta-analysis by Cochrane reported that 1 out of 3 studies showed improvement in the 6MWT distance with oxygen – the other two studies did not. This is consistent with the COPD literature. A recent study in 2016 demonstrated that supplementary oxygen did not prevent hospitalizations or death in patients with stable COPD and exercise induced desaturations [53].

A retrospective cohort study demonstrated that there was no survival benefit with oxygen therapy in IPF after adjustment for comorbidities, age, gender, and pulmonary function; however, this study was limited by its retrospective design [54].

Nocturnal hypoxemia is commonly found in IPF and it may be a predictor of mortality [55]. To date however, there are no trials that demonstrate oxygen administration in these patients improves survival or reduces pulmonary hypertension.

In summary, there is limited evidence to support the benefit of oxygen supplementation in IPF patients with resting hypoxemia. Nonetheless, given plausible mechanisms, and the beneficial survival effect previously demonstrated in COPD patients with resting hypoxemia, current guidelines recommend that IPF patients with resting hypoxemia receive oxygen supplementation. On the other hand, patients with only exertional hypoxemia or nocturnal hypoxemia have no demonstrated benefit from oxygen use.

Indication: Based on the evidence derived from the NOTT study, supplementary Oxygen therapy is indicated –and funded in some countries- in IPF patients with severe resting hypoxia, defined as PaO_2 ≤55 mmHg on Arterial Blood Gas (ABG) on room air; also in patients with PaO2 >55 ≤59 mmHg and cor pulmonale, polycythemia or pulmonary hypertension. Patients with exertional hypoxemia (≤55 mmHg or oxygen saturation ≤88%) may qualify for oxygen funding as well in some countries.

Delivery system: There are different types of oxygen reservoirs, which can be obtained from commercial oxygen providers as liquid or gas oxygen tanks (stationary or portable), and as oxygen concentrators, which "extract" the oxygen from the ambient air to deliver almost 100% of oxygen to patients, at a predetermined flow. From these oxygen reservoir systems, oxygen is delivered to patients through either masks or nasal cannulas; the later remain the most common oxygen delivery system at home.

The exact concentration of oxygen delivered to the lungs by a selected oxygen flow through nasal cannulas is variable and depends on factors such as degree of "mouth breathing" (the fraction of air inspired through mouth compared to the nose) and minute ventilation. For this reason, it is essential that patients have their oxygen saturation (SaO_2) monitored with a pulse oximeter and their oxygen flow adjusted to achieve the desired SaO_2. Oxygen flow should be prescribed as required to maintain oxygen saturations (SaO_2) of ≥92% at rest and ≥88% during exertion. Required oxygen flows to achieve these SaO_2 typically range between 1 to 5 l/min at rest and flows up to 10-15 l/min during exertion may be required in advanced IPF cases.

Because oxygen tanks have limited capacity, oxygen conservation systems -such as reservoir cannulas and demand O2 pulse devices- may be implemented; this is especially useful if required oxygen flows exceed 6L/min, which can deplete oxygen tanks too quickly.

Reservoir cannulas

Reservoir cannulas are devices that contain a space to store oxygen during expiration. In this way, oxygen boluses can be delivered during inspiration which results in a higher effective inspired fraction of oxygen. Such systems include the "moustache" and "pendant" designs.

Demand oxygen pulse device

In these devices, a sensor detects when inspiration has started and a logic board delivers a short burst of 100% oxygen to the nose. A

major limitation is the variability in oxygen concentration delivery and it is a possible for patients to be hypoxemic despite this setup, depending on their breathing pattern; patients received less oxygen than expected if they breathe through their mouth.

Transtracheal oxygen

Transtracheal Oxygen is the delivery of continuous oxygen through a small catheter inserted directly into the trachea. The technique is limited by its invasive nature and need for expertise in the catheter insertion, and management of possible complications such as bleeding and infection.

Pulmonary Rehabilitation

Pulmonary rehabilitation is a program that combines exercise training with education. It typically involves 5-12 weeks of outpatient program followed by home-based exercises. Patients receive aerobic conditioning; strength and flexibility training; education; nutritional counselling, and psychosocial support.

Pulmonary rehabilitation improves exercise tolerance by increasing anaerobic thresholds and reducing lactic acidosis. As a result, patients can have less dyspnea for the same amount of exertion and overall improved quality of life.

Two RCT's have looked specifically at pulmonary rehabilitation in IPF. A small (n=28) randomized controlled trial showed 10 week pulmonary rehabilitation improved 6MWT distance and total health-related quality of life score [56]. Another study (n=57) demonstrated that an 8 week rehabilitation program could improve the British medical research council dyspnea score by 0.7 points but these results –of doubtful clinical significance-, were not sustained at 6 months [57]. However, a meta-analysis confirmed the benefit of pulmonary rehabilitation on 6MWT distance in patients with ILDs. Pulmonary rehabilitation resulted in a 35.6 m improvement in the distance walked and in a statistically –but not clinically- significant improvement in dyspnea and quality of life [58]. Available data were insufficient to allow examination of the impact of disease severity or exercise training modality in this meta-analysis.

In addition to these controlled trials, there have been several uncontrolled trials that have reported improved quality of life and breathlessness with pulmonary rehabilitation.

In summary, there are only a few small studies looking at the benefits of pulmonary rehabilitation in IPF. There are even fewer studies assessing a sustained, long term benefit of rehabilitation. As a result, the ATS/ERS/JTS/ALAT guidelines provided a weak recommendation for pulmonary rehabilitation in IPF patients [1].

Vaccination

Because of their reduced pulmonary reserve, patients with chronic pulmonary disease are more likely to develop respiratory failure if they acquired a lower respiratory tract infection, and this is the rationale to recommend vaccination against respiratory infections. Therefore, all patients with IPF should receive yearly the influenza vaccine and also be vaccinated with the pneumococcal vaccines. There are currently two pneumococcal vaccines available: the Pneumococcal Polysaccharide Vaccine 23 (PPSV23) and Pneumococcal Conjugate Vaccine 13 (PCV13). The PPSV23 was developed in the 1970's and protects against 23 strains of pneumoccocus. The PCV13 has the advantage of being effective also in children and in preventing mucosal colonization. In patients with underlying lung disease including IPF, the PPSV23 is recommended with a repeat booster vaccination after 5 years. Both pneumococcal vaccines are recommended in all adults >65 years old.

Pulmonary Hypertension in IPF

Pulmonary Hypertension (PH) is frequently seen in patients with IPF and is attributed to hypoxic vasoconstriction and capillary destruction/obliteration due to the fibrosis affecting the interstitium, where the blood vessels are located [59]. Pulmonary hypertension is associated with increased risk of mortality in IPF [1]. The 2011 ATS/ERS/JRS/ALAT guideline on IPF provided a conditional recommendation against therapy for pulmonary hypertension, with low confidence in effect estimates. That is primarily due to lack of evidence of benefit of available treatments for pulmonary hypertension in patients with chronic pulmonary conditions. The authors looked at RCTs, which examined the treatment of patients with IPF with ambrisentan [60] and sildenafil [61,62]. ARTEMIS-IPF study is a randomized, placebo-controlled trial to evaluate the safety and effectiveness of ambrisentan in patients with and IPF and PH. It concluded that ambrisentan was not effective in treating PH in patient with IPF and that it might be associated with an increased risk for disease progression and respiratory hospitalizations.

Riociguat, an oral guanylate cyclase stimulator, was assessed in an open-label, uncontrolled pilot trial in patients with ILD -including some with IPF. The study found that at 12 weeks, riociguat increased cardiac output and decreased Pulmonary Vascular Resistance (PVR), but did not change the Mean Pulmonary Arterial Pressure (mPAP) [63]. There was also a borderline improvement in exercise tolerance (26 m in the 6MWT distance) despite a slight decline in arterial oxygen saturation (mean SaO_2 declined 1%); however, the medication was well tolerated by most patients [63]. But due to small number of patients (n=22) further randomized controlled clinical trials are required.

In the STEP-IPF trial, investigators examined the effect of sildenafil treatment on exercise performance (6MWD) in patients with IPF and carbon monoxide diffusing capacity <35%. The study did not show a benefit of sildenafil on the primary outcome. However, it showed a clinically and statistically significant improvement in dyspnea and quality of life, as measured by the St. George's Respiratory Questionnaire (SGRQ) [61]. In a post-hoc analysis, sildenafil showed an improvement in 6MWD (99.3 m; p=0.01) and in quality of life (SGRQ 14.8 points; p=0.02) compared to placebo in patients with echocardiogram-documented right ventricular systolic dysfunction; and improvement in quality of life in patients with right ventricular hypertrophy [62]. Even though the 2015 ATS/ERS/JRS/ALAT guideline committee provided no specific recommendation for the treatment of pulmonary hypertension in patients with IPF, there is an increasing supportive role for use of pulmonary arterial hypertension-approved drugs on a compassionate treatment basis for patients with IPF and severe pulmonary hypertension (mPAP >35 mmHg), or with mean PAP ≥25 mm and low cardiac index (<2.0 l/min/m^2); this requires close monitoring of gas exchange (PaO_2, $PaCO_2$), and should be done only until additional information from randomized controlled trials is available [64,65].

IPF Exacerbations

Acute respiratory worsening in IPF could be due to pneumonia, pulmonary embolism, pneumothorax and heart failure. When a cause cannot be identified, the term Acute Exacerbation of IPF (AE-IPF) is used [1]. The annual incidence of AE-IPF is typically reported at 5-15% [66] but can vary between 4 to 20 per 100 patient-years in different studies. The mortality rate of acute exacerbations is ~50% and can exceed 90% in patients admitted to an intensive care unit [66]. Historically, criteria for AE-IPF included unexplained worsening of dyspnea within the prior month, evidence of hypoxemia and new lung infiltrates on imaging studies in the absence of an alternative explanation, such as the causes mentioned above.

AE-IPF can occur at any point of the disease and could be the presenting manifestation. They have been reported following bronchoscopy and thoracic surgery [1]. Several studies have shown that AE-IPF may also be triggered by viral infections, microaspiration related to gastro-esophageal reflux, drugs, air pollution and mechanical injury to the alveolar epithelium [67]. AE-IPF have been described more frequently in the winter and spring months, providing epidemiological support for an infectious etiology [67]. AE-IPF following surgery may be related to large volumes of intraoperative fluid administration, or to high flows of oxygen or high ventilator positive pressures that may be used during anesthesia ; thus, a judicious use of intravenous fluids [68], oxygen or positive pressures may be a preventative strategy for AE-IPF in patients undergoing surgery, but proper clinical trials are required to better support these strategies.

The usual histopathological pattern on surgical biopsy or autopsy of AE-IPF is diffuse alveolar damage superimposed on the background of fibrotic lung disease with occasional evidence of organizing pneumonia.

Even though bronchoscopy has been traditionally used to rule out infection, many patients with IPF exacerbations cannot undergo bronchoscopy because of severe hypoxemia, unless they are intubated. Because of this, most patients with IPF exacerbations are treated empirically with antibiotics to cover for a possible underlying infection, and with systemic corticosteroids to treat the acute inflammatory process associated with the AE-IPF. Patients with AEIPF and hypoxemia also benefit from supplementary oxygen and in some cases from opioids for the management of dyspnea. Currently available anti-fibrotic therapies -pirfenidone and nintedanib-, have no convincing evidence of benefit in preventing or treating AE-IPF.

The observation that patients with acute exacerbations of IPF with and without documented infection have similar outcomes when treated empirically with antibiotics and systemic corticosteroids has called into question the need to perform bronchoscopy routinely in patients with AE-IPF [69]. A recent study of the role of bronchoscopy in ILD exacerbations showed that in patients with IPF who were not on immunosuppressive medications, bronchoscopy did not alter the management of patients who were already on empiric treatment, nor their mortality; and it was associated with significant procedure-related risks in non-intubated patients [70].

Thus, it is currently appropriate to treat patients with IPF exacerbations empirically with antibiotics, systemic corticosteroids and oxygen +/- opioids, after excluding causes of respiratory deterioration that have a specific treatment: pulmonary embolism (with chest CT pulmonary angiography when feasible), pneumonia, pneumothorax and heart failure.

Conclusion

IPF is a progressive and often fatal fibrotic lung disease, with an unpredictable course. Fortunately, anti-fibrotic treatments have recently shown to be effective in slowing down the progression of the disease and potentially decreasing mortality. However, we currently do not have curative treatments for IPF and lung transplantation may be an option for some patients with advance or progressive disease. For patients who worsen despite medical treatment and who are not candidates for lung transplantation, symptomatic treatment to improve quality of life -including supplementary oxygen and opioids-, should be offered. Several potentially curative treatments based on transplantation of cells that aim to repair the damaged alveolar tissue in IPF are promising, but are still in the experimental phase.

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