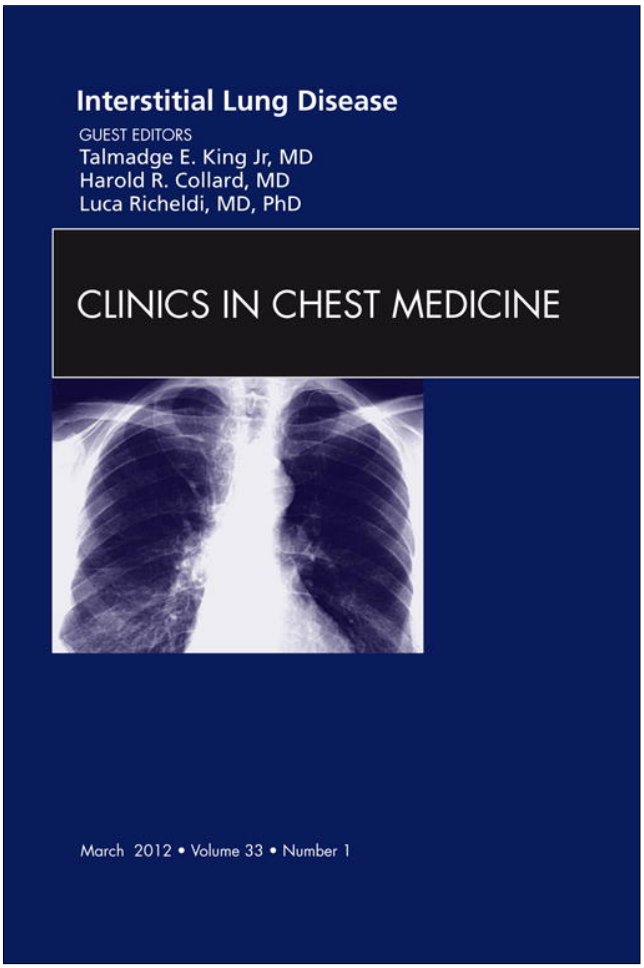

Management of Idiopathic Pulmonary Fibrosis

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KEYWORDS

- Idiopathic pulmonary fibrosis • Pirfenidone
- Corticosteroids • Randomized controlled trials
- Comorbidities

Idiopathic pulmonary fibrosis (IPF) represents one of the most challenging diseases for chest physicians. The diagnostic process is complex and requires close interaction with different specialists. The prognosis of IPF is invariably poor. Notwithstanding the many treatments used in clinical practice and evaluated in the context of controlled randomized trials, the modalities for the follow-up of patients with IPF are poorly defined. Given the lack of proof for most interventions, all decisions need to be extensively discussed and agreed upon with the patient and their families. As a consequence, few respiratory disorders require of chest physicians more interactive skills and more dedication than IPF.

PHARMACOLOGIC TREATMENTS

The pharmacologic approach to IPF management has changed as the understanding of the pathogenesis of the disease has evolved over the last decade. The initial thinking was in favor of a disease triggered by a persistent inflammatory process, resulting in the induction of fibrosis and scarring of the lungs. As such, several trials were performed evaluating the efficacy of drugs that primarily exert their functions by suppressing inflammatory or immune responses (such as corticosteroids and nonsteroid immunomodulatory agents). Current treatment approaches favor agents with antifibrotic properties. A systematic assessment of the evidence available for different therapeutic options in IPF has been recently published as an evidence-based guideline.[1] A summary of the therapeutic recommendations listed in this important document, formulated according to the Grades of Recommendation Assessment, Development and Evaluation methodology,[2] along with the reported voting results from the committee members, is provided in **Table 1**.

Anti-Inflammatory and Immunomodulatory Drugs

Patients with IPF have been (and most still continue to be) treated in many parts of the world with corticosteroids. A summary of the results available for the efficacy of corticosteroid in IPF was first published in 2003 as a Cochrane systematic review,[3] when no high-quality studies were identified and only nonrandomized, retrospective, studies were available. Hence, there was a major lack of evidence supporting the use of corticosteroids in the treatment of IPF. An update of that same systematic review, published in 2010,[4] did not identify any new additional randomized clinical trial on the use of steroids in IPF, thus confirming the persisting lack of evidence for their use in the management of IPF. This issue has been also reassessed in the current evidence-based guidelines,[1]

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Table 1
Summary of current evidence-based recommendations on management of patients with IPF

	Recommendation				Number of Votes (As in Ref.[1])			
	For		Against					
	Strong	Weak	Weak	Strong	For	Against	Abstention	Absent
Pharmacologic Therapies in Stable IPF								
Corticosteroids alone				×	0	21	2	8
Colchicine				×	0	21	2	8
Cyclosporin A				×	0	21	2	8
Cyclophosphamide + corticosteroids				×	0	21	2	8
Azathioprine + corticosteroids				×	0	21	2	8
Prednisone + NAC + azathioprine			×		3	17	3	8
NAC alone			×		5	15	3	8
Interferon gamma-1b				×	0	17	6	8
Bosentan				×	0	10	13	8
Etanercept				×	0	18	4	9
Anticoagulation therapy			×		1	20	2	8
Pirfenidone			×		4	10	17	0
Pharmacologic Therapies in Acute Exacerbations of IPF								
Corticosteroids		×			14	5	1	11
Treatment of comorbidities								
Pulmonary hypertension			×		8	14	1	8
Gastroesophageal reflux		×			15	8	0	8
Nonpharmacologic Therapies								
Long-term oxygen therapy (in case of resting hypoxemia)	×				18	0	4	9
Rehabilitation		×			19	0	3	9
Mechanical ventilation			×		2	19	2	8
Lung Transplantation (Selected Patients)	×				21	0	1	9

Official recommendations are not available for sildenafil and imatinib because evidence on these drugs was published after the publication of the ATS/ERS/JRS/ALAT 2011 guideline document.[1] See text for details.
Abbreviations: NA, not applicable; NAC, *N*-acetylcysteine.

in which a strong recommendation against the use of corticosteroid monotherapy in IPF has been made. This important recommendation relies on the availability of very-low-quality evidence and places a high value on preventing treatment-related morbidity using long-term corticosteroid therapy. From the aforementioned results, steroids alone should never be used to treat IPF.

Low-quality evidence is also available for the use of nonsteroid immunomodulatory drugs in IPF, such as colchicine, cyclosporin A, cyclophosphamide, or azathioprine, either alone or in combination with corticosteroids[5]; as such, current guidelines[1] strongly recommend against the use of immunomodulatory agents in the treatment of patients with IPF. A weak recommendation against the use of a combination therapy with azathioprine, prednisone, and the antioxidant drug *N*-acetylcysteine has also been made.[1] Regarding this combination regimen only one randomized clinical trial is available, which evaluated the effect of *N*-acetylcysteine in patients already receiving combination therapy with prednisone and azathioprine.[6] The main points of criticism regarding the results of

this trial are related to the substantial drop-out rate observed in the study (and the consequent statistical corrections needed) and to the lack of a true (ie, not taking any potentially effective drug) placebo group. Nonetheless, significant results supporting the use of the so-called triple therapy were observed in the change of vital capacity and diffusing capacity at 12 months; however, no difference was observed in mortality or in other secondary outcomes, such as dyspnea or quality-of-life scores. To further investigate the possible efficacy of *N*-acetylcysteine in the treatment of patients with IPF, a three-arm large trial sponsored by the IPFnet consortium (the PANTHER [Prednisone, Azathioprine, and N-acetylcysteine: A Study That Evaluates Response in IPF] trial) is currently recruiting patients in the United States. However, an interim results from this study showed that compared to placebo, those assigned to triple therapy had greater mortality, more hospitalizations, and more serious adverse events, while not showing any difference in lung function test changes. Therefore the National Heart, Lung, and Blood Institute (NHLBI) has recently stopped the triple-therapy arm of this study (NIH Release on October 21, 2011). The other two study arms of this IPF trial comparing NAC alone to placebo alone will continue. At present, *N*-acetylcysteine, neither alone nor in combination with prednisone and azathioprine, can be recommended for the routine treatment of IPF.

Antifibrotic and Antiproliferative Drugs

Over the last decade, the perspective on IPF pathogenesis has profoundly changed.[7] The cause of the disease has not been identified and the pathogenesis remains largely unknown. Recent findings suggest that the disease is likely the result of an aberrant reparative mechanism, following an injury that primarily targets the lung epithelium. Therefore, the disease appears to be characterized by the proliferation and accumulation of fibroblasts/myofibroblasts in the lungs, with excessive deposition of extracellular matrix, resulting in the fibrotic distortion of the lung architecture, typically observed by radiologists and pathologists in the lungs of patients with IPF. Several pathways of these processes are under investigation at present, aimed at identifying the key molecular mediators and the potential sources of myofibroblasts as well as the mechanisms responsible for the initial injury.

As such, recent randomized clinical trials on the treatment of IPF have shifted their attention to drugs with antifibrotic and antiproliferative effects. As a general observation, the rationale for using most of the drugs tested so far in clinical trials has been limited because of both the lack of a reliable animal model of the disease[8] and the relative scarcity of in vivo and ex vivo data. As a consequence, in some cases the background for conducting clinical trials is derived from post hoc analyses of previous studies, with the unavoidable risks related to no predefined statistical analyses on subgroups.[9]

Interferon gamma-1b has been one of the first agents evaluated in IPF for its antifibrotic as well as immunomodulatory properties. A first small pilot study[10] published in 1999 pioneered the era of the randomized controlled trial (RCT) in IPF, showing an unexpected and substantial improvement of lung function in the active treatment group, which prompted 2 subsequent large randomized, placebo-controlled clinical trials addressing the efficacy of this intervention.[11,12] Despite the promising initial results, both trials failed to meet the primary end points, and a recent meta-analysis on the efficacy of interferon gamma-1b failed to show any effect of this treatment on clinically relevant outcomes, such as overall survival, progression-free survival, or lung function.[5] Therefore, current guidelines include a strong recommendation against the use of interferon gamma-1b in the treatment of patients with IPF, based on high-quality evidence.[1] As a consequence, and notwithstanding the publication of small uncontrolled studies suggesting some effect in a minority of patients with IPF,[13,14] interferon gamma-1b is no longer a therapeutic option for patients with IPF.

Drugs already approved for other indications in different diseases, but with background for being effective in fibrotic disorders, have been evaluated in IPF clinical trials. Coming from the field of pulmonary hypertension (PH), the endothelin receptor A and B antagonist bosentan has been evaluated in 2 randomized placebo-controlled clinical trials. The IPF guidelines strongly recommend against the use of this drug in IPF based on the results of the first phase II trial,[15] which did not reach statistical significance in the primary outcome and only showed a positive trend toward a benefit for the drug in some secondary end points. Moreover, the results of the largest trial on bosentan in IPF[16] confirmed the lack of effect of this drug. More recently, a phase III, randomized, double-blind, placebo-controlled, multicenter study comparing ambrisentan (another endothelin receptor antagonist selective for type A receptor) to placebo in subjects with IPF (the ARTEMIS-IPF [Randomized, Placebo-Controlled Study to Evaluate Safety and Effectiveness of Ambrisentan in IPF] trial) was prematurely stopped after an interim analysis showed no efficacy of the study drug. Furthermore,

a phase II trial evaluating efficacy and safety in patients with IPF of another endothelin receptor antagonist, macitentan, is active, but not recruiting patients.

Etanercept, an anti–tumor necrosis factor α drug widely used in rheumatology, has also been evaluated in IPF. A strong recommendation against its use in IPF has been made in the current guidelines.[1] In a single, well-conducted, randomized placebo-controlled trial,[17] this drug failed to show a statistically significant difference between treatment groups, although some effects on secondary outcomes were noted.

Several novel oncological agents have been tried in patients with IPF. Imatinib mesylate, a specific tyrosine kinase inhibitor with activity against Bcr-Abl, platelet-derived growth factor (PDGF) receptors, and c-kit, has also been studied in IPF. The inhibitory activity on PDGF receptors suggested a potential activity in IPF, through the suppression of the profibrotic and proliferative pathways mediated by PDGF. However, a recently published randomized clinical trial on imatinib in patients with IPF[18] failed to demonstrate an effect of this drug compared with placebo on any of the outcomes selected for this study, and in particular did not show a statistically significant difference between the treatment and the control group in progression-free survival or in the change of lung function over time. Also, a multiple kinase inhibitor (BIBF 1120) has been evaluated in a phase II trial in patients with IPF.[19] The encouraging results of this study[20] prompted the initiation of 2 parallel phase III studies, currently ongoing and aimed at demonstrating the efficacy of this drug in IPF.

Very low-quality evidence is available for the usage of anticoagulation therapy in IPF. In fact, only one small, unblinded, RCT performed in Japan has been published, showing a survival benefit in patients receiving anticoagulation, the effect being attributed to a reduced mortality during hospitalization for acute exacerbation or disease progression.[21] A larger trial on the efficacy of the use of anticoagulation therapy in IPF (the ACE-IPF [Anticoagulant Effectiveness in Idiopathic Pulmonary Fibrosis] trial), sponsored by the IPFnet network in the United States, was recently stopped based on a lack of efficacy at interim analysis.

Pirfenidone is a small synthetic nonpeptide molecule that has antifibrotic, anti-inflammatory, and antioxidant properties, with the ability to interfere with transforming growth factor β–induced collagen synthesis. Promising results from an open-label phase II study supported the use of this drug in the treatment of IPF.[22] Subsequently, the results of 2 multicenter trials performed in Japan and 2 large international multicenter clinical trials, all randomized and placebo-controlled, assessing the efficacy of pirfenidone compared with placebo in patients with IPF, have been published.[23–25] All these trials have been found to have a sufficient methodological quality, allowing their inclusion in a recent Cochrane systematic review.[5] Based on the results of this meta-analysis, pirfenidone appears to reduce the risk of disease progression (as measured by progression-free survival) by 30% and to provide a beneficial effect on the change of lung function from baseline, in comparison with placebo. Some limitations to the interpretation of these data still apply, mostly related to a certain degree of methodological heterogeneity across studies, mainly regarding the methodologies for reporting lung-function results. Current IPF guidelines, considering the cost of therapy and the potentially relevant side effects (such as gastrointestinal adverse events, liver laboratory abnormalities, photosensitivity, and rash), expressed a weak recommendation against the use of this drug. However, the majority of panel experts abstained from this voting. On the one hand, the Food and Drug Administration has denied approval for the use of the drug in the United States, requesting additional data. Consequently, a new study (the ASCEND [Assessment of Pirfenidone to Confirm Efficacy and Safety in IPF] trial), comparing pirfenidone and placebo in patients with IPF, is currently enrolling patients in North America, Central America, South America, Australia, and New Zealand. On the other hand, pirfenidone is approved and commercially available for the treatment of patients with IPF in India and Japan; in Europe the drug has been recognized as an orphan drug, and the European Medicines Agency has approved its use in the European Community for the treatment of patients with mild to moderate IPF. Part of these discrepancies can be explained by the fact that the trials assessing the efficacy of pirfenidone have been designed with lung function as the primary end point, whereas in a disease like IPF the reduction of mortality should be seen as the main goal of treatment. Although there is increasing evidence that a change (in particular a 10% decrease) in forced vital capacity is predictive of subsequent mortality,[26–28] lung function should be seen at best as a surrogate of mortality. In any case, pirfenidone will enter the European market over the next months and a named-patient program is currently ongoing. The administration of pirfenidone to all patients with IPF is still a matter of debate. Patients willing to receive pirfenidone should be fully informed on the available evidence for the efficacy of the drug and on the possible side effects.

MANAGEMENT OF COMORBIDITIES

IPF is often associated with morbidities (eg, PH and gastroesophageal reflux) and symptoms (eg, dyspnea, exercise limitation, fatigue, anxiety, mood disturbance, sleep disorders) that dramatically affect patients' lives.

PH affects most patients with IPF at the time of initial diagnosis, and ultimately many of them during the course of the disease.[29] Patients with IPF with concomitant PH (defined as a mean pulmonary artery pressure >25 mm Hg on right heart catheterization) have more dyspnea, greater impairment of their exercise capacity, and increased 1-year mortality in comparison with their counterparts without PH.[30] Once PH has been diagnosed, it is essential to exclude any causative or contributory comorbidity, such as obstructive sleep apnea, congestive heart failure, and pulmonary emboli; in addition, hypoxia should be sought and treated.

Whether targeting of PH with medications approved for the treatment of pulmonary arterial hypertension has any utility in IPF remains unclear. In a small open-label trial, sildenafil, an oral phosphodiesterase-5 inhibitor, improved 6-minute walk distance (6MWD) and pulmonary hemodynamics without increasing shunt flow or worsening oxygenation.[31] However, a subsequent large multicenter, randomized, double-blind, placebo-controlled study did not meet the primary end point (change of 20% in 6MWD at 12 weeks), although statistically significant differences favoring sildenafil were observed in dyspnea, partial pressure of oxygen, diffusing capacity of lung for carbon monoxide, and quality of life.[32]

Bosentan, a dual endothelin receptor A and B antagonist, has been tested in a phase II RCT,[15] though in patients not evaluated for the presence of PH and thus more as an antifibrotic drug. Although the primary end point (change from baseline up to month 12 in exercise capacity, as measured by a modified 6MWD test) was not reached, the results of a post hoc analysis suggested that bosentan had a beneficial effect on time to disease progression or death and quality of life in patients who underwent surgical lung biopsy,[33] thus leading to a larger phase III study, which failed to demonstrate that bosentan delays IPF worsening or death, the primary end point.[16] As already mentioned, a phase III randomized, double-blind, placebo-controlled, multicenter study comparing ambrisentan (an endothelin receptor antagonist selective for type A receptor) with placebo in subjects with IPF (with or without associated PH) has been prematurely stopped after an interim analysis showing no efficacy of the study drug. Notwithstanding the disappointing results from these studies, it is common practice for chest physicians and cardiologists to observe how the presence of PH affects patients' functional status and portends a worse outcome. Despite limited evidence of efficacy, current guidelines weakly recommend a trial of vasomodulatory agents in patients with moderate to severe PH, as documented by right heart catheterization (ie, mean pulmonary artery pressure >35 mm Hg).[1]

Acid gastroesophageal reflux (GER) is highly prevalent in patients with IPF, up to one-half of whom are asymptomatic.[34] Experimental animal studies and descriptive studies in humans suggest that chronic microaspiration caused by GER may cause subclinical injury leading to pulmonary fibrosis.[35,36] While the pathobiological significance of GER in IPF remains to be elucidated, there is evidence that treatment of GER, either medical or surgical, may stabilize lung function.[37,38] More recently, Lee and colleagues[39] reported in a large cohort of patients with IPF that use of GER medication, (ie, suppression of gastric content acidity with either proton-pump inhibitors (PPI) or H_2 blockers) was associated with lower high-resolution computed tomography (HRCT) fibrosis score and longer survival. These authors observed an additional survival benefit to Nissen fundoplication, a surgical intervention that reduces not only acid but also weakly acidic reflux and potential microaspiration, which may also contribute to the development of lung fibrosis.[40] At present, it is unclear whether aggressive treatment of GER disease may improve or halt disease progression. In addition, PPI only affect the acidity of the refluxate without preventing reflux or microaspiration of gastric contents. Furthermore, the use of PPI has been associated with an increased risk of hip fracture and community-acquired pneumonia.[41,42] Lifestyle modifications (small meals, raising the head of the bed) seem reasonable measures to suggest for symptomatic patients.

MANAGEMENT OF ACUTE EXACERBATION OF IPF

The clinical course of IPF is usually chronic and slowly progressive, although some patients experience rapidly progressive disease.[1] Acute worsening may occur as a consequence of multiple distinct causes, including respiratory infections, pulmonary embolism, pneumothorax, and heart failure; sometimes worsening cannot be linked to any identifiable cause, and this latter case is referred to as acute exacerbation of IPF (AE-IPF)[43] (see article elsewhere in this issue). The prognosis of AE-IPF is almost invariably poor; mortality during hospitalization is as high as 65% and those

who survive have a greater than 90% mortality rate in the 6 months following discharge.[44]

If AE-IPF is suspected, the management should include chest HRCT, echocardiogram, bronchoalveolar lavage, and infection screen to rule out known and potentially treatable causes of disease progression. Many patients with AE-IPF require intensive care, particularly when respiratory failure is associated with hemodynamic instability, significant comorbidities, or severe hypoxemia requiring monitoring of arterial blood gases or mechanical ventilation.

A systematic review has been performed summarizing the current knowledge of acute exacerbations in IPF, including their treatment.[45] Treatment strategies varied in the different studies, but in almost all of them patients were administered broad-spectrum antibiotics and pulse doses of methylprednisolone (0.5–1 g/d) while the previous dose of oral steroids was also increased; in some studies, additional immunosuppression with cyclophosphamide and cyclosporine was used.

Two small studies showed that use of cyclosporine after treatment with pulse steroids can increase survival times.[46,47] Horita and colleagues[48] observed a higher survival ratio and longer survival duration in patients with AE-IPF treated with a combination therapy of tacrolimus and methylprednisolone pulse therapy. In the double-blind, prospective, placebo-controlled, randomized clinical trial by Azuma and colleagues[23] evaluating the effect of pirfenidone in patients with IPF, although statistical significance was not reached for the primary end point (ie, the change from baseline of the lowest oxygen saturation as measured by pulse oximetry during the 6-minute steady-state exercise test), the investigators observed a significant treatment effect on rates of AE-IPF, which occurred exclusively in the placebo group. As such, the study was then prematurely stopped on ethical grounds. Pirfenidone appeared also to favorably affect time to acute exacerbation and IPF-related death in the recent CAPACITY [Clinical Studies Assessing Pirfenidone in IPF: Research of Efficacy and Safety Outcomes] trials,[25] although the rate of AE-IPF was not a specific and separate end point in this study.

Kubo and colleagues[21] evaluated the effect of anticoagulant therapy on the survival of patients with IPF and found a beneficial effect on survival of combined anticoagulant and prednisolone therapy. This effect was largely driven by the reduced incidence of AE-IPF in the warfarin group.

Few nonrandomized small studies investigated the effect of polymyxin B–immobilized fiber column (PMX) hemoperfusion treatment, showing a potential beneficial effect of PMX treatment. However, these results have largely been single-center and need confirmation before affecting clinical practice.[49–51]

Given the limited evidence, pharmacologic treatment of AE-IPF is largely empiric and usually consists of intravenous corticosteroids up to 1 g/d, with or without immunosuppressive drugs. However, there are no controlled clinical trials to judge the efficacy of this therapeutic strategy, and substantial difference of opinion between clinicians exists regarding the appropriate treatment for patients suffering from this complication. Therefore, specific recommendations regarding dosage, route, and duration of corticosteroid therapy cannot be made at present.[1] Nonpharmacologic treatment of AE-IPF and progressive respiratory failure in patients with IPF are discussed below.

NONPHARMACOLOGIC TREATMENTS

Despite the lack of high-quality data demonstrating its benefit in patients with IPF, long-term oxygen therapy is commonly prescribed to patients showing resting hypoxemia or significant oxygen desaturation on exercise, and is strongly recommended by current guidelines.[1] Due to the progressive nature of IPF, higher flow rates than those commonly used in chronic obstructive pulmonary disease are likely to be required. Supplemental oxygen may improve symptoms, quality of life,[52] and endurance during rehabilitation training in selected patients without exercise-induced hypoxemia.[53] Conversely, long-term oxygen therapy does not affect survival.[54] Supplemental oxygen therapy is a critical component of the management of IPF, and recent guidelines recommend its use in patients with clinically significant resting hypoxemia.[1]

Lack of energy and fatigue is a common and disabling problem in IPF. Pulmonary rehabilitation (PR), defined as a multidisciplinary intervention for patients with chronic respiratory diseases who are symptomatic and often have reduced activities in daily life, is designed to alleviate symptoms and optimize functional status by stabilizing and/or reversing the extrapulmonary features of the disease. Typical PR programs include exercise training, nutritional modulation, occupational therapy, education, and psychosocial counseling, and consist of an initial intense component (usually 6–10 weeks) followed by a maintenance component.[55] At present, the most convincing evidence of a beneficial effect of PR on quality of life and functional mobility is derived from studies on patients with pulmonary emphysema, although it is conceivable that similar beneficial effects may be achieved in patients with comparable disability from other chronic respiratory diseases.[56] Previous

studies, in which the physical training was compared with no physical training or other therapy, were not limited to patients with IPF, thus including conditions potentially more amenable to the beneficial effect of PR. In an RCT on the effect of 8 weeks of exercise-based PR in 57 patients with interstitial lung diseases, including 34 patients with IPF, Holland and colleagues[57] observed that the increase in 6MWD and the reduction in dyspnea and fatigue among patients with IPF were not as remarkable as among the non-IPF ones. In addition, these benefits were seen immediately following training but were not sustained 6 months after intervention. Patients with IPF tend with time to discontinue any routine exercise because of increasing dyspnea, which should be discouraged whenever possible. Indeed, exercise such as daily walks or the use of a stationary bicycle improves muscle strength and increases the sense of well-being.

The clinical course (progressive disease or associated with acute exacerbation) of IPF is often complicated by respiratory failure, and patients may be referred to the intensive care unit to receive ventilator support. However, mortality during the hospitalization is high.[58,59] In addition, patients with end-stage interstitial lung disease are difficult to ventilate and are rarely successfully weaned from mechanical ventilation.[58,60] Thus, while the decision not to ventilate a patient with IPF who also has acute respiratory failure is a tricky one, mechanical ventilation should be introduced only after carefully weighing up the patient's long-term prognosis and, whenever possible, the patient's wishes. The use of mechanical ventilation is discouraged by current guidelines.[1] Lung transplantation might be regarded as the last therapeutic option for patients with acute respiratory failure, in particular in younger patients with a firmly established diagnosis. In these patients, mechanical ventilation or extracorporeal life support (extracorporeal membrane oxygenation) may be used as a direct bridge to lung transplant.[61]

The outcome of life support as compared with palliative care should be discussed with patients and their families at an earlier stage. Palliative care should start when patients with a progressive disease become symptomatic, which means that in some patients with IPF this type of intervention should start as early as the diagnosis is established. In IPF, dyspnea can be extremely distressing, thus impairing physical activity and quality of life. In selected cases of particularly severe dyspnea, morphine could be considered. In a small case series, Allen and colleagues[62] reported that low-dose diamorphine reduces dyspnea, anxiety, and cough without significant decrease in oxygen saturation. Further, oxygen therapy may be useful for palliation of dyspnea in hypoxemic patients. With disease progression, patients may also experience fear, anxiety, and depression; psychological counseling and, in selected cases, pharmacologic treatment should therefore be considered. In a recent cross-sectional study of outpatients with interstitial lung disease, including IPF, Ryerson and colleagues[63] reported that dyspnea is strongly associated with depression score, functional status (as assessed by 4 minutes walk time), and pulmonary function. These investigators demonstrated that the relationship between dyspnea and depression is independent of other clinical variables, thus suggesting that treatment of depression (observed in as many as 23% of patients in this study) may improve dyspnea and quality of life. The poor prognosis and significantly impaired quality of life in patients with IPF make palliative care an urgent need in these patients.

LUNG TRANSPLANTATION

Pulmonary fibrosis represents the second most frequent disease for which lung transplantation is performed.[64] More recently the number of lung transplants performed for IPF has steadily increased, particularly in the United States, where IPF now represents the leading indication for lung transplantation.[65] Five-year survival rates after lung transplantation in IPF are estimated at 50% to 56%.[62,66,67] Additional evidence suggests that patients with pulmonary fibrosis undergoing lung transplantation have favorable long-term survival compared with other disease indications[67] (see article elsewhere in this issue).

SUMMARY

Despite more than a decade of efforts to show a definite effect on disease course in IPF, a treatment regimen that is unanimously recognized as a standard of care is still lacking. Current guidelines recommend enrollment in clinical trials as the standard of care for patients with IPF. However, given that one drug, pirfenidone, is currently approved for the treatment of IPF in parts of the world that are home to about 2 billion people, it is reasonable to say that a major step forward has been made with the identification of this drug. Nonetheless there is no global recognition of this fact, and it is fair to say that if pirfenidone can be seen as a starting point in the treatment of IPF, it cannot be seen as a point of arrival. Based on the current knowledge of IPF pathogenesis, it is easy to predict that the future treatment of IPF will be based on multiple drugs. Although this is discouraging on

one hand, on the other hand identification of more milestone drugs is getting closer, and it seems likely that within a few years the first globally accepted standard of care will become a reality for the management of this deadly disease. The knowledge gained until now and the one that will be gained over the next few years are important and will also form the basis to approach the vast and heterogeneous spectrum represented by the other fibrotic interstitial lung diseases, for which a systematic attempt to discover an effective pharmacologic treatment is almost completely lacking. In this way, patients with IPF will lead the way in the discovery of therapies for lung fibrosis and, while achieving the important critical goal of the identification of the first effective treatment, will also help the large number of patients with non-IPF fibrotic lung disorders.

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