A comprehensive and practical approach to the management of idiopathic pulmonary fibrosis

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A comprehensive and practical approach to the management of idiopathic pulmonary fibrosis

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ABSTRACT

Introduction: Idiopathic pulmonary fibrosis (IPF) is a debilitating, progressive, and fatal fibrotic pulmonary disease with a prognosis comparable to that of lung cancer. IPF management is a complex process that involves pharmacological and nonpharmacological interventions, extensive patient education, and addressing patient needs that change through the course of the illness.

Areas covered: This review summarizes the key aspects of a multifaceted, multidisciplinary, individualized approach to IPF care that incorporates available treatment options, strategies to improve compliance with antifibrotic therapies, pulmonary rehabilitation, and the integration of palliative care for symptom management. Aspects of care discussed include the use of antifibrotic therapy and nonpharmacological treatments, targeted education and psychosocial support, evaluation and management of comorbidities, and early integration of palliative care.

Expert opinion: By incorporating this comprehensive approach to disease management, physicians can address most aspects of care for a patient with IPF to optimize survival and quality of life.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible, and fatal fibrosing lung disease with a median survival of 2–5 years from diagnosis [1–3]. The 5-year survival rate of 20–40% associated with IPF is worse than that of many cancers [4]. IPF is the most common idiopathic interstitial lung disease (ILD), affecting ∼5 million persons worldwide, particularly males; the mean age at presentation is 66 years [5,6]. Smoking, environmental exposures, gastroesophageal reflux disease (GERD), infections, and genetic predisposition are potential risk factors for the development of IPF [1,7].

The clinical course of IPF is progressive, highly variable and unpredictable in individual patients and is frequently associated with a significant symptom burden [4]. Disease progression can be accelerated by an acute exacerbation, a clinically significant, rapid decline in lung function [8,9]. Risk factors for short-term mortality include acute exacerbations, absolute and relative decline of ≥10% in % predicted forced vital capacity (FVC) over 52 weeks, high supplemental oxygen flow-rates, and respiratory-related hospitalizations [10–14]. Whether disease progression is rapid or slow, management of IPF is challenging because the needs of individual patients are variable and change throughout the course of the disease.

Current models of IPF care emphasize multidisciplinary teams, early diagnosis, the use of antifibrotic therapy, and monitoring of disease progression [15–17]. The 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) consensus guidelines recommend clinical follow-up every 4–6 months, long-term oxygen therapy if hypoxemia is present, pulmonary rehabilitation (PR), and treatment of comorbidities such as GERD for the majority of patients with IPF, as well as lung transplant for select patients [1]. In 2015, the conditional use of approved antifibrotic therapies, which slow disease progression, was added to the ATS/ERS/JRS/ALAT guidelines for IPF treatment [18].

The management of dyspnea, cough, and psychological suffering, which nearly all patients with IPF develop as the disease progresses, are important aspects of care [1,4,15,19,20]. A comprehensive care approach that includes pharmacological and nonpharmacological treatment, palliative care, patient education, and increased support throughout the course of illness is needed. Disease-centric care models focus on specific treatments for IPF but do not adequately meet all patient and caregiver needs. In addition to controlling disease, the goals for delivering care should include improving quality of life (QoL), decreasing symptom burden, providing caregiver support, and reducing the economic burden of IPF.

A single-center, retrospective cohort study (conducted before the approval of antifibrotics) in 284 patients with IPF showed that a bundled care approach for IPF based on the 2011 ATS/ERS/JRS/ALAT guidelines improved transplant-free survival [21]. This approach included semiannual visits to an ILD clinic, PR, an annual 6-minute walk distance (6MWD) test, an annual...
echocardiogram, and GERD therapy [21]. In a recent exploratory analysis of experience at a single center in Canada, a multidisciplinary collaborative care model was associated with a reduction in healthcare utilization and more at-home deaths compared with care received at the same center prior to the implementation of the collaborative care model [22]. The collaborative care team included a pulmonologist with expertise in ILD, a pulmonologist with expertise in palliative care, a nurse, a respiratory therapist, a physiotherapist, and a dietitian [22]. A single-center survey of bereaved caregivers of patients with IPF indicated that targeted education, advance care planning, and improved communication can positively impact symptom control, QoL, and caregiver burden in IPF [23]. These 3 studies highlight the benefit of a holistic approach to IPF management that encompasses all aspects of care.

In this review, we provide evidence-based recommendations when available and, in cases when no evidence-based recommendations are available, the consensus approach used by experts in the management of patients with IPF from 3 ILD centers in Canada. These recommendations based on expert opinion should be applied as appropriate, given available treatment options wherever the treating physician practices. The available evidence is derived from randomized controlled trials (RCTs) and cohort studies or extrapolated from studies of other chronic pulmonary conditions. Our goal is to provide a thorough overview of all care components that we consider important and necessary in a comprehensive approach to IPF management (Figure 1). We describe treatment options and strategies to mitigate antifibrotic-related adverse events (AEs) and explain the benefits of PR and the need for management plans that are tailored to meet the needs of the specific patient. We review the value of a multifaceted, multidisciplinary, individualized approach to treatment with early integration of palliative care to optimize symptom control, improve QoL, and ease transitions throughout the illness journey.

2. Multifaceted IPF management approach

2.1. Education

Education for patients with IPF needs to be specific to their disease and to the treatments the individual patient receives. Disease education should address patient concerns about disease progression and health deterioration and help them to prepare for the future [24]. Important components of education include patient empowerment that prepares patients to cope and to live well with IPF [25,26]. Internet resources alone are inadequate, and clinicians should consider the informational needs of both patients and caregivers throughout the course of the illness [27–30]. Specialist ILD nurses and nurse practitioners are well positioned to support education, AEs management, and adherence [31–33]. Several specific aspects of patient education are noted in the relevant sections throughout this review.

2.2. Antifibrotic therapy

The two currently available antifibrotic therapies, pirfenidone (ideal dose, 801 mg 3 times daily [TID]) and nintedanib (ideal...
dose 150 mg twice daily (BID)), were approved for the treatment of IPF in Canada in 2012 and 2014, in Europe in 2011 and 2015, and in the United States in 2014 and 2014, respectively, and received a conditional recommendation in the 2015 ATS/ERS/JRS/ALAT treatment guidelines in 2015 [18]. Both antifibrotics can slow disease progression as measured by the rate of decline in % predicted FVC [34–37].

A meta-analysis of the phase 3 ASCEND (Study 016, NCT01366209) and CAPACITY (Studies 004 and 006; NCT00287716 and NCT00287729, respectively) trials and 2 Japanese trials (Shionogi) of pirfenidone vs. placebo showed that pirfenidone reduced the risk of all-cause mortality (HR, 0.52; P = 0.01) and IPF-related mortality (HR, 0.35; P = 0.003) [38]. Post hoc analyses also found that pirfenidone reduced the risk of respiratory-related hospitalizations (HR, 0.52; P = 0.001) [39]. The INPULSIS-1 and -2 trials (NCT01335464 and NCT01335477) showed that nintedanib had a nonsignificant trend toward reducing all-cause mortality (HR, 0.70; P = 0.14) [40]. The reasons for differences between nintedanib and pirfenidone regarding mortality and acute exacerbations are not well understood, but the magnitude of the reduction in FVC (ml) decline was very similar in the phase 3 trials [34–37]. Open-label long-term extension studies of pirfenidone (RECAP [NCT00662038] and INSULINS-ON [NCT01619085]) supported the safety findings of the phase 3 trials [41,42].

A treatment benefit for either pirfenidone or nintedanib has been shown in patients with less-advanced vs. more-advanced disease across a range of lung function criteria (% baseline FVC ≤50–90%) in post hoc analyses of clinical trial data and in real-world studies [43–48]. A post hoc analysis of data from ASCEND and CAPACITY showed that patients who experienced ≥10% absolute decline in % predicted FVC during the first 6 months of treatment and continued treatment with pirfenidone had lower risk of further decline in % predicted FVC or death during the subsequent 6 months compared with placebo [49]. In a post hoc analysis of patients with IPF who had ≥10% absolute decline in FVC in the first 24 weeks of treatment with nintedanib in the INPULSIS trials, continued treatment was not associated with further FVC decline in the following 24 weeks compared with placebo [50].

Important factors to consider when selecting antifibrotic therapy include a patient’s preferences, individual burden of comorbidities, and potential risks. The selection between pirfenidone and nintedanib may be influenced by the patient’s lifestyle and clinical conditions. Pirfenidone requires avoidance of direct sun exposure (due to treatment-associated photosensitivity); nintedanib should be used with caution in patients with a risk of bleeding or gastrointestinal (GI) perforation, including those receiving concomitant antiaggregants, corticosteroids, or nonsteroidal anti-inflammatory drugs (due to treatment-associated increased bleeding risk) [51–56]. It is important to note that patients with recent history of myocardial infarction or stroke were excluded from the antifibrotic clinical trials; however, an increased risk of these AEs has not been observed in post hoc analyses [34–37,57,58]. Pirfenidone is metabolized by cytochrome P450 1A2 (CYP1A2) and should not be used in combination with CYP1A2 inhibitors (e.g. fluvoxamine [absolute contraindication] and ciprofloxacin [permitted at 750 mg BID with a reduced dose of pirfenidone 534 mg TID), amiodarone, omeprazole, esomeprazole) due to increased exposure and thus increased risk of AEs. Consumption of grapefruit juice is associated with CYP1A2 inhibition and should be avoided during pirfenidone treatment. Pirfenidone should be avoided in combination with CYP1A2 inducers (e.g. rifampin, phenytoin, carbamazepine) due to reduced exposure [51]. Nintedanib is contraindicated in patients with peanut or soy allergies and during pregnancy; nintedanib should be used cautiously (possibly at reduced dose) in combination with P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) inhibitors (e.g. ketoconazole, erythromycin) due to increased exposure and should be carefully considered in combination with P-gp and CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, St. John’s Wort) due to decreased exposure [54–56].

A new formulation of pirfenidone was approved in Canada, the United States, and Europe in 2017: 801-mg tablets TID with meals for patients maintaining full dose; this new formulation reduces the pill burden associated with the 267-mg capsules, which are used for initial pirfenidone titration [59]. However, the approval of the new 801-mg tablets was based on a single-dose pharmacokinetics study performed in healthy volunteers; fewer AEs were reported in patients who received pirfenidone after a meal than after an overnight fast [59]. Therefore, it is important to monitor patients who switch to 801-mg tablets; patients who experience significant AEs may be switched back to the 267-mg capsules to accommodate dose reductions instead of discontinuing treatment.

2.2.1. Consideration of early initiation of antifibrotic therapy

Patients may benefit from early initiation of antifibrotics for several reasons. Lung function decline is irreversible; therefore, the goal of antifibrotic treatment is to slow disease progression [15,16,60]. Baseline % predicted FVC itself does not predict disease progression [43,44]. Patients with less-advanced disease (i.e. baseline % predicted FVC ≥50%) experience benefit from antifibrotics similar to that in patients with more-advanced disease [43–48]. Finally, disease progression, as measured by either absolute or relative decline in % predicted FVC, and lower % predicted FVC are associated with an increased risk of IPF exacerbations and mortality [10–13,61,62]. Despite these findings, some countries do not provide reimbursement for patients with less-advanced disease. Patients in these countries should be monitored frequently, so antifibrotics can be initiated as early as possible in the course of the disease.

2.2.2. Antifibrotic-related adverse events

In the clinical trials, the most commonly reported treatment-emergent AEs (TEAEs) associated with antifibrotic therapies were GI TEAEs (Figure 2) [63–65]. In the pooled phase 3 pirfenidone clinical trials, the most common TEAEs were nausea (pirfenidone vs. placebo, 35.5% vs. 15.1% of patients), cough (23.1% vs. 24.0%), diarrhea (24.6% vs. 18.8%) upper respiratory tract infection (22.6% vs. 20.2%), fatigue (23.0% vs. 16.8%), headache (20.5% vs. 18.1%), and rash (29.2% vs. 9.0%) [66]. Other GI TEAEs reported in ≥10% of pirfenidone-treated patients were dyspepsia, GERD, and vomiting [66]. GI TEAEs were most likely to occur within the first 3–6 months of
Although both pirfenidone and nintedanib are associated with gastrointestinal adverse events, the frequency of individual adverse events is different with each drug. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CV, cardiovascular; GI, gastrointestinal.

In the clinical trials, pirfenidone-specific TEAEs included skin-related TEAEs, such as photosensitivity (pirfenidone vs. placebo, 9.3% vs. 1.1%) and rash (30.2% vs. 10.3%), whereas nintedanib-specific TEAEs included cardiovascular (nintedanib vs. placebo, 2.5% vs. 0.8%) and bleeding events (10% vs. 7%) [35,36,51,54,63,64,66]. Results from INPULSIS-ON, the open-label extension study of the INPULSIS trials, showed rates of cardiovascular and bleeding events that were similar to those observed in the placebo groups of INPULSIS and were not significantly different between previous nintedanib and previous placebo groups [42].

The safety and tolerability profiles of antifibrotics observed in these large, RCTs have been supported by real-world data and postmarketing experiences, in which patients typically have more-advanced disease and significantly more comorbidities than those in the clinical trials. In a single-center retrospective study of 351 patients who received pirfenidone over 4.5 years, TEAEs were mostly GI-related and similar to those observed in the clinical trials; 61% of pirfenidone-treated patients experienced ≥ 2 AEVs [68]. The majority of pirfenidone-associated TEAEs were tolerable or manageable by dose reduction and slower dose titrations, and approximately 1 in 5 (20%) TEAEs resulted in treatment discontinuation [68]. Over 4.5 years, 29% of patients discontinued pirfenidone compared with 12% of patients who discontinued over 1 year in the phase 3 trials [66,68]. The same study also reviewed TEAEs in 124 patients receiving nintedanib over 1.5 years [68]. Most nintedanib-associated TEAEs were GI-related, similar to the clinical trial findings [40,68]. Most patients (82%) experienced ≥ 2 TEAEs, and 26% of patients discontinued nintedanib over 1.5 years compared with 20.6% who discontinued over 1 year in the clinical trials [40,68]. Consistent with these findings, a separate, single-center, retrospective chart review study of 129 pirfenidone-treated patients and 57 nintedanib-treated patients with IPF reported discontinuation rates of 21% and 26% over a mean observation period of 1 year for pirfenidone and nintedanib, respectively [69].

2.2.3. Prevention and management of antifibrotic-related adverse events

A stepwise approach can be adopted to help patients prevent and manage AEVs associated with antifibrotics and continue treatment (Table 1). Real-world studies indicate that access to an ILD nurse can play a critical role in AE management and adherence to antifibrotics through continued patient education [32,33]. The goal is to provide patients with information and resources to help prevent the onset of AEVs and, if AEVs do arise, to implement effective strategies to mitigate the duration and severity of symptoms. It is important for patients to understand the progressive and fatal nature of the disease and the benefits of current treatment options. Education should begin early, ideally at the time of diagnosis, and continue along the illness trajectory as each patient’s experience will be different. Whenever feasible, patients should be enrolled in patient support groups.

If AE symptoms occur, dose reduction or temporary dose interruptions should be considered to maintain ongoing treatment with either pirfenidone or nintedanib [64,70,71]. In PASSPORT, a safety study of pirfenidone in European patients, dose modifications were frequent (39% of patients who had an AE associated with treatment), and patients who underwent dose modifications were less likely to discontinue treatment due to AEVs (20% vs. 31%) [72,73]. Similarly, in an Expanded Access Program with pirfenidone in US patients, almost half of patients who had dose modifications were able to return to the full dose [74]. Furthermore, analyses of the pirfenidone and nintedanib clinical trials indicate that efficacy is maintained at doses below the full recommended dose [36,37,42,75,76]. If AE symptoms persist or are severe, temporary treatment interruption can be used as a mitigating...
<table>
<thead>
<tr>
<th>AE type</th>
<th>Pirfenidone</th>
<th>Nintedanib</th>
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<tbody>
<tr>
<td>AE prevention</td>
<td>- Take pirfenidone with a substantial meal, specifically the full dose at the end of a meal, or spread out during a meal</td>
<td>- Take nintedanib with or at the end of a meal</td>
</tr>
<tr>
<td></td>
<td>- Titrate over a period of 4 weeks instead of 2 weeks</td>
<td>- Monitor liver chemistry (ALT, AST, bilirubin) before treatment and monthly during the first 6 months of treatment and then every 3 months thereafter</td>
</tr>
<tr>
<td></td>
<td>- Avoid or minimize direct and indirect exposure to sunlight or intense artificial light</td>
<td>- Monitor liver chemistry (ALT, AST, bilirubin) before treatment and monthly during the first 3 months of treatment and periodically thereafter (i.e. at each patient visit)</td>
</tr>
<tr>
<td></td>
<td>- Apply sunscreen (≥SPF-50, active against UVA/UVB) every 2 hours as needed</td>
<td>- Antidiarheal (loperamide, ≤8 tablets per day or ≤16 mg/day)*</td>
</tr>
<tr>
<td></td>
<td>- Wear protective clothing (e.g. hat, sunglasses, and gloves) even when driving or exposed to sun through windows</td>
<td>- Antiemetic therapy</td>
</tr>
<tr>
<td></td>
<td>- Avoid use of other medications associated with phototoxicity</td>
<td>- Adequate hydration</td>
</tr>
<tr>
<td></td>
<td>- Monitor liver chemistry (ALT, AST, bilirubin) before treatment and monthly during the first 6 months of treatment and then every 3 months thereafter</td>
<td>- For AST and ALT elevations (&gt;3 × ULN) occur, the dose may be reduced or interrupted until values return to normal. Once levels have returned to baseline values, re-introduce treatment at 100 mg BID and increase to recommended dose as tolerated</td>
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<thead>
<tr>
<th>AE treatment</th>
<th>Prokinetics and PPIs may help mitigate GI AEs</th>
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<tbody>
<tr>
<td></td>
<td>- Treat severe phototoxicity with steroids or silver sulfadiazine</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>- For mild to moderate photosensitivity or rash, reduce dose to 1 capsule TID for 7 days and re-escalate to the full dose</td>
</tr>
<tr>
<td></td>
<td>- If AST and ALT elevations (&gt;3 to ≤5 × ULN) occur without symptoms or hyperbilirubinemia, the dose may be reduced or interrupted until values return to normal. Once resolved, treatment may be re-escalated to the recommended dose as tolerated</td>
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<tr>
<td></td>
<td>- For diarrhea of 4–6 extra stools per day or IV fluids &lt;24 hours that continues ≥8 days, reduce dose to 100 mg BID</td>
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<tr>
<td></td>
<td>- If symptoms persist despite supportive care, dose reduction or interruption may be required. Treatment may be resumed at a reduced dose of 100 mg BID or at the full recommended dose</td>
</tr>
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<tr>
<th>Dose interruption</th>
<th>If AEs persist, temporarily discontinue treatment until symptoms resolve or become tolerable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- For rash persisting &gt;7 days despite dose reduction, discontinue treatment for 15 days followed by a slow re-escalation back to full dose as tolerated.</td>
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<tr>
<td></td>
<td>- For severe rash, discontinue until resolved and slowly re-escalate to the recommended dose as tolerated</td>
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<td></td>
<td>- If patients exhibit &gt;5 × ULN, permanently discontinue</td>
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<tr>
<td></td>
<td>- If AST and ALT elevations (&gt;3 to ≤5 × ULN) are accompanied by hyperbilirubinemia, permanently discontinue</td>
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<td></td>
<td>- For diarrhea of &gt;6 extra stools per day or IV fluids &gt;24 hours or hospitalization, interrupt therapy plus administer an antidiarheal until &lt;4 extra stools per day; discontinue if diarrhea recurs for ≥8 days</td>
</tr>
<tr>
<td></td>
<td>- If severe symptoms persist despite symptomatic treatment, discontinue treatment</td>
</tr>
</tbody>
</table>

| AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; GI, gastrointestinal; IV, intravenous; PPI, proton pump inhibitor; SPF, sun protection factor; TID, 3 times daily; ULN, upper limit of normal; UVA/UVB, ultraviolet A/B. |

* In patients who experience AEs associated with loperamide, natural antidiarrheals (e.g. diosmectite, gelatin tannate) could be considered.
strategy. Once symptoms have resolved, the patient’s dose should be slowly titrated back to the full dose or to the maximum tolerated dose. Slow dose titration at treatment initiation can be considered with either pirfenidone or nintedanib, particularly in patients with history of GI conditions.

### 2.3. Smoking cessation

Resources to assist in the cessation of smoking should be provided to patients who are smokers. These may include discussions, websites (American Lung Association [www.lung.org/stop-smoking/] and National Cancer Institute [www.smokefree.gov]), and referral for PR or counseling. At many transplant centers, in accordance with the 2014 International Society for Heart and Lung Transplantation (ISHLT) guidelines, tobacco addiction within the past 6 months is an absolute contraindication to lung transplant [77]. Finally, pharmacokinetics studies have revealed that both antifibrotics clear more rapidly in smokers vs. nonsmokers, resulting in lower exposure to the medications [51,54]. Thus, cigarette smoking should be avoided to prevent reduced exposure to antifibrotics.

### 2.4. Management of gastroesophageal reflux disease and other comorbidities

GERD is highly prevalent in patients with IPF, but only 25–50% of patients are symptomatic [78,79]. Chronic microaspiration secondary to GERD may play a role in IPF pathogenesis and progression and may trigger acute exacerbations [80–82]. Antacid treatment has received a conditional recommendation in the 2015 update to the ATS/ERS/JRS/ALAT treatment guidelines, but with very low confidence in estimates of effect [18].

A post hoc analysis of data from ASCEND and CAPACITY found that patients receiving antacid therapy (histamine H₂ blockers and/or proton pump inhibitors [PPIs]) and pirfenidone had similar disease progression (absolute decline in % predicted FVC ≥10%, decline in 6MWD ≥50 m, or death) and all-cause mortality compared with those receiving pirfenidone without antacids; a similar analysis of the INPULSIS trials found no additional benefit of antacids in combination with nintedanib [83,84]. An analysis of the placebo groups of 3 IPF Clinical Research Network clinical trials showed that patients receiving antacids had less decline in FVC (mL) and fewer acute exacerbations at 30 weeks than those without antacids [85]. A study in patients with IPF from 2 US academic centers found that antacids (88% of patients received PPIs) were associated with longer survival and decreased radiologic pulmonary fibrosis [80].

A recent meta-analysis reported that pharmacologic treatment of GERD is associated with a reduction in IPF-related mortality but not overall mortality [86]. However, the beneficial effects of antacids on mortality observed in patients with IPF in observational studies may be due to immortal time bias because in several studies, ≥12 months’ exposure to antacids was required for inclusion in survival analysis; thus, patients had a 12-month ‘immortal’ time period [86]. A separate meta-analysis found beneficial effects for antacids in 4 studies that were affected by immortal time bias but no beneficial effects in 5 studies that avoided immortal time bias [87].

In summary, data suggest a beneficial role for antacids, PPIs in particular, in slowing disease progression and reducing mortality in patients with IPF, but the findings are inconsistent, highlighting a need for RCTs to clarify the role of antacids in IPF [85]. A recently published phase 2 trial of omeprazole in 45 patients with IPF, which included patients who were receiving stable antifibrotics (≥4 weeks before enrollment), showed a reduction in cough in omeprazole-treated patients compared with placebo, but larger studies are needed to determine the role of PPIs in other clinically relevant outcomes [88]. The phase 2 WRAP-IPF trial of laparoscopic antireflux surgery in patients with IPF demonstrated the safety of the procedure, but additional data are needed to determine if a clear benefit exists [89]. In addition to antacids, dietary changes, including the avoidance of heavy or fatty foods and the avoidance of caffeine and alcohol ≤3 hours before bedtime, and elevating the head of the bed 4–6 inches may be useful GERD management strategies in patients with IPF [85].

Several other key comorbidities require monitoring and management in patients with IPF. Patients with IPF should be evaluated for obstructive sleep apnea (OSA) because OSA is highly prevalent in the IPF population [90]. If OSA is present, continuous positive airway pressure therapy may improve night-time oxygenation [91]. Coexisting chronic obstructive pulmonary disease (COPD) and emphysema in patients with IPF should be evaluated with pulmonary function tests and high-resolution computed tomography (HRCT), respectively; although evidence for treatments is lacking, inhaled bronchodilators could be considered if any of these conditions is present [92]. Pulmonary hypertension (PH) is common in patients with more-advanced IPF and increases mortality risk; however, to date no therapies have been approved to treat PH in the IPF population [1,18,93,94]. A recent trial of nintedanib with concomitant sildenafil in patients with advanced IPF (diffusing capacity for carbon monoxide [DLCO] ≤35%) did not meet the primary endpoint of change in St. George’s Respiratory Questionnaire over 12 weeks, and a trial is ongoing to evaluate pirfenidone with concomitant sildenafil in patients with advanced IPF (DLCO ≤40%) and risk of PH [95,96]. Lung cancer is more prevalent in patients with IPF than in the general population, but treatment options are lacking [97,98]. Whether antifibrotics can be combined with chemotherapy or radiation therapy remains an open question, and patients with more-advanced IPF may not be eligible for surgical resection, radiation therapy, or other treatments that can impair lung function [99,100].

### 2.5. Transplant referral

The 2011 ATS/ERS/JRS/ALAT and 2014 ISHLT treatment guidelines strongly recommend early lung transplant referral for patients with IPF, so modifiable contraindications (e.g. obesity and deconditioning) can be managed accordingly despite the unpredictability of disease progression [1,77]. Patients must be appropriately educated, with discussions starting at the time of diagnosis, about appropriate expectations, the realities of life posttransplant, and managing contraindications. Palliative care and opioids are not a barrier for transplant in most centers and should not be delayed if needed [101]. Similarly, prior use of antifibrotics has not been
observed to compromise wound healing in patients undergoing lung transplant; therefore, patients who are listed for transplant can receive antifibrotics [102]. Finally, when referred for transplant, patients should also be referred for PR and encouraged to exercise regularly while awaiting a transplant evaluation to maintain as much physical function as possible.

The estimated 5-year survival rates after lung transplant for IPF are 50–56% [103]. One single-center study identified a 75% reduced risk of death at 5 years in 46 patients with IPF who had lung transplants [104]. Many patients with IPF (14–67%) die after listing and before receiving a lung transplant due to shortage of donor organs [103].

2.6. Psychosocial support

Patients with IPF should be assessed for the presence of anxiety and depression, as these conditions frequently occur during IPF progression [19,20]. Offering counseling for both patients and caregivers, providing connections to individual or group support networks, and promoting overall well-being are all important when addressing a patient’s psychological distress throughout their illness. These means of support are optimally addressed by a multidisciplinary team. Medications can be prescribed as necessary, although RCTs in this patient population are lacking: such as methylphenidate (to improve energy and reduce fatigue); serotonin and norepinephrine reuptake inhibitors (for anxiety and depression); serotonin selective reuptake inhibitors (for depression); less commonly used tricyclic antidepressants (for depression and sleep disturbances); bupropion (for depression); mirtazapine (for depression, to improve appetite, sleep, and potentially cough), which should be avoided in combination with CYP1A2 inhibitors and pirfenidone; benzodiazepines (use cautiously for anxiety or sleep); and buspirone (for sleep) [51,105].

In addition to reducing the psychological burden of IPF, participation in patient support groups may improve adherence to antifibrotic therapy and other treatments [32]. Online support groups, such as the Pulmonary Fibrosis Foundation website (www.pulmonaryfibrosis.org), may benefit patients who have limited mobility or live in rural areas. Patients and caregivers have also expressed the need for more community-based medical support, including at-home disease monitoring with mechanisms to identify decline and to respond appropriately before the next clinic visit [28]. This can be facilitated through community support systems and working collaboratively to monitor and support patients at home [106,107].

2.7. Updated vaccinations

Respiratory infections may trigger acute exacerbations of IPF [108]. Therefore, the vaccination status of patients should be assessed. No specific studies regarding vaccinations in patients with IPF have been performed. The specific vaccination policies and recommendations vary from country to country regarding schedules for the annual influenza vaccination, 23-valent pneumococcal polysaccharide vaccine, and 13-valent pneumococcal vaccine based on a patient’s age and medical history [109,110]. Clinicians should consult local guidelines.

2.8. Regular exercise/pulmonary rehabilitation

Per the 2011 ATS/ERS/JRS/ALAT treatment guidelines, PR should be used in the majority of patients with IPF and encouraged immediately after diagnosis before disease progression reduces their functional status [1]. The goals of PR are to reduce dyspnea, depression, anxiety, and fatigue, leading to the benefits of increased exercise capacity, QoL, and cognitive function [111]. Several RCTs in patients with IPF or ILD have assessed the benefits of PR. One study showed that 6MWD was significantly improved immediately following PR (+36 m, P = 0.0004) [112]. Increased endurance and improved dyspnea during exertion were reported when supplementary oxygen was provided to patients with IPF without resting hypoxemia [113]. A meta-analysis in patients with IPF found that PR had short-term benefits in exercise capacity and health-related QoL but no detectable effects at long-term follow-up (6–12 months) [114]. In contrast, a recent RCT in 60 patients with ILD showed exercise and health benefits of a 6-month PR program persisted for an additional 6 months after completion [115]. Continued PR is important for improving exercise capacity, particularly in patients waiting to receive a lung transplant.

Prior to initiating PR, the patient’s safety should be ensured [116]. An evaluation of baseline lung function and comorbidities should be conducted, and before exercise initiation, a patient’s supplemental oxygen supply should be assessed to confirm that it is adequate. No specific guidelines for PR exist for IPF. Existing education and exercise programs for patients with COPD may not be optimal for those with IPF [24]. Patients must be well rested prior to exercise. Desaturation should be expected, so a supply of supplemental oxygen sufficient to maintain peripheral capillary oxygen saturation (SaO2 ≥88%) should be ensured. Before and after enrollment of patients in a PR program, encouraging patients to remain active by performing an aerobic exercise matching their interest and capability (e.g. walking, swimming, and cycling) is advised; however, it is important to assess the need for supplemental oxygen during exertion.

2.9. Supplemental oxygen therapy

The 2011 ATS/ERS/JRS/ALAT treatment guidelines strongly recommend that patients with IPF with clinically significant resting hypoxemia should be treated with long-term oxygen therapy [1]. However, no data on long-term oxygen therapy are available in IPF; indirect evidence from COPD has demonstrated a survival benefit, and limited evidence has shown that oxygen therapy improves exercise capacity in patients with resting hypoxemia and walk distance in patients with exertional hypoxemia [1]. Recently, the prospective, open-label, crossover-controlled AmbOx trial showed a benefit with supplemental oxygen in health-related QoL measures in patients with ILD [117]. Therefore, prescribing supplemental oxygen and titrating to maintain SaO2 at ≥92–95% at rest and ≥88% during exertion is recommended. This value should be rechecked every 60–90 days (or more frequently via self-monitoring), adjusting the supplemental oxygen as required.

Patients prescribed supplemental oxygen frequently lack adequate education about the effective use and availability of appropriate, ambulatory equipment [118]. The involvement
of multiple stakeholders, including patient organizations, professional organizations, and industry partners, is needed to improve oxygen access and use in the IPF population. Heterogeneity exists in supplemental oxygen use in clinical practice due to differences in policies around the world. Clinicians and ILD nurses should engage in patient education to ensure both frequent monitoring of SaO\textsubscript{2} and the availability of sufficient supply to meet the oxygen needs of each individual patient.

Patient-reported experiences of air travel with supplemental oxygen indicate that the experience can be challenging but manageable with preparation [119]. In preparation for travel, a high-altitude simulation test should be performed to assess the need for in-flight oxygen in patients who may not be fit to fly and in those with severe restrictive disease (vital capacity <1 L), advanced COPD (forced expiratory volume in 1 second <30%) especially with resting hypoxemia or hypercapnia, or pulmonary hypertension (New York Heart Association functional class III or IV) [120]. Patients deemed to require oxygen should be instructed how to monitor and adjust the oxygen flow-rate to ensure that SaO\textsubscript{2} is ≥90% in flight [120,121]. The patient should be advised to arrange oxygen supply logistics well in advance of the specific flight, inquiring about specific supplemental oxygen policies with the airline and arranging for local oxygen supply at their destinations [120].

### 2.10. Symptom management and palliative care

An important component of symptom management is educating patients about common symptoms that arise if disease progression occurs and how they can best monitor their symptoms. Patients are more likely to engage in self-monitoring if they understand both why symptoms occur and what their role is managing them. Key symptoms to discuss include breathlessness, fatigue, cough, anxiety, and depression, plus it is important to ensure that patients understand their oxygen needs.

The goals of early integration of palliative care for patients with IPF are to (1) establish regular monitoring and optimize symptom management; (2) introduce appropriate medications, such as opioids, with close monitoring and titration of dose; (3) assist patients in understanding the trajectory of the illness; (4) engage in discussions about goals of care, including long-term goals and advance care planning; (5) facilitate transitions from ambulatory and/or hospital-based care to home-based or hospice care as appropriate; (6) discuss end-of-life care expectations with the patient and family members and to mobilize resources close to home to support end-of-life care; (7) arrange transfer to alternate locations if optimal care provision is not possible in the patient’s home; and (8) ultimately optimize QoL as much as possible [22].

Physicians should consider implementing a palliative care approach at the onset of symptoms of progressive respiratory disease, concurrent with curative or restorative care in an individualized manner [105–107]. Preliminary evidence suggests a benefit of initiating palliative care early after an IPF diagnosis because the disease is a progressive, life-limiting illness. Suggested criteria for referral to palliative care include a score of 4 or 5 on the Medical Research Council dyspnea scale, the need for supplemental oxygen at rest or with exertion, increasing supportive care needs, and/or declining functional status (Palliative Performance Scale ≤50%) [105,122].

To provide effective palliative care, symptom management needs to be patient-centered and individualized [123]. A systematic assessment of symptoms and patient needs must lead to the prioritization of integrated symptom management and an understanding of the pathophysiology causing the symptoms. Specific instructions for each medication prescription—dosing, timing, and route of administration, as well as education about monitoring and managing medication AEs—should be provided to the patient according to the patient’s age and other comorbidities. Drugs that are ineffective or unnecessary for an individual patient should be discontinued to limit polypharmacy. Changes in medications or doses should be implemented one at a time, with frequent reassessments to monitor the effect. Encouraging patients to keep a diary of symptoms, medication effectiveness, and AEs is also important.

For worsening dyspnea, there is no satisfactory treatment, but several options can be explored [105]. PR can instruct patients in techniques that may help manage dyspnea, and supplemental oxygen use should be evaluated. Medications such as low-dose opioids, methotrimeprazine, anxiolytics, mucolytics, and occasionally antibiotics can help some patients, but direct evidence of efficacy in patients with IPF is lacking. For initial dyspnea management, we suggest immediate-release morphine 2.5 mg (or 5 mg in patients with high body mass index (BMI)) orally (PO) every 4 hours (q4h) while awake. Hydromorphone 0.5 mg (or 1 mg in patients with high BMI) q4h while awake may be considered if morphine should be avoided [106,107]. The opioid dose should be titrated to the lowest effective dose that decreases the sensation of dyspnea and minimizes AEs. After the appropriate dose has been determined, initiation of a controlled-release opioid could be considered for ease of administration. If a patient is nearing the end of life, then immediate-release formulations are recommended to allow more rapid dose titration depending on the patient’s needs (titration after ≥24 hours at a specific dose). In addition, it may become necessary to replace orally administered opioids with equipotent parenteral opioids (subcutaneous/intravenous) when rapid symptom relief is needed or if patients can no longer take medications orally. Alternative therapies (e.g., relaxation therapy, acupuncture, imagery) and a fan blowing cool air across the face may help some patients control dyspnea [124].

For worsening cough, opioids are commonly prescribed [125]. Hydrocodone cough syrup is not more effective than other opioids, so it should not be added to other opioid prescriptions. Systematic assessments should be performed to identify and treat other etiologies of cough, such as sinusitis, GERD, and respiratory infections. Treatment could be initiated with a low dose of opioid with regular reassessment and titration as needed. Inhaled corticosteroids or long-acting beta-agonists can be tried if concomitant asthma or COPD is present.

Common side effects from opioids include drowsiness and nausea, both of which are transient, typically resolving in 4–6 days; constipation, which typically worsens with dose escalation; confusion and urinary retention, which are more frequent in the elderly with comorbidities and polypharmacy.
For opioid-induced nausea, metoclopramide 5 or 10 mg PO or haloperidol 0.5 or 1 mg PO q4h as needed can be considered. Patients should be monitored for the development of opioid-induced constipation. A bowel routine should be initiated concurrently with the initiation and titration of opioids. The following regimens are suggested: senna glycoside 8.6 mg (2 tablets) PO at bedtime, increased as needed (maximum 8 tablets/day), or the total dose may be divided into BID dosing. Alternatively, polyethylene glycol 3350 at 8.5 g/day (one-half capful or one-half packet) or 17 g/day (1 capful, 1 packet, or ≈1 heaping tablespoon) dissolved in 250 mL of liquid may be used and increased to BID if needed to ensure soft, easy-to-pass stool every 1–2 days.

### 2.11. IPF exacerbations

Acute worsening or the development of dyspnea, typically occurring over the course of <30 days, may be an acute exacerbation. IPF exacerbations are also characterized by new bilateral ground glass opacities on HRCT, not fully explained by hydrostatic pulmonary edema (heart failure and fluid overload) [9]. Alternative diagnoses should be considered in a patient with acute worsening dyspnea. In a patient with a history of smoking, emphysema, or chronic bronchitis, a COPD exacerbation should be considered if imaging studies do not show evidence of IPF exacerbation, because IPF can mask COPD in pulmonary function tests, due to the increased elastic recoil of the lungs secondary to fibrosis, resulting in increased airflows [9,126].

A chest x-ray can be used as an initial diagnostic test to eliminate differential diagnoses, such as atelectasis, pneumonia, pneumothorax, or congestive heart failure. If a patient’s chest x-ray is unchanged, a computed tomography pulmonary angiogram (CTPA) should be considered to determine whether pulmonary embolism is present, provided renal function allows administration of the intravenous contrast required for CTPA [9]. The presence of ground glass opacities on CTPA or on chest HRCT would support the diagnosis of an IPF exacerbation.

IPF exacerbations are relatively uncommon (annual risk of 5–15%), but have a very high short-term mortality (=50%); therefore, the prevention, prompt diagnosis, and management of IPF exacerbations are all very important [127]. Commonly reported risk factors or triggers of IPF exacerbations include more-advanced disease (low FVC or low DLco), infections, GERD with microaspiration, air pollution, bronchoscopy, and surgical procedures [9,108,128]. High pressures during mechanical ventilation and high oxygen use during anesthesia have been proposed as possible causes of alveolar injury leading to an IPF exacerbation [9]. Therefore, if mechanical ventilation or anesthesia is required, judicious use of oxygen and low pressures is recommended. Other proposed preventive measures for IPF exacerbations are antacids, antifibrotics (to slow the IPF progression to advanced stages), and vaccinations against influenza and pneumococcus [127].

The management of IPF exacerbations typically includes supportive treatment, supplemental oxygen, and, despite very limited evidence, systemic corticosteroids [1,94]. The PANTHER-IPF trial found increased risk of mortality in patients receiving prednisone, azathioprine, and N-acetylcysteine, and a single-center nonrandomized study of 24 patients with IPF who experienced acute exacerbations found lower survival in those who had previously received immunosuppressive therapy compared with those who had not [129,130]. Additional data are needed to evaluate the safety and efficacy of corticosteroids and immunosuppressive therapy in patients who experience an IPF exacerbation [131].

We cautiously suggest initiating intravenous high-dose corticosteroids (intravenous methylprednisolone 125–500 mg every 12 hours) for 3 days followed by oral prednisone (50–100 mg/day) with a plan of tapering to discontinuation over 2–4 weeks. Oral methylprednisolone or dexamethasone might be considered instead of prednisone, due to their lack of mineralocorticoid effect, in patients with congestive heart failure, systemic hypertension, or fluid retention (e.g. leg edema).

Small nonrandomized studies have reported associations between other treatments and improved survival in patients with IPF exacerbations; these treatments include preventative antacids, cyclophosphamide, cyclosporine, tacrolimus, and combined rituximab with plasma exchange and intravenous immunoglobulin [9]. Initiation of empiric broad spectrum antibiotics during IPF exacerbations is also routinely recommended by experts because bacterial infections are frequent triggers of exacerbations and they are difficult to exclude in critically ill patients [132]. Whenever possible, sputum culture and sensitivity should be ordered to guide antimicrobial therapy, especially in patients with suspected bacterial lower respiratory tract infection. Routine bronchoscopy in the clinical assessment of acute respiratory failure in patients with ILD is not indicated because diagnostic yield is low (13%), the procedure is high risk in these patients, and it does not change management approaches or in-hospital mortality [133]. Supplemental oxygen, especially high-flow oxygen by nasal cannula or noninvasive ventilation, are recommended in patients with IPF exacerbations to manage their dyspnea and hypoxemia [134]. Intubation and mechanical ventilation are not recommended by the 2011 ATS/ERS/JRS/ALAT treatment guidelines, based on the high rates of in-hospital mortality (90%) in these patients [1].

Patients with IPF should self-monitor for increased breathlessness or fatigue, new or worsening cough, anxiety or depression, and SaO2. A home pulse oximeter is an objective method that patients can use to assess whether their worsening dyspnea is due to hypoxemia, to determine the proper flow-rate of oxygen at rest and during exertion, and to detect any increase in oxygen requirements. If a patient notices any changes in symptoms, they should inform their physician or home care nurse (if applicable) because the change could indicate an acute exacerbation of IPF. Patients should seek immediate medical attention for any sudden worsening of dyspnea or increase in oxygen needs.

### 2.12. Nutrition

Both IPF itself and GI-related AEs associated with antifibrotic therapy can affect patients’ nutritional status, and their BMI should be considered in many management decisions [63–65,135,136]. The needs for nutritional support to optimize calories with protein and fat content varies in individual
patients; both patients and their caregivers should be included in discussions related to appropriate nutrition [136]. Dietary changes may be needed to address obesity, which is a contraindication for lung transplant, or to control GERD symptoms. Eating full meals can also help in the management of gastrointestinal AEs associated with antifibrotic therapy, and dose reductions or interruptions should be considered in patients with nausea or reduced appetite, with the knowledge that pirfenidone and nintedanib can maintain their efficacy at doses less than recommended [51,54,64,71]. In patients with progressive weight loss due to nausea and reduced appetite despite antifibrotic dose reductions and the use of PPIs and prokinetics (e.g. domperidone or metoclopramide), consider nutritional supplements (e.g. Ensure, Boost), a possible trial of oral cannabis where medical cannabis is permitted, and referral to a dietician.

2.13. End-of-life preparations

End-of-life care should be discussed as early as possible to ensure that patients and their families have the support they need to help the patient live as fully and comfortably as possible [23,105]. This care can be provided in multiple settings, including a hospital, hospice facility, or the patient’s home. Documentation of a patient’s goals of care should include specific information on their values, wishes, and beliefs; their desired level of medical interventions; the preferred site of care delivery; and their life-support preferences. Documentation should provide a clear understanding of a patient’s goals of care and should be communicated to the patient’s family, loved ones, and physicians. These are dynamic discussions that should begin early in the illness and continue throughout the course of the disease, especially at transition points, such as significant worsening of pulmonary status or a decline in the patient’s functional abilities. An interdisciplinary approach to palliative and end-of-life care is paramount and should include the physicians, nurses, and social worker and could also include a spiritual health practitioner, volunteers, and counselors.

3. Conclusion

In summary, managing the care of a patient with IPF requires a multifaceted approach that combines disease-specific strategies for slowing disease progression and extending patient survival, simultaneously with palliative care to improve symptom management and QoL. This approach includes the following components: early initiation of antifibrotic therapy, assessment of physical and psychological needs, early integrated symptom management as part of a palliative care approach, patient and caregiver education and support, open and often difficult communications, shared decision-making to facilitate time-sensitive decisions and advance care planning, and ongoing reassessment of the patient’s goals of care as the disease progresses. A patient’s preferences and comorbidities should be considered prior to choosing antifibrotics, and TEAEs can be mitigated through education and dose modifications. In addition to antifibrotics and integrated palliative care, PR, supplemental oxygen therapy, lung transplant evaluation and referral, and advance care planning should be established early in the disease course. Throughout IPF progression, oxygen requirements and the management of dyspnea and cough need to be continually monitored. The use of opioids, antifibrotics, and a palliative care approach are not barriers for lung transplant. Frequent communications should occur with the patient and family to ensure their understanding of the disease, treatment goals, and specific patient goals and plans, particularly around end-of-life care. Finally, the importance of promoting collaborative practice between interdisciplinary team members needs to be highlighted. Use of a multifaceted approach that targets all aspects of IPF management throughout the course of the illness will ensure that patients receive the most appropriate, comprehensive, and patient-centered care possible.

4. Expert opinion

IPF management is complex: a multifaceted approach to management that includes antifibrotic therapy, consideration of referral for lung transplant, treatment of comorbidities, palliative care for symptom management, nutritional assessment, psychosocial support for patients, and caregiver support may improve QoL in patients with IPF. As new clinical trials are conducted to improve therapeutic options for patients with IPF and IPF-associated comorbidities, there is need for research to identify opportunities for improving and standardizing comprehensive care delivery in this patient population. A key challenge to achieving the goal of improved comprehensive care is limited resources – both time and allied healthcare providers – available to physicians who manage patients with IPF within and outside of specialized centers. Here, we highlight the need for multidisciplinary care to effectively manage this complex illness and to optimize patient survival and QoL. We hypothesize that the emergence of new pharmacological treatments and active research across the fields of pulmonology, nursing, palliative care, and lung transplantation will continue to lead to robust improvements in survival and QoL in patients with IPF over the next decade.

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Papers of special note have been highlighted as either of interest (i) or of considerable interest (++) to readers.


- The new international guidelines on the diagnosis of IPF updated the 2011 diagnostic guidelines


- The 2011 international guidelines on the treatment of IPF were updated in 2015 after the approval of antifibrotic therapies


- This retrospective study found improved outcomes in patients with IPF who received multidisciplinary care from a team including an ILD expert pulmonologist, a palliative care pulmonologist, a nurse, a respiratory therapist, a physiotherapist, and a dietician.


- This patient survey highlighted the needs of patients and their families for additional education about IPF and how to make lifestyle changes that improve quality of life.


This open-label extension study of 1058 patients with IPF who completed the phase 3 ASCEND or CAPACITY trials supported the long-term safety of pirfenidone.


This open-label extension study of 734 patients with IPF who completed the phase 3 INPULSIS trials supported the long-term safety and efficacy of nintedanib.


These post hoc analyses of data from an open-label long-term extension study found that pirfenidone’s efficacy with regard to slowing lung function decline was maintained over long-term treatment.


Esbrit (pirfenidone) [monograph]. Missisaua, ON, Canada: F. Hoffmann-La Roche Ltd.; 2018.


Ofev (nintedanib) [monograph]. Burlington, ON, Canada: Boehringer Ingelheim (Canada) Ltd.


Ofev (nintedanib) capsules, for oral use [summary of product characteristics]. Ingelheim am Rhein, Germany: Boehringer Ingelheim International GmbH; 2018.


This post hoc analysis of phase 3 trials data found that patients receiving pirfenidone who underwent dose reductions and interruptions maintained a relatively high dose of treatment, without compromising the treatment effect.


• This ongoing phase 2b trial is investigating the efficacy of pirfenidone plus sildenafil vs. pirfenidone plus placebo in patients with IPF and risk of PH.


• In this randomized controlled trial of 60 patients with ILD, a 6-month pulmonary rehabilitation program was associated with benefits in exercise capacity and health status 6 months after the program ended.


• This open-label, mixed-method, crossover trial found that ambulatory oxygen improved quality of life in patients with ILD.


