

Recent Advances in Treatment of Idiopathic Pulmonary Fibrosis

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Introduction

- Definition
 - IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with histological and/or radiologic pattern of UIP

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ATS/ERS/JRS/ALAT International IPF guidelines 2011

- Diagnosis
 - Exclusion of other known causes of ILD
 - environmental exposure, CTD, drug toxicity
 - UIP pattern on HRCT (Pt not subjected to Lung Biopsy)
 - Specific combinations of HRCT and Surgical Lung Biopsy in Patients subjected to Lung Biopsy

Note: Multi Disciplinary Discussion (Pulmonary, Radiology & Pathology) has been shown to improve accuracy of diagnosis

Am J Respir Crit Care Med 2004;170:904–910

COMBINATION OF HRCT AND SURGICAL LUNG BIOPSY FOR THE DIAGNOSIS OF IPF

HRCT Pattern	Surgical Lung Biopsy Pattern (When Performed)	Diagnosis of IPF?
UIP	UIP / Probable UIP/ Possible UIP/ Nonclassifiable fibrosis Not UIP	YES No
Possible UIP	UIP /Probable UIP Possible UIP/ Nonclassifiable fibrosis Not UIP	YES Probable No
Inconsistent with UIP	UIP / Probable UIP/ Possible UIP / Nonclassifiable fibrosis Not UIP	Possible No

NATURAL HISTORY OF IPF

- Progressive decline in subjective and objective pulmonary function until eventual death from respiratory failure or complicating comorbidity
- a median survival time from 2 to 3 years from the time of diagnosis
- Some patients remain stable while others have an accelerated decline, some patients may experience episodes of acute respiratory worsening.

NATURAL HISTORY OF IPF

RISK OF MORTALITY IN IPF

- **Baseline factors**

- Level of dyspnea
- DLCO < 40% predicted
- Desaturation < 88% during 6MWT
- Extent of honeycombing on HRCT
- Pulmonary hypertension

- **Longitudinal factors**

- Increase in level of dyspnea
- Decrease in FVC by > 10% absolute value
- Decrease in DLCO by > 15% absolute value
- Worsening of fibrosis on HRCT

TREATMENT

- Pharmacological Therapies
- Non-pharmacologic Therapies
 - LTOT
 - Lung Transplantation
 - Mechanical ventilation
 - Pulmonary Rehabilitation

TREATMENT

- Treatment of complications and comorbid conditions
 - Acute Exacerbation
 - Pulmonary hypertension
 - GERD
 - Obesity
 - Emphysema
 - OSA

TREATMENT

- Palliative Care
 - Focuses on reducing symptoms and providing comfort to patients, rather than treating patients' disease
 - Advanced directives and end-of-life care

Pharmacological Therapies

ATS GRADE criteria

Quality of Evidence	Study Design	Lower If:	Higher If:
High	Randomized controlled trial	<ul style="list-style-type: none"> ● Limitation in study quality 	<ul style="list-style-type: none"> ● Strong association, no plausible confounders
Moderate	Downgraded randomized controlled trial or upgraded observational study	<ul style="list-style-type: none"> ● Indirectness ● Important inconsistency 	<ul style="list-style-type: none"> ● Evidence of a dose-response gradient ● Plausible confounders would have reduced the effect
Low	Well done observational study with control groups	<ul style="list-style-type: none"> ● Sparse or imprecise data 	
Very low	Any other evidence (e.g., case reports, case series)	<ul style="list-style-type: none"> ● High probability of publication bias 	

Am J Respir Crit Care Med 2006;174:605–614.

ATS GRADE criteria

Quality of the Evidence (GRADE)	The quality of the evidence is a judgment about the extent to which we can be confident that the estimates of effect are correct. These judgments are made using the GRADE system, and are provided for each outcome. The judgments are based on the type of study design (randomized trials versus observational studies), the risk of bias, the consistency of the results across studies, and the precision of the overall estimate across studies. For each outcome, the quality of the evidence is rated as high, moderate, low, or very low using the following definitions:
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (⊕⊕⊕○)	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low (⊕⊕○○)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low (⊕○○○)	We are very uncertain about the estimate. (For more information about the GRADE system, see: www.gradeworkinggroup.org)

Am J Respir Crit Care Med 2006;174:605–614.

Corticosteroid Monotherapy

- No randomized controlled trials have been conducted with corticosteroid monotherapy

Cochrane Database Syst Rev 2003; (3):CD003134.

Cochrane Database Syst Rev 2003;(3):CD002880.

- Uncontrolled studies have reported no survival benefits

Thorax 1980;35:593–599.

Am J Respir Crit Care Med 1998;157:1063–1072.

Am J Med 2001;110:278–282.

- There is substantial morbidity from long-term corticosteroid therapy

Am J Respir Crit Care Med 1998;157:1063–1072

- Controlled data have found no survival benefit

Am J Respir Crit Care Med 2000;161:1172–1178.

- ATS/ERS/JRS/ALAT Recommendation
 - Patients with IPF should not be treated with corticosteroid mono therapy(strong recommendation, very low-quality evidence)

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Colchicine

- Colchicine has been shown to inhibit fibroblast proliferation and collagen synthesis in vitro.

Lung 1997;175:41–51.

- Several prospective clinical trials have compared colchicine to various treatment regimens showing no difference in clinical outcomes.

Chest 1998;114:507–512.

Am J Respir Crit Care Med 1998;158:220–225

Eur Respir J 2006;28:496–504.

Eur Rev Med Pharmacol Sci 2008;12:105–111.

- ATS/ERS/JRS/ALAT Recommendation
 - IPF patient should not be treated with colchicine(strong recommendation, very low-quality evidence)

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Cyclosporin A

- Early reports in small, uncontrolled groups of patients with IPF suggested a possible benefit

A. Respir Med 1989;83:277–279.

Thorax 1991;46:592–595

- A retrospective study of 10 patients with IPF showed no apparent benefit.

Intern Med 2005;44:1144–1150

- Two studies of small groups of post-lung transplant(single lung) patients with IPF treated with cyclosporine containing immunosuppressive regimens have shown progression of disease in the native lung.

Respiration 2008;76:139–145.

Chest 2002;121:2072–2076.

- ATS/ERS/JRS/ALAT Recommendation

- IPF patient should not be treated with cyclosporine A

(strong recommendation, very low-quality evidence)

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Corticosteroid and Immunomodulator

- Corticosteroid+Azathioprine

v/s

Corticosteroid

- A small ,prospective ,double-blind, randomized, placebo-controlled clinical trial showed a trend toward a survival benefit with combination therapy.

Am Rev Respir Dis 1991;144:291–296

- Corticosteroid+ Cyclophosphamide

v/s

No Therapy

Study done in 164 patients and found no survival difference

Chest 2004;125:2169–2174

- Corticosteroid+ Cyclophosphamide

v/s

Corticosteroid

Study done in 82 patients and found survival benefit with combination therapy

Respir Med 2006;100:340–347.

- ATS/ERS/JRS/ALAT Recommendation
 - IPF patient should not be treated with combination corticosteroid and immunomodulator therapy
- (strong recommendation, low-quality evidence)

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Corticosteroid, Azathioprine and Acetylcysteine

- Acetylcysteine

- NAC, a derivative of the cysteine amino acid, has been demonstrated to augment the synthesis of anti-oxidant glutathione (GSH).

Eur Respir J., 1994, 7, 431–436.

N. Engl. J. Med. 353:2285-2287 (2005).

- GSH plays an important role as a defense mechanism against intra and extracellular oxidative stress.

- There is four-fold decrease in the levels of GSH in patients with IPF.

Am J Respir Crit Care Med 1997; 156: 1897-1901

- **V. M. Felton et al**, investigated the effects of *N-acetylcysteine* on TGF- β 1-induced epithelial-mesenchymal transition (EMT) in a rat epithelial cell line (RLE-6TN) and in primary rat alveolar epithelial cells (AEC) and found that NAC prevents EMT in AEC in vitro, at least in part through replenishment of intracellular GSH stores and limitation of TGF- β 1-induced intracellular ROS generation.

- ***Dorota M. et al*** ,evaluate the effect of NAC on interleukin-8 (IL-8) and matrix metalloproteinase-9 (MMP-9) production as well as intercellular cell adhesion molecule-1(ICAM-1) expression by BAL cells from interstitial lung diseases

Pharmacological Reports,2010,62, 131-138

- Cultured unstimulated BAL cells were treated with increasing doses of NAC (1–30 mM)
- NAC exerted a dose dependent inhibitory effect on IL-8 and MMP-9 release and ICAM- expression by BAL macrophages and lymphocytes from patients with IPF and sarcoidosis
- NAC inhibits production of factors playing a key role in the etiopathogenesis of interstitial lung diseases

- ***Therefore it is rational therapeutic strategy in IPF is to augment GSH levels on the respiratory epithelial surface to enhance the antioxidant defenses and to control fibroblast proliferation***

The IFIGENIA Trial

(Idiopathic pulmonary Fibrosis International Group Exploring NAC I Annual)

- A randomized controlled trial comparing the effect of high-dose acetylcysteine versus placebo in patients receiving prednisone plus azathioprine has been completed.
- 600 mg tid NAC (effervescent tablets) + standard therapy (azathioprine 2 mg/kg/day + prednisolone 0.5 mg/kg/day) ,
- multinational, double-blind, randomized, placebo-controlled, parallel-group trial.
- 155 patients, 12 months
- Endpoints: Absolute changes in vital capacity and DLco between baseline and at 12 month

N Engl J Med 2005; 353:2229-2242

- The 12-month declines in vital capacity and diffusing capacity were significantly less in the acetylcysteine-containing arm
- **Vital capacity:** 0.18 liter difference; 95% confidence interval [CI], 0.03–0.32; $P=0.02$;
- **Diffusion capacity:** 0.75 mmol/min/kilopascal difference; 95% CI, 0.27–1.23; $P=0.003$.

- There was no observed difference in mortality or other secondary endpoints including dyspnea, quality of life, exercise physiology, or radiographic appearance.
- There was no observed difference in adverse events occurring in NAC and placebo group

- Bone marrow toxicity occurred in 4 % of patients receiving acetylcysteine (3 of 80) and in 13 % of those receiving placebo (10 of 75) ($P=0.03$).
- There was a significant reduction in bone marrow toxicity in the NAC group.
- This suggests that NAC may confer protection from the toxic side effects of azathioprine.

- Limitations
 - substantial drop-out (approximately 30%)
 - the lack of a true “no treatment” arm

- ATS/ERS/JRS/ALAT Recommendation
 - The majority of IPF patient should not be treated with combination *corticosteroid, azathioprine and acetylcysteine* therapy but it may be reasonable choice in a minority

(weak recommendation, low-quality evidence)

Remark: This treatment may be appropriate in patients who are willing to accept possible adverse consequences even if expected benefits are small

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Acetylcystein Monotherapy

- ***Tomioaka H et al*** done a pilot study of aerosolized N-acetylcysteine on 30 IPF patients and found significant improvement in the extent of ground glass on computed tomography and reduction in KL-6 levels

Respirology 2005;10:449–455.

(KL-6) Krebs von den Lungen-6 is a high-molecular-weight glycoprotein, classified as human MUC1 mucin, that is produced by regenerating type II pneumocytes

- No differences in physiologic measurements were found between NAC and placebo group

That are

Quality of life

Exercise Capacity

Adverse Effects

Vital Capacity

Oxygen saturation

- **ATS/ERS/JRS/ALAT Recommendation**

The majority of patients with IPF should not be treated with acetylcysteine monotherapy, but this therapy may be a reasonable choice in a minority

(weak recommendation, low-quality evidence)

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Interferon-gamma 1b

- IFN- γ -1b regulates both macrophage and fibroblast function.
- IFN- γ -1b is an agent with antifibrotic and immunomodulatory properties
- It down regulates molecules associated with fibrosis, inflammation, and angiogenesis.

N. Engl. J. Med. 341(17): 1302-1304 (1999).

- **Ziesche R et al**, done a pilot study on long-term treatment with interferon γ -1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis and suggested benefits with IFN- γ -1b

N Engl J Med 1999;341:1264–1269.

- **Raghu G et al**, done a placebo-controlled trial of interferon γ -1b in patients with idiopathic pulmonary fibrosis. This was first clinical trial evaluated the time to clinical worsening or death in 330 patients with IPF.

N Engl J Med 2004;350:125–133

- Patients were randomized 1:1 to receive IFN- γ 200 μ g three times a week subcutaneously or placebo, with low-dose prednisone being allowed as concomitant medication in both groups .
- The primary endpoint was not different between two groups.

INSPIRE Study Group

- **King TE Jr et al**, Studied the effect of interferon γ -1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE)
- It was multicentre, randomized, placebo-controlled trial on 800 patients with physiologically mild disease.
- There was no difference in over all mortality (14.5% in the IFN- γ group compared with 12.7% in the placebo arm)

Lancet 2009;374:222–228.

- ATS/ERS/JRS/ALAT Recommendation

The patients with IPF should not be treated with IFN- γ .

(Strong recommendation, high-quality evidence)

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Bosentan

- Bosentan, a dual endothelin receptor A and B antagonist
- Endothelin-1 (ET-1) is a powerful vasoconstrictor and growth factor that is involved in the pathogenesis of pulmonary hypertension and potentially of IPF.
- Elevated endothelin levels in serum and BAL, and exaggerated expression of endothelin receptors and ET-1 in lung tissue have been observed in patients with IPF

Expert Opin Pharmacother 2004;5:1671–1686

BUILD-1 Study

- **King TE Jr et al**, done a placebo-controlled trial of bosentan in patient with idiopathic pulmonary fibrosis.

Am J Respir Crit Care Med 2008;177:75–81.

- To determine the effects of bosentan on exercise capacity and time to disease progression in patient with IPF
- Double blind, multicenter trial, patient were randomized to receive oral bosentan 62.5 mg BD for 4 wk, increase to 125 mg BD thereafter, or placebo, for 12 months or longer.

- Bosentan showed no superiority over placebo in 6MWD up to 12 months (primary end point)
- A trend in favor of bosentan was observed in the secondary endpoint of time to death or disease progression

(hazard ratio , 0.613; 95% confidence interval, 0.328-1.144; p=0.119)

- A trend in favor of bosentan was more pronounced in patient subgroup diagnosed using surgical lung biopsy.

(HR, 0.315; 95% CI, 0.126-0.789; p=0.009)

- A successor study is ongoing to investigate whether bosentan benefits patients with IPF who have undergone surgical lung biopsy

- ATS/ERS/JRS/ALAT Recommendation

The patients with IPF should not be treated with bosentan.

(Strong recommendation, moderate-quality evidence)

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Etanercept

- Etanercept is a recombinant soluble human tumor necrosis factor (TNF) receptor that binds to TNF and neutralizes its activity in vitro

J Immunol 1993;151:1548–1561

- **Sime PJ et al**, shown that transfer of tumor necrosis factor-alpha to rat lung induces severe pulmonary inflammation and patchy interstitial fibrogenesis with induction of transforming growth factor-beta1 and myofibroblasts.

Am J Pathol 1998;153:825–832.

- **Piguet PF et al**, have shown the expression and localization of tumor necrosis factor-alpha and its mRNA in idiopathic pulmonary fibrosis.

Am J Pathol 1993;143:651–655.

- **Raghu G et al.** done a randomized controlled study of etanercept for patients with IPF.
- This study failed to show a difference in primary endpoint of change in FVC over 48 weeks.

Am J Respir Crit Care Med 2008;178:948–955.

- ATS/ERS/JRS/ALAT Recommendation

The patients with IPF should not be treated with etanercept.

(Strong recommendation, moderate-quality evidence)

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Anticoagulants

- Increased local procoagulant activity is a characteristic feature of IPF , with extravascular generation of tissue factor, factor VIIa, factor Xa, and thrombin.
- These coagulation factors can all exert cellular effects through the activation of proteinase-activated receptors (PARs), particularly PAR1.
- Expression of this receptor is increased in IPF

Kubo et al published the results of a unblinded, randomized trial of 56 patients with IPF compared corticosteroids alone or corticosteroids plus anticoagulation (oral warfarin for outpatients and unfractionated or low-molecularweight heparin for hospitalized patients).

Chest 2005; 128:1475–1482

- He reported a significant increase in survival in the anticoagulant group.

(63% survival at 3 years in the anticoagulant group v/s 35% in the nonanticoagulant group)

- Both groups had a comparable incidence of acute exacerbations, but mortality associated with acute exacerbation was lower in the anticoagulant group (18% v/s 71%).

- Limitations of Study
 - The absence of blinding
 - Differential drop-out rates
 - Failure to exclude pulmonary embolism as potential cause of deterioration
 - Suboptimal documentation of quality of anticoagulation during outpatient

- ATS/ERS/JRS/ALAT Recommendation

The patients with IPF should not be treated with anticoagulants but this therapy may be reasonable choice in a minority.

(weak recommendation, very low-quality evidence)

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Pirfenidone

- Pirfenidone is orally bioavailable synthetic pyridone compound with pleiotropic, antiinflammatory, antifibrotic, and antioxidant properties, with antagonism of TGF- β 1 effects.
- It was shown to regulate the activity of transforming growth factor (TGF) β and tumour necrosis factor (TNF) α in vitro.

J Pharmacol Exp Ther 1999; 291: 367–73

Am J Respir Cell Mol Biol 2006; 35: 366–77

- It inhibit fibroblast proliferation and collagen synthesis and reduce cellular and histological markers of fibrosis in animal models of lung fibrosis.

Eur J Pharmacol 2008; 590: 400–08

Am J Respir Cell Mol Biol 2006; 35: 366–77

J Pharmacol Exp Ther 1999; 289: 211–18

Exp Lung Res 1998; 24: 119–32.

J Lab Clin Med 1995; 125: 779–85.

- **Raghu G et al.** done a prospective, open-label study in which treatment was administered on a compassionate basis (open-label). Fifty-four patients (mean age 62 yr)were followed for mortality, change in lung function, and adverse effects of IPF with pirfenidone.
- Over a period of 15 d, oral pirfenidone was slowly increased to 40 mg/kg/d up to a maximum of 3,600 mg/d in divided doses.
- Patients were not allowed to take other concurrent medications that were currently used in the treatment of IPF.

AM J RESPIR CRIT CARE MED 1999;159:1061–1069.

- 1- and 2-yr survival was **78%** (95% CI 66%, 89%) and **63%** (95% CI 50%, 76%), respectively.
- Patients whose lung functions had deteriorated prior to enrollment appeared to stabilize after beginning of treatment.
- Adverse effects were relatively minor.
- The results of this study were encouraging

- **Sonoko Nagai et al.** Open-label Compassionate Use One Year-treatment with Pirfenidone to Patients with Chronic Pulmonary Fibrosis to evaluate the therapeutic efficacy, tolerance, and clinical courses after treatment.
- Oral pirfenidone (40 mg/kg/Day) was administered to 8 patients with advanced IPF and 2 with interstitial pneumonia associated with diffuse systemic sclerosis.

Internal Medicine Vol. 41, No. 12 (December 2002)

- The plasma concentration of the drug was serially followed.
- Radiographic scores, PFT and ABG were compared at three time points: at one-year before treatment, at the time of entry, and at one-year after entry.
- The pirfenidone did not show a definite therapeutic effect on overall survival (2 years after entry).
- During one-year treatment, there was no significant deterioration in terms of chest radiographic scores and arterial oxygen pressure.
- The drug was well tolerated with minimal adverse effects within the ranges .

- **Arata Azuma et al.** done a double blind, placebo-controlled, randomized, multicenter, prospective clinical trial conducted at 25 sites in Japan , 107 patients were prospectively evaluated for efficacy of pirfenidone.
- They prospectively designed a novel study using the change in the lowest SpO₂ reached during the 6-minute-walk test as the primary endpoint

- The difference in the change in the lowest oxygen saturation by pulse oximetry (SpO₂) during a 6-MET (the primary endpoint) from baseline to 6 months was not significant between the two groups (p 0.0722)
- In a subset of patients who maintained a SpO₂ greater than 80% during a 6-MET at baseline, the lowest SpO₂ improved significantly during a 6-MET in the pirfenidone group at 6 and 9months (p0.0069 and 0.0305, respectively).
- Changes in TLC, DLCO, and resting PaO₂ between the two groups were not significant statistically at either 6 or 9 months.

- Positive treatment effect was demonstrated in secondary endpoints:
 - At 9 months, the difference in decline of VC between the placebo group (0.13 L) and the pirfenidone group (0.03 L) was statistically significant (p 0.0366)
 - Acute exacerbation of IPF was manifested in 14% of the placebo group (5/35) and in **none** of the pirfenidone group during the 9 months
(p 0.0031)

- This trial was stopped prematurely after a secondary endpoint—as acute exacerbation was found significantly more frequently in the placebo group as compared with the active treatment arm.
- Significant adverse events were associated with pirfenidone; however, adherence to treatment regimen was similar between pirfenidone and placebo groups.
- They concluded that treatment with pirfenidone improved VC and prevented acute exacerbation of IPF during the 9 months of follow-up.

- **H. Taniguchi et al.** done a multicentre, double-blind, placebo-controlled, randomised phase III clinical trial. It was conducted in Japanese patients with well-defined IPF to determine the efficacy and safety of pirfenidone, over 52 weeks.
- 275 patients randomised (high-dose, 1,800 mg/day-1; low-dose, 1,200 mg/day-1; or placebo groups in the ratio 2:1:2)

Eur Respir J 2010; 35: 821–829

- Significant differences were observed in VC decline (primary end-point) between the placebo group (-0.16 L) and the high-dose group (-0.09 L) ($p=0.0416$).
- Significant differences were observed in the progression-free survival defined by death or >10% decline in VC(the secondary end-point) favoring the pirfenidone group ($p=0.0280$).

- Pirfenidone was relatively well tolerated in patients with IPF.
- Photosensitivity, a well-established side-effect of pirfenidone, was the major adverse event in this study, it was mild in severity in most of the patients.
- They concluded that treatment with pirfenidone may decrease the rate of decline in VC and may increase the PFS time over 52 weeks in patients with IPF.

- **H. Taniguchi et al.** also done a phase III clinical trial of pirfenidone for patients with IPF in Japan.
- Improvement ratings based on 5% change in absolute VC, i.e., “improved (VC \geq 5% increase)”, “stable (VC < 5% change)”, and “worsened (VC \geq 5% decrease)” at month 3, 6, 9 and 12 were compared between high-dose pirfenidone (1800 mg/day; n=108) and **placebo (n=104)** groups, and (high-dose and low-dose (1200 mg/day; n=55)) **pirfenidone (n=163)** and placebo groups.

Respiratory Research 3 February 2011, **12:93** doi:10.1186/1465-9921-12-93

- The progression-free survival (PFS) times with defining the disease progression as death or a $\geq 5\%$ decline in VC were compared between high-dose pirfenidone and placebo groups, and low-dose pirfenidone and placebo groups and statistically significant difference was observed.
- They concluded that the efficacy of pirfenidone in Japanese phase III trial was supported by the rating of 5% decline in VC, and the VC changes at month 3 may be used as a prognostic factor of IPF.

CAPACITY trial

Pirfenidone in patients with IPF

- ***Paul W Noble et al.*** done two concurrent trials (004 and 006), patients (aged 40–80 years) with IPF were randomly assigned to oral pirfenidone or placebo for a minimum of 72 weeks in 110 centers in Australia, Europe, and North America

www.thelancet.com

Published online May 14, 2011 DOI:10.1016/S0140-6736(11)60405-4

- In **study 004**, patients were assigned in a 2:1:2 ratio.
- 174 of 435 patients were assigned to pirfenidone 2403 mg/day, 87 to pirfenidone 1197 mg/day, and 174 to placebo.

- In **study 006**, patients were assigned in a 1:1 ratio , 171 of 344 patients were assigned to pirfenidone 2403 mg/day, and 173 to placebo.
- Treatments were administered orally, 801 mg or 399 mg three times a day
- The primary endpoint was change in percentage predicted forced vital capacity (FVC) at week 72

- In **study 004** shown that pirfenidone reduced decline in FVC ($p=0.001$). Mean FVC change at week 72 was -8.0% (SD 16.5) in the pirfenidone 2403 mg/day group and -12.4% (18.5) in the placebo group (difference 4.4%, 95% CI 0.7 to 9.1) A significant treatment effect was noted at all time points from week 24 and in an analysis over all study timepoints ($p=0.0007$)
- Mean change in percentage FVC in the pirfenidone low dose group was intermediate to that in the pirfenidone high dose and placebo groups

- In **study 006**, the difference between groups in FVC change at week 72 was not significant ($p=0.501$).
- Mean change in FVC at week 72 was -9.0% (SD 19.6) in the pirfenidone group and -9.6% (19.1) in the placebo group.

- *However in the pirfenidone 2403 mg/day groups there was*
 - Fewer overall deaths (19 [6%] vs 29 [8%])
 - *Fewer deaths* related to idiopathic pulmonary fibrosis (12 [3%] vs 25 [7%])

- An assessment of baseline characteristics in studies 004 and 006 showed that study 006 had a greater proportion of patients with a recent diagnosis of idiopathic pulmonary fibrosis.
- The placebo group in study 006 had a greater proportion of patients with obstructive airway disease, characteristics associated with reduced FVC decline.
- These baseline imbalances, with the intrinsic variability in rates of FVC decline in patients with idiopathic pulmonary fibrosis, could partly account for the attenuated rate of FVC decline in the placebo group in study 006.

- Patients in the pirfenidone 2403 mg/day group had higher incidences of adverse effects as compared with placebo.
 - Nausea (125 [36%] of 345 vs 60 [17%] of 347)
 - *Dyspepsia* (66 [19%] vs 26 [7%])
 - *Vomiting* (47 [14%] vs 15 [4%])
 - Anorexia (37 [11%] vs 13 [4%])
 - *Photosensitivity* (42 [12%] vs 6 [2%])
 - *Rash* (111 [32%] vs 40 [12%])
 - *Dizziness* (63 [18%] vs 35 [10%])

- The CAPACITY trial show pirfenidone has a favorable benefit risk profile and represents an appropriate treatment option for patients with idiopathic pulmonary fibrosis.

- **C.M. Rubino et al. done** an open-label, single-dose crossover study, the pharmacokinetics (PK) of pirfenidone was investigated with or without food and antacids in older healthy adult volunteers (50 and 79 years)
- Coadministration with food decreased the rate and, to a lesser degree, the extent of pirfenidone absorption . Analysis of adverse events revealed a correlation between pirfenidone C_{max} and the risk of GI adverse events, suggesting that food may reduce the risk of certain adverse events associated with pirfenidone.
- Administration of pirfenidone with food has a modest effect on overall exposure but results in lower peak concentrations, which may improve tolerability.

- ATS/ERS/JRS/ALAT Recommendation

The majority of patients with IPF should not be treated with pirfenidone, but this therapy may be reasonable choice in a minority.

(weak recommendation, low-to moderate-quality evidence)

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Therapies without Recommendations

- **Sildenafil** (an oral phosphodiesterase 5 inhibitor) that has been shown to safely reduce pulmonary vascular pressures in patients with IPF

Lancet 2002;360:895–900.

- The Idiopathic Pulmonary Fibrosis Clinical Research Network have done a phase III randomized controlled trial of sildenafil in patients with IPF and a severely reduced DLCO (<35% predicted) in advanced idiopathic pulmonary fibrosis.
- There were statistically significant differences in the change in dyspnea, PaO₂, DLCO, and quality of life in favor of sildenafil.

N Engl J Med 2010;363:620–628.

- **Jackson RM et al.** randomized 29 subjects with IPF to sildenafil or placebo
- The primary endpoint was the change in 6-minute-walk distance at 6 months.
- There was no significant difference in the primary endpoint. There was also no difference in change in exertional dyspnea.

Lung 2010;188:115–123.

Imatinib

- It is a tyrosine kinase inhibitor with activity against platelet-derived growth factor receptors
- **Daniels CE et al.** done a phase II randomized placebo-controlled trial, 121 patients were randomized to oral imatinib 600 mg OD or placebo for up to 96 weeks.
- No difference in disease progression was observed.
- Imatinib was associated with a higher incidence of adverse event–related dropouts (22% versus 10%).

Am J Respir Crit Care Med 2010;181:604–610.

Nonpharmacologic Therapies: LTOT

- **Morrison DA et al** observed a limited evidence demonstrating improvement in exercise capacity in patients with resting hypoxemia using oxygen.

Chest 1992;102:542–550.

- There are indirect evidence from two large randomized trials in obstructive lung disease has demonstrated a clear survival benefit with long-term oxygen therapy.

- Nocturnal Oxygen Therapy Trial Group.

Ann Intern Med 1980;93:391–398

- Long-term domiciliary oxygen therapy MRC Working Party.

Lancet 1981;1:681–686.

- ATS/ERS/JRS/ALAT Recommendation

The patients with IPF and clinically significant resting hypoxemia should be treated with long-term oxygen therapy

(strong recommendation, very low-quality evidence).

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Lung Transplantation

- Five-year survival rates after lung transplantation in IPF are estimated at 50 to 56% .
- The patients with pulmonary fibrosis undergoing lung transplantation have favorable long-term survival compared with other disease indications.

Ann Thorac Surg 2007;84:1121–1128

Transplant Proc 2009;41:289–291

- ATS/ERS/JRS/ALAT Recommendation

The appropriate patients with IPF should undergo lung transplantation.

(strong recommendation, low-quality evidence).

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Mechanical Ventilation

- There is high hospital mortality rate in mechanical ventilation patients with IPF and respiratory failure.

Chest 2001;120:209–212

Eur Respir J 2006;27:143–150.

Crit Care Resusc 2009;11:102–109.

Respiration 2010;79:209–215

- ATS/ERS/JRS/ALAT Recommendation

The majority of patients with respiratory failure due to IPF should not receive mechanical ventilation, but mechanical ventilation may be a reasonable intervention in a minority

(weak recommendation, low quality evidence).

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Pulmonary Rehabilitation

- It involve aerobic conditioning, strength and flexibility training, educational lectures, nutritional interventions, and psychosocial support.
- **Holland AE et al.** Thorax 2008;63:549–554.
- **Nishiyama O et al.** Respirology 2008;13:394–399
 - have demonstrated an improvement in walk distance and symptoms or quality of life following exercise training in interstitial lung disease
- **Ferreira A et al.** shown that the beneficial effects of pulmonary rehabilitation are more pronounced in patients with worse baseline functional status.

Chest 2009;135:442–447.

- ATS/ERS/JRS/ALAT Recommendation

The majority of patients with IPF should be treated with pulmonary rehabilitation, but pulmonary rehabilitation may not be reasonable in a minority (weak recommendation, low-quality evidence)

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Acute exacerbation of IPF

- There are no controlled trials although high-dose corticosteroids are commonly prescribed for the treatment of acute exacerbation of IPF

Am J Respir Crit Care Med 2007;176:636–643

AJR Am J Roentgenol 1997;168:79–83

Eur Respir J 2003;22:821–82.

Eur Respir J 2006;27:143–150

Chest 2005;128:3310–3315.

- Cyclosporin A and anticoagulation have also been used without conclusive results.

Chest 2005;128:1475–1482.

Intern Med 2005;44:1144–1150.

Intern Med 2010;49:109–115.

- ATS/ERS/JRS/ALAT Recommendation

The majority of patients with acute exacerbation of IPF should be treated with corticosteroids, but corticosteroids may not be reasonable in a minority (weak recommendation, very low-quality evidence)

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Pulmonary Hypertension

- IV and aerosolized epoprostenol

Am J Respir Crit Care Med 1999;160:600–607

- Oral bosentan

Respir Med 2008;102:1015–1020.

- Oral sildenafil

Lancet 2002;360:895–900.

Vascul Pharmacol 2006;44:372–376

Chest 2007;131:897–899.

some studies favor other show no benefits.

- ATS/ERS/JRS/ALAT Recommendation

Pulmonary hypertension should not be treated in the majority of patients with IPF, but treatment may be a reasonable choice in a minority

(weak recommendation, very low-quality evidence).

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Asymptomatic GERD

- Abnormal GER is highly prevalent in patients with IPF, and up to one half of patients are asymptomatic.

Eur Respir J 2006;27:136–142.

Am J Respir Crit Care Med 1998;158: 1804–1808.

J Thorac Cardiovasc Surg 2007;133:1078–1084

- Abnormal GER is a risk factor for aspiration, which is a known cause of pneumonitis, and may contribute to chronic airways inflammation and fibrosis .

N Engl J Med 2001;344:665–671

Mayo Clin Proc 2006;81:172–176. J

Thorac Cardiovasc Surg 2003;125:533–542.

- The retrospective case series describe stabilization of pulmonary function and oxygen requirements with medical and surgical management of GER.

Raghu G et al. Eur Respir J 2006;27:136–142.

Linden PA et al. J Thorac Cardiovasc Surg 2006;131:438–446.

- ATS/ERS/JRS/ALAT Recommendation

Asymptomatic GERD should be medically treated in the majority of patients with IPF, but treatment may not be reasonable in a minority

(weak recommendation, very low-quality evidence).

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Palliative Care

- Chronic Cough - Corticosteroids
Thalidomide
- Severe Dyspnea - Chronic Opioids
- Advanced directives and end-of-life care issues should be addressed in the ambulatory setting in all patients with IPF

SUMMARY CONCLUSIONS

ATS/ERS/JRS/ALAT International IPF guidelines 2011

- A. The recommendation **against** the use of the following agents for the treatment of IPF is **strong** (most people in this situation would not want the intervention and only a small proportion would)

Corticosteroid monotherapy	+
Colchicine	+
Cyclosporine A	+
Combined corticosteroid and immune-modulator therapy	++
Interferon gamma 1b	++++
Bosentan	+++
Etanercept	+++

B. The recommendation **against** the use of the following agents for the treatment of IPF is **weak** (For the well-informed patient who strongly desires pharmacologic treatment, it is suggested that the choice of agent may be made from therapies that received a weak recommendation against their use)

Combined acetylcysteine and azathioprine and prednisone	++
Acetylcysteine monotherapy	++
Pirfenidone	++
Anticoagulation	+

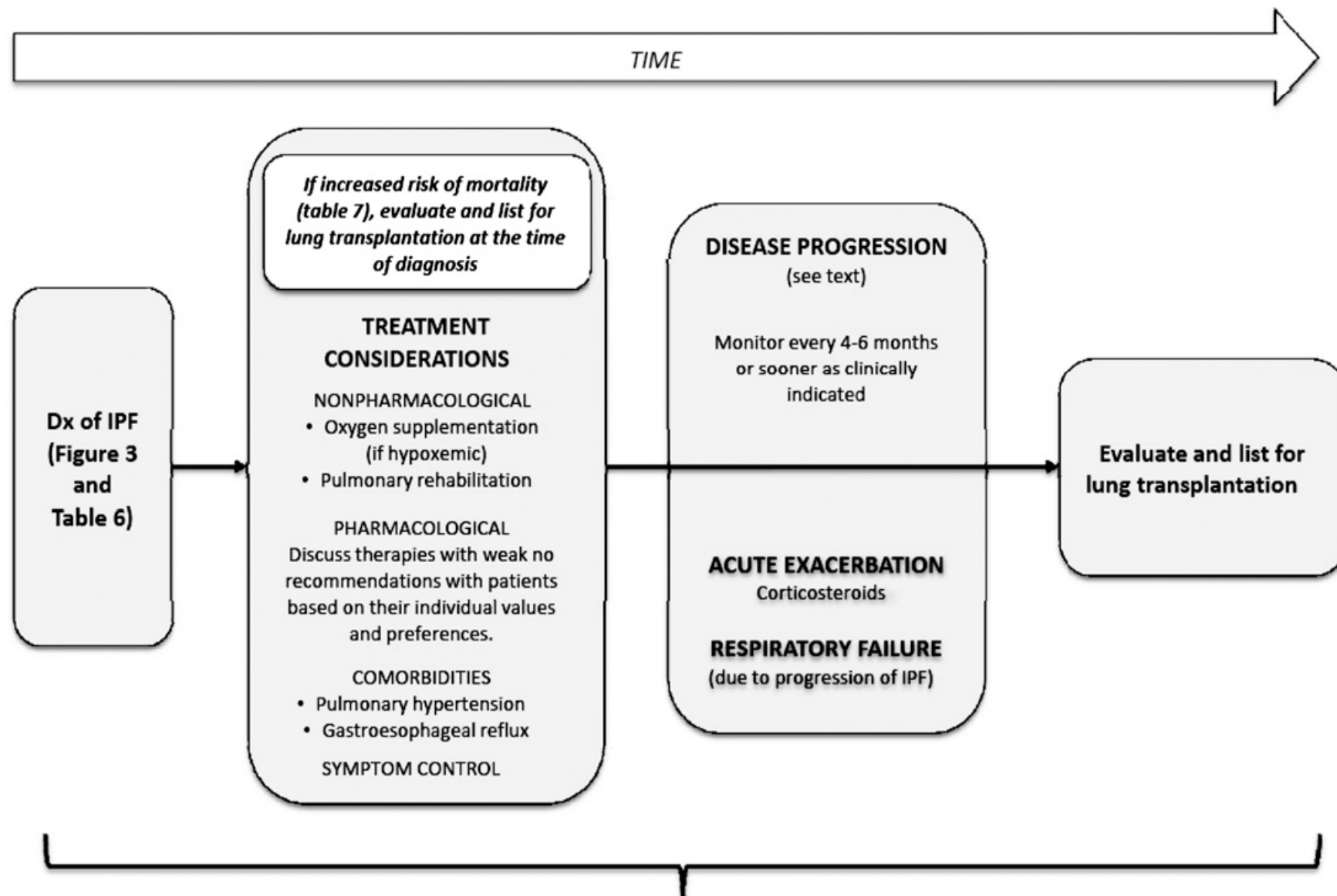
Recommendations for Treatment:

ATS/ERS/JRS/ALAT International IPF guidelines 2011

C. Other recommendations

LTOT in patients with IPF and clinically significant resting hypoxemia	+	Strong recommendation
Lung transplantation in appropriate patients with IPF	+	Strong recommendation
Mechanical ventilation in patients with respiratory failure due to IPF	++	Weak against recommendation
Pulmonary rehabilitation in patients with IPF	++	Weak recommendation

Corticosteroids in patients with acute exacerbation of IPF	+	Weak recommendation
Treatment of pulmonary hypertension associated with IPF	+	Weak against recommendation
Treatment of asymptomatic GER patients with IPF	+	Weak recommendation



Patients should be made aware of available clinical trials for possible enrollment at all stages.