INTERSTITIAL LUNG DISEASES
Recent Advances That Change Practice

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San Francisco, CA
I have the following, real or perceived conflicts of interest that relate to this presentation.

- InterMune (Drug Study Steering committees)
- Actelion (Drug Study Steering Committees)
- ImmuneWorks (Scientific Advisory Committee)
- Daiichi Sankyo Pharma (Consultant)
- NIH IPFnet (principal investigator)
Screening CT scans

HRCT in diagnosis of IPF

2013 Revised ATS/ERS IIP Consensus Statement

Role of acute exacerbations in the IIPs

PANTHER TRIAL

Chronic microaspiration in IPF

Value of marginal declines in lung function

Scoring system to predict outcome in IPF

Causes of death in IPF
Screen-detected Subclinical Interstitial Lung Abnormalities are Common

Elderly

Smokers
ILD present in over half of asymptomatic elderly individuals who have no pulmonary function deficit, and these CT findings are absent in younger individuals.

Lung morphology in the elderly: comparative CT study of subjects over 75 years old versus those under 55 years old.


Radiology 2009; 251:566-73.
Subclinical Interstitial Lung Abnormalities are Common in Smokers -- HRCT

Cigarette Smoking Is Associated with Subclinical Parenchymal Lung Disease
The Multi-Ethnic Study of Atherosclerosis (MESA)–Lung Study

David J. Lederer¹, Paul L. Enright², Steven M. Kawut³,⁴, Eric A. Hoffman⁵, Gary Hunninghake⁶, Edwin J. R. van Beek⁶, John H. M. Austin⁷, Rui Jiang¹,⁸, Gina S. Lovasi⁹,¹⁰, and R. Graham Barr¹,⁸

Am J Respir Crit Care Med 2009;180:407–414,

The radiological patterns of interstitial change at an early phase: Over a 4-year follow-up

Kenji Tsushima¹,a,b,*, Shusuke Sone¹, Sumiko Yoshikawa¹, Toshiki Yokoyama¹, Toshiro Suzuki¹, Keishi Kubo¹

Respir Med 2010;104: 1712-21

†ILA found in 194/2416 subjects (8%)
†Decreased TLC
†Lower likelihood of meeting COPD criteria
†Decreased quantitative % emphysema

Lung Volumes and Emphysema in Smokers with Interstitial Lung Abnormalities

George R. Washko, M.D., M.M.Sc., Gary M. Hunninghake, M.D., M.P.H., Isis E. Fernandez, M.D., Mizuki Nishino, M.D., Yuka Ollajma, M.D., Tsuneo Yamashiro, M.D., James C. Ross, M.S., Raúl San José Estévar, Ph.D., David A. Lynch, M.D., John M. Brehm, M.D., M.P.H., Katherine P. Andriole, Ph.D., Alejandro A. Díaz, M.D., Ranin Khorasani, Ph.D., Katherine D’Aco, M.S., Frank C. Scirba, M.D., Edwin K. Silverman, M.D., Ph.D., Hiroto Hatabu, M.D., Ph.D., and Ivan O. Rosas, M.D., for the COPDGene Investigators‡

Screen-detected lung fibrosis: 0.5-1%
Smoking-related changes in the background lung of specimens resected for lung cancer: a semiquantitative study with correlation to postoperative course

Y Kawabata, E Hoshi, K Murai, T Ikeya, N Takahashi, Y Saitou, K Kurashima, M Ubukata, N Takayanagi, H Sugita, S Kanauchi & T V Colby

Clinically occult interstitial fibrosis in smokers: classification and significance of a surprisingly common finding in lobectomy specimens

Anna-Luise A. Katzenstein MD, Sanjay Mukhopadhyay MD, Conrado Zanardi MD, Elizabeth Dexter MD

Human Pathology (2010) 41, 316–325
# Lung Volumes and Emphysema in Smokers with Interstitial Lung Abnormalities

George R. Washko, M.D., M.M.Sc., Gary M. Hunninghake, M.D., M.P.H., Isis E. Fernandez, M.D., Mizuki Nishino, M.D., Yuka Okajima, M.D., Tsuneo Yamashiro, M.D., James C. Ross, M.S., Raúl San José Estépar, Ph.D., David A. Lynch, M.D., John M. Brehm, M.D., M.P.H., Katherine P. Andriolet, Ph.D., Alejandro A. Díaz, M.D., Ramin Khorasani, Ph.D., Katherine D’Aco, M.S., Frank C. Scirurba, M.D., Edwin K. Silverman, M.D., Ph.D., Hiroto Hatabu, M.D., Ph.D., and Ivan O. Rosas, M.D.,
for the COPDGene Investigators


<table>
<thead>
<tr>
<th>HRCT Pattern</th>
<th>Potential Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrilobular or peribronchial ground glass opacities sparing the peripheral lung parenchyma (19%)</td>
<td>Respiratory bronchiolitis</td>
</tr>
<tr>
<td>Subpleural reticular, nodular, or ground-glass opacities (55%),</td>
<td>A predominant age-related finding</td>
</tr>
<tr>
<td>Centrilobular and subpleural, or mixed, findings (20%)</td>
<td></td>
</tr>
<tr>
<td>Radiologic interstitial lung disease (6%)</td>
<td>Combined pulmonary fibrosis and emphysema</td>
</tr>
</tbody>
</table>
Limited data suggest that many of the subclinical changes in the lungs in smokers are

- reversible in their natural clinical course or after smoking cessation, and

- that persistence or worsening is largely confined to those who continue to smoke or are found to have a defined interstitial lung disease.

Is this an opportunity to prevent IPF?
HRCT is an essential component of the diagnostic pathway in IPF.
An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernando J. Martinez, Juergen Behr, Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky, David A. Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros, Carlos Carvalho, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Kim, Talmadge E. King, Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca Richeldi, Moisés Selman, Rosalind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schünemann, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

Am J Respir Crit Care Med 2011; 183:788–824
Diagnostic criteria for UIP

**UIP pattern**

- Subpleural, basal predominance
- Reticular abnormality
- Honeycombing with or without traction bronchiectasis
- Absence of features inconsistent with UIP pattern

Diagnostic criteria for UIP

**UIP pattern**

- Subpleural, basal predominance
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- Honeycombing with or without traction bronchiectasis
- Absence of features inconsistent with UIP pattern


David Lynch
Diagnostic criteria for UIP

Possible UIP pattern

- Subpleural, basal predominance
- Reticular abnormality
- Absence of features inconsistent with UIP pattern


David Lynch
Diagnostic criteria for UIP

Possible UIP pattern

- Subpleural, basal predominance
- Reticular abnormality
- Absence of features inconsistent with UIP pattern

Honeycombing in UIP

- Present in 70-80% of cases of UIP
- Strongest indicator of UIP on CT
- Median survival
  - UIP with honeycombing: 2.1 years
  - UIP without honeycombing: 5.8 years

Inconsistent with UIP pattern

- Upper or midlung predominance
- Peribronchovascular predominance
- Extensive ground glass abnormality (>reticular)
- Profuse micronodules (bilateral, predominantly upper lobes)
- Discrete cysts (multiple, bilateral, away from areas of honeycombing)
- Diffuse mosaic attenuation (bilateral, in three or more lobes)
- Consolidation in segments or lobes

UIP Honeycomb Pattern

UIP: usual interstitial pneumonia
Honeycombing in UIP

- Present in 70-80% of cases of UIP
- Strongest indicator of UIP on CT
- Median survival
  - UIP with honeycombing: 2.1 years
  - UIP without honeycombing: 5.8 years

Definition of honeycombing

Clustered cysts
Definition of honeycombing

- Clustered cysts
- Single layer of subpleural cysts
Definition of honeycombing

- Clustered cysts
# Predictive value of CT diagnosis of UIP

<table>
<thead>
<tr>
<th>Study</th>
<th>Correctness of first choice diagnosis of UIP</th>
<th>Correctness of confident first choice diagnosis</th>
<th>% cases of UIP without confident CT diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathieson</td>
<td>89%</td>
<td>95%</td>
<td>72%</td>
</tr>
<tr>
<td>Hunninghake</td>
<td>85%</td>
<td>96%</td>
<td>52%</td>
</tr>
<tr>
<td>Flaherty</td>
<td>100%</td>
<td>100%</td>
<td>63%</td>
</tr>
<tr>
<td>Tsubamoto</td>
<td>100%</td>
<td>91%</td>
<td>9%</td>
</tr>
<tr>
<td>Elliot</td>
<td>88%</td>
<td>88%</td>
<td>50%</td>
</tr>
<tr>
<td>Silva</td>
<td>84%</td>
<td>100%</td>
<td>67%</td>
</tr>
</tbody>
</table>
2013 Revised ATS/ERS
IIP Classification

• MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS
  • Idiopathic pulmonary fibrosis
  • Idiopathic nonspecific interstitial pneumonia
  • Respiratory bronchiolitis interstitial lung disease
  • Desquamative interstitial pneumonia
  • Cryptogenic organizing pneumonia
  • Acute interstitial pneumonia

• RARE IDIOPATHIC INTERSTITIAL PNEUMONIAS
  • Idiopathic lymphoid interstitial pneumonia
  • Idiopathic pleuropulmonary fibroelastosis

• UNCLASSIFIABLE IDIOPATHIC INTERSTITIAL PNEUMONIAS
Diffuse Parenchymal Lung Disease

- DPLD of known cause e.g. drugs or association e.g. collagen vascular disease
- Idiopathic interstitial pneumonia (IIPs)
- Granulomatous DPLD e.g. sarcoidosis
- Other forms of DPLD e.g. LAM, HX etc.

Non-familial (> 80%)
- Chronic Fibrosing
  - Idiopathic pulmonary fibrosis
  - Idiopathic nonspecific interstitial pneumonia
- Acute/Subacute Fibrosing
- Smoking-related
  - Respiratory bronchiolitis interstitial lung disease
  - Desquamative interstitial pneumonia
- Familial (2-20%)
  - Cryptogenic organizing pneumonia
  - Acute interstitial pneumonia
Rare IIPs described:

- Idiopathic lymphoid interstitial pneumonia (LIP)
- Idiopathic pleuropulmonary fibroelastosis (PPFE)
- Acute fibrinous and organizing pneumonia (AFOP)
- Interstitial pneumonias with a bronchiolocentric distribution
Idiopathic Pleuropulmonary Fibroelastosis (PPFE)

- Adults (median age of 57 years) with no sex predilection.
- ~50% experienced recurrent infections.
- Familial ILD and nonspecific auto-antibodies.
- HRCT = dense subpleural consolidation with traction bronchiectasis, architectural distortion and upper lobe volume loss.
- Fibrosis involving the pleura and subpleural lung parenchyma
- Disease progression in 60% of patients; death from disease in 40%.
Acute fibrinous and organizing pneumonia (AFOP)

- **Path:** intra-alveolar fibrin deposition and associated organizing pneumonia (hyaline membranes absent).

- **HRCT** = bilateral basal opacities and areas of consolidation.

- May represent a histologic pattern that can occur in the clinical spectrum of DAD and OP or it may reflect a tissue sampling issue.

- Idiopathic or associated with CVD, HP or drug reaction.
GERD - Not just heartburn
Does Chronic Microaspiration Cause Idiopathic Pulmonary Fibrosis?

Joyce S. Lee, MD, Harold R. Collard, MD, Ganesh Raghu, MD, Matthew P. Sweet, MD, MS, Steven R. Hays, MD, Guilherme M. Campos, MD, FACS, Jeffrey A. Golden, MD, Talmadge E. King, Jr., MD

American Journal of Medicine, Vol 123, April 2010
• HH is more common in IPF than COPD or asthma.
• HH correlated with higher DeMeester scores, confirming abnormal acid GER.
• Presence of HH alone was not associated with decreased lung function.
Gastroesophageal reflux is prevalent in patients with IPF. However, significance is unclear.

Stabilization of Pulmonary Function With Medical or Surgical Treatment Of GER


• Confirms GER-related findings are common in IPF
• Suggests that the reported use of GER medications is associated with less radiologic fibrosis and longer survival time in these patients.
• Although preliminary, these findings further support the hypothesis that GER and silent microaspiration may play a role in the pathobiology of IPF.
Gastroesophageal Reflux Therapy Is Associated with Longer Survival in Patients with Idiopathic Pulmonary Fibrosis

Joyce S. Lee, Jay H. Ryu, Brett M. Elicker, Carmen P. Lydell, Kirk D. Jones, Paul J. Wolters, Talmadge E. King, Jr., and Harold R. Collard

Am J Respir Crit Care Med 2011; 184:1390-1394

**GER Symptoms**

- Presence of GER Symptoms: no
- Absence of GER Symptoms: yes

**HR = 0.62, p value = 0.03**

**GER Diagnosis**

- Presence of GER Diagnosis: yes
- Absence of GER Diagnosis: no

**HR = 0.56, p value < 0.01**

**GER Medication Use**

- Taking GER Medications: yes
- Not taking GER Medications: no

**HR = 0.51, p value < 0.01**

**Nissen Fundoplication**

- History of Nissen Fundoplication: yes
- No Nissen Fundoplication: no

**HR = 0.29, p value = 0.04**
Causes of Death in IPF


CAUSES OF DEATH IN IPF

- Most deaths (77%) due to a **respiratory** cause.
  - 61% of respiratory deaths occur as a **subacute** process.
  - 39% occur as **acute** process (<4 weeks after onset of acute worsening).
  - Causes: progression of IPF, acute exacerbations, acute lung injury, pneumonia, and cor pulmonale.

- **Nonrespiratory** deaths due to cardiac causes, sepsis, gastrointestinal conditions, stroke, cancer, and other causes.
Acute exacerbations are major cause of death in the IIPs

Baseline

5 months later
Acute exacerbation of IIP

- Bilateral ground glass attenuation
  - Peripheral
  - Multifocal
  - Diffuse
- ± consolidation
- Superimposed on background reticular abnormality/honeycombing


David Lynch
Plasma from patients with acute exacerbation of IPF showed significant elevations in markers of type II alveolar epithelial cell injury and/or proliferation, endothelial cell injury, and coagulation. This profile differed from the biomarker profile in patients with acute lung injury.

These findings support the hypothesis that type II alveolar epithelial cells are centrally involved in the pathobiology of acute exacerbation of IPF.

Furthermore, they suggest that acute exacerbation of IPF has a distinct plasma biomarker profile from that of acute lung injury.
This study uses the most current genomics-based technologies to investigate the possible infectious etiology of acute exacerbations of IPF.

Most cases demonstrate no evidence of viral infection.

Torque teno virus was present in a significant minority of cases, and cases of acute lung injury.
Acute exacerbation of IPF occurred more frequently between December and May (75.7%) than between June and November (24.3%) \((p = 0.01)\).

In-hospital mortality was 27% and median survival was 4.2 months (range 0.2–36.6).

Longer time between admission and initiation of treatment is poor prognostic factor.
Tacrolimus and Steroid Treatment for Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Nobuyuki Horita, Makiko Akahane, Yukinori Okada, Yosuke Kobayashi, Takahiko Arai, Izuki Amano, Tomoko Takezawa, Masako To and Yasuo To

Background: Clinical significance of circulating autoantibodies in IPF is unclear

Methods: Prevalence of circulating autoantibodies compared between IPF patients and healthy controls (n = 52).

Results: Positive autoantibodies: IPF = 22%; healthy controls = 21.

Conclusions: The frequency of circulating autoantibodies in patients with idiopathic pulmonary fibrosis is no different compared to healthy controls, but may be associated with longer survival.
Why Did We Use Corticosteroids to Treat IPF?

- **Rationale:** treat inflammation, slow fibroblastic proliferation and prevent irreversible fibrosis

- Some patients experience a precipitous decline when steroids were stopped, so, they appeared to be working

- **No other therapy available**

“If you remember I did mention possible side effects.”
Treatment of IPF With Combination Therapy Corticosteroids + Cytotoxic Drugs
Azathioprine Combined with Prednisone in the Treatment of Idiopathic Pulmonary Fibrosis: A Prospective Double-blind, Randomized, Placebo-controlled Clinical Trial

GANESH RAGHU, WILLIAM J. DEPASO, KEVIN CAIN, SAMUEL P. HAMMAR, CLAUDE E. WETZEL, DAVID F. DREIS, JOHN HUTCHINSON, NEELEY E. PARDEE, and RICHARD H. WINTERBAUER

Raghu G et al., Amer Rev Respir Dis 1991; 144:291-6
Cyclophosphamide Appears to Improve Survival in IPF


% Still alive

Years

Prednisolone + Cyclophosphamide (n=21)

Prednisolone (n=22)

p = N.S.
Combined corticosteroid and cyclophosphamide therapy does not alter survival in idiopathic pulmonary fibrosis.

Collard HR, Ryu JH, Douglas WW, Schwarz MI, Curran-Everett D, King TE Jr, Brown KK.

Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment
International Consensus Statement

This Joint Statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS Board of Directors, July 1999 and by the ERS Executive Committee, October 1999

The authors thank Drs. Thomas Colby, David Hansell, Masanori Kitaichi, and William Travis for their critical review of the manuscript.

This statement was prepared by an ad-hoc committee of the Assembly on Clinical Problems. Members of the committee are:

Talmadge E. King, Jr., M.D., Chair
Ulrich Costabel, M.D.
Jean-François Cordier, M.D.
Guillermo A. Dopico, M.D.
Roland M. du Bois, M.D.
David Lynch, M.B.
Joseph P. Lynch, III, M.D.
Jeffrey Myers, M.D.
Ralph Panos, M.D.
Ganesh Raghun, M.D.
David Schwartz, M.D.
Cecilia M. Smith, D.O.
Until adequate studies are conducted that define the best treatment for patients with IPF, this committee suggests the following combined therapy (corticosteroid and either azathioprine or cyclophosphamide) for those patients who have been given adequate information regarding the merits and pitfalls of treatment and who possess features consistent with a more likely favorable outcome (see above):

- **Corticosteroid** therapy (prednisone or equivalent) at a dose of 0.5 mg/kg (lean body weight [LBW]) per day orally for 4 wk, 0.25 mg/kg (LBW) per day for 8 wk, and then tapered to 0.125 mg/kg (ideal body weight [IBW]) daily or 0.25 mg/kg (LBW) every other day as initial therapy for IPF. (Lean body weight is the ideal weight expected for a patient of this age, sex, and height)

- **Azathioprine** at 2–3 mg/kg lean body weight (LBW) per day to a maximum dose of 150 mg/d orally. Dosing should begin at 25–50 mg/d and increase gradually, by 25-mg increments, every 7 to 14 d until the maximum dose is reached

or

- **Cyclophosphamide** at 2 mg/kg LBW per day to a maximum dose of 150 mg/d orally. Dosing should begin at 25–50 mg/d and increase gradually, by 25-mg increments, every 7 to 14 d until the maximum dose is reached
IFIGENIA Trial

(Idiopathic pulmonary Fibrosis International Group Exploring NAC I Annual)

High-Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis

Maurits Demedts, M.D., Juergen Behr, M.D., Roland Buhl, M.D., Ulrich Costabel, M.D., P.N., Richard Dekhuijzen, M.D., Henk M. Jansen, M.D., William MacNee, M.D., Michiel Thomeer, M.D., Benoit Wallaert, M.D., François Laurent, M.D., Andrew G. Nicholson, M.D., Eric K. Verbeken, M.D., Johny Verschakelen, M.D., Christopher D.R. Flower, M.D., Frédérique Capron, M.D., Stefano Petruzzelli, M.D., Paul De Vyyst, M.D., Jules M.M. van den Bosch, M.D., Eulogio Rodriguez-Becerra, M.D., Giuseppina Corvasce, Ph.D., Ida Lankhorst, M.D., Marco Sardina, M.D., and Mauro Montanari, Ph.D., for the IFIGENIA Study Group*

IFIGENIA Trial

(Idiopathic pulmonary Fibrosis International Group Exploring NAC I Annual)

Mortality

9%

11%

VC (% Predicted)

Baseline  Endpoint 6m  Endpoint 12m

Pred/Aza/NAC (n=)

80  63  55

Pred/Aza/Placebo (n=)

75  60  51

NEJM 2005; 353: 2229-42
Addition of NAC to low-dose prednisone and azathioprine may help to preserve pulmonary function in patients with IPF.

However, a drop-out rate of ~30% (including deaths) raised concerns regarding the clinical relevance and robustness of the treatment effect.
Commonly used agents* for IPF (survey of pulmonologists in US)

The percentage of respondents who prefer to use each of the commonly used agents for patients with mild or advanced IPF

IPFnet is a network of ~26 medical centers across the U.S.A. dedicated to the study of IPF.
PANTHER-IPF Trial
Prednisone, Azathioprine, and N-Acetylcysteine: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis

Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

PANTHER Randomization

IPF patients (N = 236)

Pred + Aza + NAC (N = 77)

NAC + Placebo (N = 81)

Placebo (N = 78)
Primary Endpoints

Change in serial measurements of FVC over 60 weeks.

The study was designed to detect a 0.15 L difference between groups over the 60 weeks.
October 14, 2011 NHLBI stops arm based on DSMB review—mean 32 weeks of follow-up

- IPF patients (N = 236)
  - Pred + Aza + NAC (N = 77)
  - NAC + Placebo (N = 81)
  - Placebo (N = 78)
# Selected Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Triple Therapy (n=77)</th>
<th>Matched Placebo (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68.8 ± 7.3</td>
<td>67.9 ± 8.1</td>
</tr>
<tr>
<td>Female sex</td>
<td>23%</td>
<td>27%</td>
</tr>
<tr>
<td>History of smoking</td>
<td>70.1%</td>
<td>74.3%</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>69.3 ± 15.1</td>
<td>72.1 ± 14.4</td>
</tr>
<tr>
<td>DLCO (% pred)</td>
<td>42.1 ± 10.2</td>
<td>45.3 ± 12.4</td>
</tr>
<tr>
<td>CPI</td>
<td>53.7 ± 11.7</td>
<td>49.8 ± 13.5</td>
</tr>
</tbody>
</table>
### Primary Endpoints: FVC

<table>
<thead>
<tr>
<th>FVC (liters)</th>
<th>Triple Therapy</th>
<th>Matched Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.24 (-0.33, -0.15)</td>
<td>-0.23 (-0.32, -0.14)</td>
<td>0.85</td>
<td></td>
</tr>
</tbody>
</table>
## Safety End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Combination Therapy (N=77)</th>
<th>Placebo (N=78)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no. (%)</td>
<td>8 (10)</td>
<td>1 (1)</td>
<td>0.01</td>
</tr>
<tr>
<td>From any cause</td>
<td>8 (10)</td>
<td>1 (1)</td>
<td>0.01</td>
</tr>
<tr>
<td>From respiratory causes</td>
<td>7 (9)</td>
<td>1 (1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospitalization for any cause — no. (%)</td>
<td>23 (30)</td>
<td>7 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute exacerbation — no. (%)</td>
<td>5 (6)</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>Serious adverse event — no. (%)</td>
<td>24 (31)</td>
<td>8 (10)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Kaplan–Meier Curve for the Time until Death

HR 9.26 (95% CI 1.16-74.1)  
P = 0.01

Kaplan–Meier Curve For The Time Until A Composite Of Death or Disease Progression (Decrease in Forced Vital Capacity of ≥10%)

HR 1.46 (95% CI: 0.70–3.05)  
P = 0.30

Kaplan–Meier Curve For The Time Until A Composite Of Death Or Hospitalization

HR: 3.74 (95% CI: 1.68–8.34)  
\( p < 0.001 \)

9.26 (1.16–74.1) 0.01
## Study Drug Adherence

<table>
<thead>
<tr>
<th></th>
<th>At Week 15</th>
<th></th>
<th>At Week 30</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Triple Therapy N=52</td>
<td>Matched Placebo N=57</td>
<td>Triple Therapy N=36</td>
<td>Matched Placebo N=44</td>
</tr>
<tr>
<td>Azathioprine or placebo</td>
<td>73%</td>
<td>98%</td>
<td>64%</td>
<td>98%</td>
</tr>
<tr>
<td>Prednisone or placebo</td>
<td>83%</td>
<td>100%</td>
<td>78%</td>
<td>100%</td>
</tr>
<tr>
<td>NAC or placebo</td>
<td>87%</td>
<td>98%</td>
<td>78%</td>
<td>98%</td>
</tr>
<tr>
<td>All three study agents</td>
<td>73%</td>
<td>98%</td>
<td>64%</td>
<td>98%</td>
</tr>
</tbody>
</table>

P-values for “All three study agents”; Week 15 p-value = .0001; Week 30 p-value < .0001
Conclusions

Increased risks of death and hospitalization were observed in patients with IPF who were treated with a combination of prednisone, azathioprine, and NAC, as compared with placebo.

These findings provide evidence against the use of this combination in such patients.

Goals of effective IPF management

- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Prevent disease progression
- Reduce mortality

These goals should be reached with a minimum of side effects from treatment.
RCTs That Give Hope

- Pirfenidone
- N-acetylcysteine (Fluimucil®)
- Sildenafil (advanced disease)
- BIBF 1120 (oral, potent angiokinase inhibitor)
THANK YOU FOR YOUR ATTENTION.
For patients with IPF, there are currently no validated surrogate endpoints.

"We argue that it is fundamentally flawed and unfair to patients with IPF to hold their disease(s) to a threshold that is not feasible."

In summary, we are vehemently opposed to the idea that mortality data should be required for drug registration in IPF."
Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis

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Recent Articles – Key Findings

- Screening CT scans = ILAs, especially in elderly smokers
- HRCT = diagnostic of IPF
  - Honeycombing = critical features
- Chronic microaspiration seen in IPF and treatment may improve survival
- Gene mutations and polymorphisms in IPF
- Marginal declines in FVC predict survival
- Scoring system to predict outcome in IPF
- Causes of death in IPF = respiratory (subacute & acute)
  - Acute exacerbations seen in many forms of ILD (e.g., IIPs and HSP)
  - Viral infections may play role in some
- New Treatment for lymphangioleiomyomatosis - sirolimus
Gene mutations and polymorphisms have been shown in both sporadic IPF and familial pulmonary fibrosis.

There are no genetic factors consistently associated with sporadic IPF.
MUC5B is a gel-forming mucin expressed by bronchial epithelial

Dense accumulation of MUC5B observed in areas of microscopical honeycombing and involved patchy staining of the metaplastic epithelia lining the honeycomb cysts.

Accumulation also observed in the mucous plugs within the cysts.