Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension

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Ege University Hospital Chest Clinic
İzmir-Turkey
Outline

• Classification of ILD
• PH-IPF prevalences
• Impact on survival
• Parameters correlating with PH-IPF
• Diagnosis of PH-IPF
• PH-IPF treatment
Known Causes
- Drugs
- Collagen Vascular
- Exposures
- Genetic

IIPs: Idiopathic Interstitial Pneumonias
- IPF: Idiopathic Pulmonary Fibrosis 55%
- iNSIP: Nonspecific Interstitial Pneumonia 25%
- AIP: Acute Interstitial Pneumonia <2%
- COP: Cryptogenic Organizing Pneumonia 5%

Granulomatous Lung Diseases
- RB-ILD: Respiratory Bronchiolitis Interstitial Lung Disease 10-15%
- DIP: Desquamative Interstitial Pneumonia

Unique Entities
- PAP
- EG and EP
- LAM
- Capillaritis

Granulomatous Lung Diseases
- Sarcoidosis
- Fungal
- Mycobacterial

IIPs: Idiopathic Interstitial Pneumonias
- IPF: Idiopathic Pulmonary Fibrosis
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- EG and EP
- LAM
- Capillaritis

Rare IIPs: iLIP IPPFE

Unclassifiable IIPs

Travis et al. Am J Respir Crit Care Med. 2013: 188: 733-748
Background

IPF – The challenge
Estimated number of deaths from idiopathic pulmonary fibrosis clinical syndrome, age standardised to the 2008 population of England and Wales ICD, International Classification of Disease.

Navaratnam V et al, Thorax 2011
1. Pulmonary arterial hypertension
   1.1 Idiopathic
   1.2 Heritable
     1.2.1 BMPR2 mutation
     1.2.2 Other mutations
   1.3 Drugs and toxins induced
   1.4 Associated with:
     1.4.1 Connective tissue disease
     1.4.2 Human immunodeficiency virus (HIV) infection
     1.4.3 Portal hypertension
     1.4.4 Congenital heart disease (Table 6)
     1.4.5 Schistosomiasis

1’. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
   1’.1 Idiopathic
   1’.2 Heritable
     1’.2.1 EIF2AK4 mutation
     1’.2.2 Other mutations
   1’.3 Drugs, toxins and radiation induced
   1’.4 Associated with:
     1’.4.1 Connective tissue disease
     1’.4.2 HIV infection

1”. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
   2.1 Left ventricular systolic dysfunction
   2.2 Left ventricular diastolic dysfunction
   2.3 Valvular disease
   2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
   2.5 Congenital /acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
   4.1 Chronic thromboembolic pulmonary hypertension
   4.2 Other pulmonary artery obstructions
     4.2.1 Angiosarcoma
     4.2.2 Other intravascular tumors
     4.2.3 Arteritis
     4.2.4 Congenital pulmonary arteries stenoses
     4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
   5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
   5.2 Systemic disorders, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension
PH and IPF Epidemiology
PH Prevalance in IPF

- Munich 2004: 28%
- IFH 2008: 41%
- UCLA 2007: 42%
- UNOS 2007: 46%
- Mayo 2008: 45%
- Mayo 2005: 84%
- Cleveland Clinic 2009: 46%
- Artemis IPF 2011: 14%
Pulmonary hypertension in IPF

- IPF assessed for transplantation:
  - MPAP ≥ 40: 79
  - MPAP 25-40: 376
  - MPAP ≥ 25: 118
  - Overall: 2525

- IPF clinics:
  - MPAP ≥ 40: 41
  - MPAP 25-40: 61
  - MPAP ≥ 25: 61
  - Overall: 124

References:

- Chest 2006; 129:746–752
- Am J Respir Crit Care Med 2006; 174:659–664
- Chest 2007; 131:657–663
- Chest 2007; 132:998-1006

- Respir Care 2010;55:584–588
- Chest 2007; 131:650-656
- Respir Med 2007; 101: 2153–2159
- Respir Med 2012;106.6: 875-82
- Respiration 2013;85:456–463
- Respir Med 2012; 106: 1613–1621

Mogulkoc N
Pulmonary hypertension in combined pulmonary fibrosis and emphysema (CPFE)


Mogulkoc N
Pulmonary hypertension in combined pulmonary fibrosis and emphysema (CPFE)
PH and ILD
Impact on Survival
IPF Deaths Compared to Cancer

Number of deaths in the UK per year

Source: Adapted from Cancer Research UK, Cancer incidence and mortality (2011), 2014
IPF Survival Compared to Common Cancers

Source: Adapted from Cancer Research UK, England and Wales survival (2010-2011), 2014
IPF survival over the last decade

Strongman, Kauser, Bogman and Maher, BTS 2013
IPF and PH

n = 79, RHC

n = 54

n = 25

P < 0.001

mPAP > 25 mmHg

1-year mortality rate
- 28% in patients with PH
- 5.5% in those without PH

n = 88, echocardiography

sPAP > 50 mmHg: median survival of 0.7 year

versus sPAP < 50 mmHg more than 4 years


Progression of PH in IPF

38% to 87%
PH and ILD
Impact on functional parameters
## Correlates of PH

<table>
<thead>
<tr>
<th>DLco</th>
<th>Pulmonary capillary wedge pressure</th>
<th>PFT</th>
<th>Reduced PaO₂</th>
<th>6MWT O₂ saturation</th>
<th>6MWT distance</th>
<th>Mortality</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>Odds ratio 2.6</td>
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<td>Chest 2006; 129:746</td>
<td>![arrow down]</td>
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<tr>
<td>Chest 2007; 131:657</td>
<td>![arrow down]</td>
<td>![arrow up]</td>
<td>FVC &gt; 70%</td>
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<tr>
<td>Eur Respir J 2007; 30:715</td>
<td>![arrow up]</td>
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<td>FEV₁</td>
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<td>Chest 2007; 132:998</td>
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<td>Chest 2007; 13:650</td>
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<td>RR 2.2</td>
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<td>Respir Med 2007; 101:2153</td>
<td>![arrow down]</td>
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<td>![arrow down]</td>
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<tr>
<td>Respiration 2013; 85:456</td>
<td>![arrow down]</td>
<td>![arrow up]</td>
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<td>HR 6.4% for each mmHg</td>
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<tr>
<td>Respir Med 2012; 106:1613</td>
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</table>

Mogulkoc N
IPF and PH: Functional Impact

Impact of PH

dyspnea ↑
gas exchange at rest ↓
$DL_{CO}$ ↓
rapid desaturation upon exercise ↑
brain natriuretic peptide (BNP) levels ↑
right heart dilatation
exercise capacity ↓


PH and ILD Detection
Suspect PH complicating ILD:

- Low $\text{DL}_{CO}$
- Rapid desaturation with exertion
- Right heart enlargement (ECG, CXR, Echo)
- Elevated BNP
- Dyspnea > expected
ILD and PH: detection

Assessment and definition of PH due to chronic lung diseases (group 3)

- Echocardiography
  - Initial modality for noninvasive diagnosis of PH
  - Comparison of echocardiographic data with RHC in lung disease patients
    - positive predictive values 68%
    - negative predictive values 67%


Recommendations when to Perform RHC in Chronic Lung Disease

When

1) evaluation for lung transplantation is deemed necessary

2) clinical worsening and progressive exercise limitation disproportionate to ventilatory impairment

3) progressive gas exchange abnormalities disproportionate to ventilatory impairment

4) accurate prognostic assessment is critical

5) severe PH is suspected by noninvasive measures and further therapy or inclusion in clinical trials or registries are being considered

6) there is suspicion of left ventricular systolic/diastolic dysfunction and categorization of the pulmonary artery occlusion pressure might alter management

Diagnostic algorithm in ILD patients with suspected PH

Patients with persistent or “out of proportion” dyspnea

- PFTs
- CT angiogram r/o pulmonary embolism
- 6MWT

**PFTs**
- DLco < 35%*
- FVC/DLco ratio > 1.5 (ILD)*

**CT angiogram**
- PA segment > ~30 mm
- Desaturation < 88% during RA 6MWT*
- Distance < 200–300 meters*
- Pulse rate recovery < 13 beats/min*

**6MWT**
- Supportive Evidence
  - ↑NT pro-BNP

**Transthoracic echocardiogram**
- RVSP > 35 mm Hg*
  - TR > 2.5 m/s*
  - Right ventricular dilation or dysfunction

**Consider RHC**

Pulmonary artery size as a predictor of outcomes in idiopathic pulmonary fibrosis

Stephanie Shin¹, Christopher S. King², Nitin Puri³, Oksana A. Shlobin², A. Whitney Brown², Shahzad Ahmad², Nargues A. Weir² and Steven D. Nathan²
PH and ILD
Treatment
PH specific therapies in IPF
Phosphodiesterase 5 inhibitors

• Mechanism:
  – vasodilatory effects
  – antiproliferative capacity in the pulmonary vasculature

• Evidence
  – STEP-IPF study of sildenafil
  – patients with advanced IPF with complicating PH
  – Neg primary end point: 20% increase in 6MWT distance, \( p = 0.39 \)
  – Pos
    • change in quality of life measures
    • DLCO
    • partial pressure of arterial oxygen (\( \text{PaO}_2 \)) favoring the treatment arm.
    • a trend towards a mortality benefit after 24 weeks of follow up
      – Placebo: 11 † vs treatment 4 †
    • those patients with echocardiographic evidence of right ventricular dysfunction revealed
      a favorable effect in the treatment arm based on the 6MWT distance

This provides proof of concept, to the potential targeting of PH in patients with IPF

Bosentan in Pulmonary Hypertension Associated with Fibrotic Idiopathic Interstitial Pneumonia

Tamera J. Corte\textsuperscript{1,2*}, Gregory J. Keir\textsuperscript{1,3*}, Konstantinos Dimopoulos\textsuperscript{4}, Luke Howard\textsuperscript{5}, Paul A. Corris\textsuperscript{6}, Lisa Parfitt\textsuperscript{4}, Claire Foley\textsuperscript{7}, Monica Yanez-Lopez\textsuperscript{7}, Daphne Babalis\textsuperscript{7}, Philip Marino\textsuperscript{4}, Toby M. Maher\textsuperscript{1}, Elizabeth A. Renzoni\textsuperscript{1}, Lisa Spencer\textsuperscript{3}, Charlie A. Elliot\textsuperscript{9}, Surinder S. Birring\textsuperscript{10}, Katherine O’Reilly\textsuperscript{11}, Michael A. Gatzoulis\textsuperscript{4}, Athol U. Wells\textsuperscript{1}, and Stephen J. Wort\textsuperscript{4,12}; for the BPHIT Study Group

\textsuperscript{1}Interstitial Lung Disease Unit, \textsuperscript{4}National Pulmonary Hypertension Service, and \textsuperscript{7}Clinical Trial Evaluation Unit, Royal Brompton Hospital, London, United Kingdom; \textsuperscript{2}Department of Respiratory Medicine, Royal Prince Alfred Hospital and Sydney University, Sydney, Australia; \textsuperscript{3}Department of Respiratory Medicine, Princess Alexandra Hospital, Brisbane, Australia; \textsuperscript{5}National Pulmonary Hypertension Service, Hammersmith Hospital, London, United Kingdom; \textsuperscript{6}National Pulmonary Hypertension Service, The Freeman Hospital, and Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom; \textsuperscript{8}Department of Respiratory Medicine, University Hospital Aintree, Liverpool, United Kingdom; \textsuperscript{9}National Pulmonary Hypertension Service, Royal Hallamshire Hospital, Sheffield, United Kingdom; \textsuperscript{10}Department of Respiratory Medicine, Kings College Hospital, London, United Kingdom; and \textsuperscript{11}Department of Respiratory Medicine, Southampton General Hospital, Southampton, United Kingdom; and \textsuperscript{12}National Heart and Lung Institute, Imperial College, London, United Kingdom
PH specific therapies in IPF

Bosentan

Fisher p=1.00

% of patients achieving primary endpoint

Placebo (n=14) 28.6%

Bosentan (n=25) 28.0%
# Treatment of Idiopathic Pulmonary Fibrosis With Ambrisentan

## A Parallel, Randomized Trial

Ganesh Raghu, MD; Juergen Behr, MD; Kevin K. Brown, MD; Jim J. Egan, MD; Steven M. Kawut, MD; Kevin R. Flaherty, MD; Fernando J. Martinez, MD; Steven D. Nathan, MD; Athol U. Wells, MD; Harold R. Collard, MD; Ulrich Costabel, MD; Luca Richeldi, MD; Joao de Andrade, MD; Nasreen Khalil, MD; Lake D. Morrison, MD; David J. Lederer, MD; Lixin Shao, MD; Xiaoming Li, PhD; Patty S. Pedersen, BSN; A. Bruce Montgomery, MD; Jason W. Chien, MD; Thomas G. O’Riordan, MD, and the ARTEMIS-IPF Investigators*

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## Table

<table>
<thead>
<tr>
<th>End Point</th>
<th>Placebo (n = 163)</th>
<th>Ambrisentan (n = 329)</th>
<th>Log-Rank P Value</th>
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<tbody>
<tr>
<td></td>
<td>Events, n</td>
<td>Proportion (95% CI)*</td>
<td>Events, n</td>
</tr>
<tr>
<td>Disease progression</td>
<td>28</td>
<td>17 (12 to 24)</td>
<td>90</td>
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<tr>
<td>Lung function decline</td>
<td>19</td>
<td>12 (7 to 18)</td>
<td>55</td>
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<tr>
<td>Respiratory hospitalization</td>
<td>9</td>
<td>6 (3 to 10)</td>
<td>44</td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
<td>4 (1 to 8)</td>
<td>26</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Placebo (n = 163)</td>
<td>Ambrisentan (n = 329)</td>
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<td>---------------------------------------------------</td>
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<tr>
<td>Mean age (SD), y</td>
<td>66.1 (7.1)</td>
<td>65.8 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>111 (68.1)</td>
<td>244 (74.2)</td>
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<tr>
<td>White, n (%)</td>
<td>145 (89.0)</td>
<td>293 (89.1)</td>
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<tr>
<td>Smoking status, n (%)</td>
<td></td>
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<tr>
<td>Never</td>
<td>53 (32.5)</td>
<td>105 (31.9)</td>
<td></td>
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<tr>
<td>Current</td>
<td>5 (3.1)</td>
<td>7 (2.1)</td>
<td></td>
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<tr>
<td>Former</td>
<td>104 (63.8)</td>
<td>217 (66.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary hypertension, n (%)</strong></td>
<td><strong>16 (9.8)</strong></td>
<td><strong>32 (9.7)</strong></td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (SD), mm Hg</td>
<td>20.6 (8.0)</td>
<td>20.3 (6.3)</td>
<td></td>
</tr>
<tr>
<td>SLB-confirmed diagnosis of IPF, n (%)*</td>
<td>76 (46.6)</td>
<td>154 (46.8)</td>
<td></td>
</tr>
<tr>
<td>Mean disease duration (SD), y</td>
<td>0.9 (1.2)</td>
<td>1.1 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Mean FVC (SD), % predicted</td>
<td>69.9 (13.8)</td>
<td>68.7 (13.1)</td>
<td></td>
</tr>
<tr>
<td>Mean hemoglobin-adjusted Dl,co (SD), % predicted</td>
<td>45.6 (13.3)</td>
<td>42.0 (13.8)</td>
<td></td>
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<tr>
<td>Mean CPI score (SD)</td>
<td>50.6 (10.4)</td>
<td>53.0 (10.5)</td>
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<tr>
<td>Mean 6MWD (SD), m</td>
<td>420.5 (121.4)</td>
<td>410.4 (118.7)</td>
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<tr>
<td>Mean SGRQ score (SD)</td>
<td>40.5 (21.1)</td>
<td>44.5 (21.6)</td>
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<tr>
<td>Mean TDI score (SD)</td>
<td>7.6 (2.5)</td>
<td>7.3 (2.4)</td>
<td></td>
</tr>
</tbody>
</table>

CPI = composite physiologic index; Dl,co = diffusion capacity for carbon monoxide; IPF = idiopathic pulmonary fibrosis; SGRQ = St. George's Respiratory Questionnaire; 6MWD = 6-min walk distance; SLB = surgical lung biopsy; TDI = Transition Dyspnea Index.

* Patients were stratified by this variable.
PH specific therapies in IPF

Riociguat

Direct stimulator and activators of the soluble guanylate cyclase

- **Mechanism**
  - strong pulmonary vasodilatory
  - antiproliferative potency in experimental models of PH

- **Evidence**
  - **PH-ILD**
    - phase II trial
    - No reduction in PAP (prim end point)
    - but demonstrated the efficacy in
      - PVR↓
      - systemic vascular resistance ↓
      - cardiac output↑
      - 6MWD ↑

Dear Dr Nesrin Mogulkoc,

Re: Bayer announces the termination of RISE-IIP (Riociguat in pulmonary hypertension associated with idiopathic interstitial pneumonia)

Following a recommendation yesterday from our independent data safety monitoring board (DMC) and steering committee (SC) Bayer is terminating study 13605 /RISE-IIP for riociguat (BAY63-2521) with immediate effect. The DMC observed that patients randomized to riociguat (0.5 – 2.5 mg TID) showed increased mortality and more serious adverse events than patients in the placebo group. The risks appear to be greatest early after drug initiation and during the dose titration period, and is less pronounced among those subjects able to tolerate riociguat and continue to their optimal dose. The exact causes or physiological mechanisms for the excess deaths and adverse events are not
## 2015: PH due to Interstitial Lung Disease

### Classification and management of PH in the setting of interstitial lung disease

<table>
<thead>
<tr>
<th>Underlying lung disease</th>
<th>mPAP &lt; 25 mmHg</th>
<th>25 ≥ mPAP &lt; 35 mmHg</th>
<th>mPAP ≥ 35 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IPF with FVC ≥ 70% of predicted</strong>&lt;br&gt;No gross parenchymal or airway abnormalities on CT</td>
<td>No PH&lt;br&gt;No PAH treatment recommended</td>
<td>Meets criteria for IPAH&lt;br&gt;PAH treatment guidelines may apply</td>
<td>Meets criteria for IPAH&lt;br&gt;PAH treatment guidelines may apply</td>
</tr>
<tr>
<td><strong>IPF with FVC &lt; 70% of predicted</strong>&lt;br&gt;Combined pulmonary fibrosis and emphysema on CT</td>
<td>No PH&lt;br&gt;No PAH treatment recommended</td>
<td>PH-IPF, PH-CPFE&lt;br&gt;No data support treatment according to PAH treatment guidelines</td>
<td>Severe PH-IPF, severe PH-CPFE&lt;br&gt;Refer to a center with expertise in both PH and interstitial lung disease for individualized patient care&lt;br&gt;RCTs urgently needed&lt;br&gt;Potential use of PAH treatment as a bridge to lung Tx in endstage disease</td>
</tr>
</tbody>
</table>
Conclusions

• Almost all types of ILDs can be associated with pulmonary hypertension
• Cause is multifactorial, although hypoxemia plays a role
• The presence of PH is invariable associated with a poor outcome
• PAH specific treatment has no proven benefit in these diseases