Paul W. Noble, MD, received his Bachelor of Arts degree from Haverford College in Pennsylvania, and his medical degree from New York University School of Medicine. He completed his medical residency and chief residency at the University of California, San Francisco Hospitals. He completed his pulmonary and critical care fellowships at the University of Colorado and the National Jewish Center in Denver, Colorado.

From 1992–1997 Dr. Noble was Assistant Professor at Johns Hopkins School of Medicine, where he established the Interstitial Lung Disease Clinic. He moved to Yale University School of Medicine in 1997, where he became Professor of Medicine in 2004. He served as Director of the ILD Program at Yale-New Haven Hospital until 2006, when he moved to Duke University as the Chief of the Division of Pulmonary, Allergy and Critical Care Medicine. In January 2013, he moved to Cedars-Sinai Medical Center as Chair of the Department of Medicine.

Dr. Noble is a physician scientist with an active research laboratory focused on elucidating the basic mechanisms of lung fibrosis. His research laboratory has been funded by the National Institutes of Health since 1992. Dr. Noble has been involved in industry-sponsored clinical trials evaluating new therapies in IPF and participated in both the pirfenidone and nintedanib programs that led to the first FDA approved treatments for IPF. He continues to have an active clinical practice in ILD.

Dr. Noble is an elected member of the American Society of Clinical Investigation and the American Association of Physicians. He is a Deputy Editor of the *Journal of Clinical Investigation*.

**OBJECTIVES:**
Participants should be better able to:
The Challenges of Fibrosing Lung Diseases in the Setting of Connective Tissue Disease: Why Doesn’t the Lung Behave Like a Joint?

Paul W. Noble, MD
Chair, Department of Medicine
Director, Women’s Guild Lung Institute
Vera and Paul Guerin Distinguished Family Chair in Pulmonary Medicine
Cedars-Sinai Medical Center

Disclosures

- Consultant for Industry Development of Therapies for Idiopathic Pulmonary Fibrosis
  - Genentech
  - Boehringer-Ingelheim
Case Presentation

- 63 y/o gentleman who presented with shortness of breath and cough for many months
- In 2009 he was treated for cough with inhaled steroids and nasal steroids for PND
- His symptoms improved
- Over the last few months he has noted DOE and fatigue
- GERD symptoms
- No joint pains or myalgias

Social History

- Works as a television producer
- He has a dog he likes to walk on the beach in Malibu where he lives
- No birds, down feathers or mold in the home
- He is a lifelong nonsmoker
- Born and raised in Philadelphia
- Attended Brown University
Laboratory Screening

• CBC, BMP WNL
• ANA 1:40
• RF negative
• ESR 12

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Ref</th>
<th>Pre Mass</th>
<th>%</th>
<th>CI Ratio</th>
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<td>FVC</td>
<td>Liters</td>
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<td>Liters</td>
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<td>63</td>
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<td>FEV1/FVC %</td>
<td>75</td>
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<td>FEF25-75%L/sec</td>
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<td>MVV</td>
<td>L/min</td>
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<td>87</td>
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<th>Lung Volumes</th>
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<td>TLC</td>
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<td>VC</td>
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<td>FRC N2</td>
<td>Liters</td>
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<tr>
<td>FRC PL</td>
<td>Liters</td>
</tr>
<tr>
<td>ERV</td>
<td>Liters</td>
</tr>
<tr>
<td>RV</td>
<td>Liters</td>
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<tr>
<td>RV/TLC %</td>
<td>38</td>
</tr>
<tr>
<td>IF</td>
<td>Liters</td>
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<table>
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<th>Diffusion</th>
<th>Ref</th>
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<tr>
<td>DLCO</td>
<td>mL/mmHg/min</td>
</tr>
<tr>
<td>DL Adj</td>
<td>mL/mmHg/min</td>
</tr>
<tr>
<td>DLCO/VA</td>
<td>mL/mmHg/min/L</td>
</tr>
<tr>
<td>VA</td>
<td>Liters</td>
</tr>
</tbody>
</table>
Case Presentation

- 60 y/o female who presented with shortness of breath and cough for the last 2 months
- She initially presented to her PCP and was told that she may have had a pneumonia and was given a course of azithromycin
- This did not improve her symptoms and she was given additional courses of ciprofloxacin and then moxifloxacin
- Again there was no improvement in her symptoms
Diagnostic Evaluation of ILD

- What is the gold standard?
  - History and Physical Exam
  - Laboratory Evaluation
  - Radiographic Evaluation
    • HRCT
  - Physiologic Evaluation
    • Exercise gas exchange
  - Pathologic Evaluation

Key Systemic Diseases with ILD

- Scleroderma
- Rheumatoid Arthritis
- MCTD/Overlap
- Polymyositis
  • Classic (weakness > ILD)
  • Anti-synthetase syndrome (ILD > weakness)
- “Undifferentiated” CTD
Chronic Lower-Zone ILD Not Associated with Systemic Disease

• Idiopathic Interstitial Pneumonias
• Chronic (occult) HSP
• Occult Aspiration
• Drug Reaction (Amiodarone)

• Age and Gender Matter

Laboratory Tests To Exclude Systemic Disease

• ESR (>100-not IPF)
• ANA (titre 1:2560- not IPF)
• RF
• CCP
• Scl-70
• RNP/Sm/Ro/La
• CPK, aldolase (statins may influence)
• Jo-1 (anti-synthetase syndrome)
• Myositis-plus
Myositis-Plus Panel

- PM/SCL
- MI-2
- PL-7
- PL-12
- EJ
- OJ
- Ku
- U2 SN RNP
- SRP

Jo-1 Polymyositis
NSIP (Anti-Synthetase Syndrome)

Undifferentiated Connective Tissue Disease
Interstitial Pneumonia with Autoimmune Features

TABLE 1. DIAGNOSTIC CRITERIA FOR PATIENTS WITH UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Presence of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms associated with connective tissue disease</td>
<td>At least one of the following symptoms:</td>
</tr>
<tr>
<td>1. Raynaud’s phenomenon</td>
<td></td>
</tr>
<tr>
<td>2. Arthralgia/multiple joint swelling</td>
<td></td>
</tr>
<tr>
<td>3. Photosensitivity</td>
<td></td>
</tr>
<tr>
<td>4. Unintentional weight loss</td>
<td></td>
</tr>
<tr>
<td>5. Morning stiffness</td>
<td></td>
</tr>
<tr>
<td>6. Dry mouth or dry eyes (sicca features)</td>
<td></td>
</tr>
<tr>
<td>7. Dysphagia</td>
<td></td>
</tr>
<tr>
<td>8. Recurrent unexplained fever</td>
<td></td>
</tr>
<tr>
<td>9. Gastroesophageal reflux</td>
<td></td>
</tr>
<tr>
<td>10. Skin changes (rashes)</td>
<td></td>
</tr>
<tr>
<td>11. Oral ulceration</td>
<td></td>
</tr>
<tr>
<td>12. Nonerosive arthralgia</td>
<td></td>
</tr>
<tr>
<td>13. Proximal muscle weakness</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Evidence of systemic inflammation in the absence of infection</th>
<th>Positive findings for at least one of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Antinuclear antigen</td>
<td></td>
</tr>
<tr>
<td>2. Rheumatoid factor</td>
<td></td>
</tr>
<tr>
<td>3. Anti-SCl 70 antibody</td>
<td></td>
</tr>
<tr>
<td>4. SS-A or SS-B</td>
<td></td>
</tr>
<tr>
<td>5. Jo-1 antibody</td>
<td></td>
</tr>
<tr>
<td>6. Sedimentation rate (&gt; two times normal), C-reactive protein</td>
<td></td>
</tr>
</tbody>
</table>

Kinder et al
AJRCCM 2007
176:691
Classification of Idiopathic Interstitial Pneumonias

- Idiopathic interstitial pneumonia (IIP)
  
  - Idiopathic pulmonary fibrosis/usual interstitial pneumonia (UIP)
  - Nonspecific interstitial pneumonia (NSIP)
  - Desquamative interstitial pneumonia (DIP)
  - Respiratory bronchiolitis-associated interstitial lung disease (RBILD)
  - Acute interstitial pneumonia (AIP)
  - Hamman-Rich

70% ?15-25%

"Idiopathic Interstitial Pneumonias"

- IPF
- NSIP
- DIP
- RBILD
Idiopathic Pulmonary Fibrosis

Fatal disease of unknown etiology

>100,000 patients in US

2 FDA approved therapies

Lung transplant only therapy to prolong survival in end-stage disease
Classic IPF/UIP = Diagnostic HRCT

subpleural honeycombing

“Classic” Idiopathic UIP
Early HRCT Findings in IPF

Usual Interstitial Pneumonia
Fibrotic Non Specific Interstitial Pneumonia

Different Patterns of Fibrosis

NSIP  

UIP
Desaturation Defined as a Fall in $O_2$ Saturation to 88% or Less During 6MWT

Survival Probability

Desaturators
Non-desaturators

Years

Survival Probability

0.0 0.2 0.4 0.6 0.8 1.0

0 1 2 3 4 5


February 2015
Antisynthetase Syndrome

Follow up HRCT

prednisone 10 mg
mycophenolate 1 gm
## Trend Report

Physician: NOBLE PAUL W

<table>
<thead>
<tr>
<th>Date</th>
<th>FVC</th>
<th>FVC Post</th>
<th>FEV1</th>
<th>FEV1 Post</th>
<th>FEF25-75%</th>
<th>FEF25-75% Post</th>
<th>PEF</th>
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<td>Liter(s)</td>
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<td>L/sec</td>
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<td>Liter(s)</td>
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<td>8.99</td>
<td>L/sec</td>
<td>3.86</td>
<td>11.5</td>
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<tr>
<td>10/06/15</td>
<td>2.38</td>
<td>Liter(s)</td>
<td>2.00</td>
<td>Liter(s)</td>
<td>3.10</td>
<td>L/sec</td>
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<td>L/sec</td>
<td>3.55</td>
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<tr>
<td>05/12/15</td>
<td>2.37</td>
<td>Liter(s)</td>
<td>2.06</td>
<td>Liter(s)</td>
<td>2.97</td>
<td>L/sec</td>
<td>5.49</td>
<td>L/sec</td>
<td>3.21</td>
<td>12.8</td>
</tr>
</tbody>
</table>
Additional Information

- Rheum panel
  - RF 13 (nl <20)
  - Anti-SCL70 negative
  - ANA 1:2560
  - Anti-JO1 positive
  - Anti-RO positive
  - Anti-LA positive
  - ESR 22
  - Aldolase 25.9 (nl <7.5)
  - CK 735

- Patient did admit that she was having some muscle fatigue when getting up from a chair
After high dose prednisone
Post wean of steroids
Follow up HRCT

prednisone 10 mg
mycophenolate 2 gm
2014 was a watershed year for IPF
Is all fibrotic lung disease the same?

Progressive disease leading to transplant within 3 years

Alive and well without oxygen for 8 years with judicious immunosuppression

Idiopathic Pulmonary Fibrosis

• Chronic fibrosing lung disease of unknown cause
• No exposure to fibrosing agents (asbestos, amiodarone, etc)
• No systemic illness (Collagen vascular disease)
• HRCT with UIP pattern
• Surgical lung biopsy with UIP pattern
• 5 year survival is approximately 30%
Usual Interstitial Pneumonia

Epithelial Dysfunction in the Pathobiology of Progressive Fibrosis

Environmental insults
- Viral infection
- Smoking

Genetic predisposition
- Mutations in surfactant protein genes, telomerase, mucin genes

Epithelial cell dysfunction

Misfolded proteins in the ER
- UPR
- ER stress
- Apoptosis

Senescence
- Impaired progenitor cell renewal and reprogramming
- Fibrosis

Noble et al, JCI 2012
Reduced Type II alveolar epithelial cells in IPF lungs

Self-renewal and differentiation of AEC2 stem cells in 3D organoid culture

Barkauskas et al., JCI 2013
Reduced stem cell renewal of AEC2 cells from IPF lung

Why is fibrosis progressive and destructive in IPF?
Cell suspension placed in upper chamber

Invasive cells pass through Matrigel layer and cling to the bottom of the Boyden chamber membrane. Non-invasive cells stay in the upper chamber

After removal of non-invasive cells, invasive cells are stained and quantified

Invasive Capacity = # cells invaded matrigel/20x hpf

Fibroblasts from IPF patients spontaneously invade Matrigel and express HAS2 during invasion

Yi et al., J. Exp. Med, 2011
Paradigm for the development of severe pulmonary fibrosis

Possible Mechanisms of Pirfenidone Action

- Antifibrotic
- Molecular target unclear
- Active in several animal models of fibrosis (lung, liver, kidney)
ASCEND 2014

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group

ASCEND Study Design

Inclusion Criteria

- Age 40-80
- Confirmed IPF
- 50 - 90% FVC pred
- 30 - 90% DLco pred
- FEV1/FVC ≥ 0.80
- 6-MWD ≥ 150 m

555 Patients

52 Weeks

Endpoints

1st: Δ FVC or death
2nd: 6-MWD
PFS
Dyspnea
Death

Oral Pirfenidone
2403 mg Daily

Placebo

PFS - Progression-free survival

Primary ASCEND Endpoint Achieved

Patients with ≥ 10% FVC Decline or Death (%)

Week

Primary Endpoint

P < 0.001

P < 0.001

P < 0.001

P < 0.001

48% Relative Reduction

Pirfenidone Increased Progression-Free Survival*

Patients (%)

Week

P < 0.001

*Progression is first occurrence of death, 10% ↓ FVC, or 50 m ↓ 6MWD

Possible Mechanisms of Nintedanib Action

- Triple kinase inhibitor
- Phosphatase activator
- Antiangiogenic, antitumor activity

Nintedanib

VEGF  PDGF  FGF  SHP-1

Pleiotropic Effects


INPULSIS 2014

The New England Journal of Medicine

ORIGINAL ARTICLE

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

**INPULSIS-1 and INPULSIS-2 Study Design**

**Inclusion Criteria**
- Age ≥ 40
- IPF ≤ 5y
- ≥ 50% FVC pred
- 30 - 79% DLCO pred
- HRCT within 1y

**Endpoints**
1. ΔFVC
2. Time to first AE
3. Δ SGRQ

**1066 Patients**

AE – Acute Exacerbation
SGRQ – St. George’s Respiratory Questionnaire

**Primary INPULSIS Endpoint Achieved**

**Annual Rate of Change of FVC**

**INPULSIS-1**
- Nintedanib, 150 mg Twice Daily (N=509)
- Placebo (N=204)
- 52% Relative Reduction
- Difference, 125.3 (95% CI: 77.7 - 172.8)
- P<0.001

**INPULSIS-2**
- Nintedanib, 150 mg Twice Daily (N=439)
- Placebo (N=219)
- 45% Relative Reduction
- Difference, 116.6 (95% CI: 44.8 - 182.7)
- P<0.001

Management of Fibrotic Lung Disease

- IPF/UIP
  - Pulmonary rehab
  - Transplant evaluation
  - Treatment with pirfenidone or nintedanib
  - Clinical trials
- CTD/UIP
  - Immunosuppressive therapy vs Antifibrotic therapy

Collaborators

Advanced Health Sciences Pavilion
Cedars-Sinai Medical Center