ILD highlights from the ERS 2017 congress
Sep 09 – Sep 13 / Milan, Italy

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Objective and focus of this report

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Objective and focus

ERS congress 2017
The congress programme 2017 included sessions highlighting the cutting-edge advancements in the field of interstitial lung disease (ILD) and idiopathic pulmonary fibrosis (IPF).

Objective of this report
Provide current expert perspectives on the clinical importance of the data for healthcare professionals in research and daily practice.

Focus of this report
Up to date developments, main topics of discussion and highlights on idiopathic pulmonary fibrosis (IPF) and interstitial lung diseases (ILDs) presented in numerous sessions at the ERS 2017.

Please note that these slides report the data presented during the ERS 2017 in Milan, Italy.

We have reported on posters and oral presentations. These are marked OAXXXX for an oral presentation, and PAXXXX for a poster presentation.

If you wish to download the abstracts or eposters, they are available at http://k4.ersnet.org/prod/v2/front/program/?e=42.

Please check your local regulations and guidelines when prescribing treatment and managing patients with ILD.
Topic overview

► **ILD clinical year in review**
  • New insights in ILD and IPF

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  • Interstitial lung diseases in children
  • Transbronchial cryobiopsy
  • Diagnostic markers for ILD subtypes
  • Early detection of pulmonary fibrosis

► **New insights into ILD management**
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  • Management of acute exacerbations
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  • Dyspnoea and respiratory failure
  • Treatment adherence

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  • INSIGHTS-IPF registry
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► **New data on antifibrotic treatments**
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  • Real-life data

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  • Non-coding RNAs
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  • Shared pathways in IPF and COPD

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  • CT fibrosis scores and disease outcome
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  • Prescribing information
  • Acknowledgements
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New insights in ILD and IPF\textsuperscript{1}: The experts’ selection

**IPF diagnosis**
- In diagnosis of 70 ILD cases, expert physicians could diagnose IPF with similar accuracy to their respective multidisciplinary team\textsuperscript{2}
- 404 respiratory physicians and 34 IPF experts assessed 60 ILD cases. For physicians to match diagnostic accuracy for IPF of MDT meetings, they required > 20 years’ experience, although non-university hospital physicians did not quite reach expert levels of accuracy\textsuperscript{3}
- Attendance of weekly MDT meetings improved diagnostic accuracy\textsuperscript{3}

**ILD management**
- Post-hoc analysis of the INPULSIS\textsuperscript{®} trials showed that nintedanib slowed disease progression with ~50\% reduction in FVC decline, both in patients with honeycombing and/or UIP, and those without honeycombing (n=1061)\textsuperscript{4}
- In post-hoc analysis of the CAPACITY/ASCEND (n=1247) trials, patients in GAP stages I and II/III showed clinically significant disease progression, and pirfenidone was similarly efficacious in both groups of patients\textsuperscript{5}

**Pathogenesis**
- Lung fibrosis is a predictor of higher mortality in chronic hypersensitivity pneumonitis (cHP), a condition that can show matching clinical behaviour to IPF\textsuperscript{6}
- The MUC5B promoter variant rs35705950 and short telomere length were associated with pulmonary fibrosis in cHP\textsuperscript{6}
- Short telomere length was also associated with reduced survival and UIP in cHP\textsuperscript{6}

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Expert comments

IPF may be diagnosed with high confidence by MDT but also by ILD expert physicians with > 20 years of experience. Proper diagnosis of cHP and NSIP is more problematic.

Long-term data and further sub-group analyses confirm the safety and efficacy of nintedanib and pirfenidone for the treatment of IPF.

A MUC5B variant and short telomere length are associated with a fibrotic pattern and poor prognosis in cHP.
Recent advances in ILD diagnosis
Interstitial lung diseases in children (chILD)

Diffuse parenchymal lung diseases in children¹

- Distribution of chILD disease entities were analysed in patients (n=366) with chILD reported to the European Management Platform for Childhood Interstitial Lung Diseases (see table)
- A classification system that includes cases without lung biopsy and also respiratory medications prescribed was used

Installation of a multidisciplinary team (MDT) review board for children's interstitial lung disease (ILD)²

- A multidisciplinary web-linked tool for peer review was installed on the European management platform for children’s interstitial lung disease
- Over a time span of 3 years 346 cases were reviewed, 302 times diagnosis was confirmed, 32 times specified and 12 times changed

<table>
<thead>
<tr>
<th>Types of chILD and drugs used in cohort</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most commonly diagnosed types of chILD</td>
<td></td>
</tr>
<tr>
<td>chILD related to alveolar surfactant region</td>
<td>194</td>
</tr>
<tr>
<td>chILD related to systemic disease</td>
<td>60</td>
</tr>
<tr>
<td>Specific conditions of undefined aetiology</td>
<td>59</td>
</tr>
<tr>
<td>chILD of the immune intact host</td>
<td>46</td>
</tr>
<tr>
<td>Most commonly prescribed drugs</td>
<td></td>
</tr>
<tr>
<td>Glucocorticosteroids</td>
<td>175</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>88</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>50</td>
</tr>
</tbody>
</table>

chILD: Children’s interstitial lung disease

¹ Carlens J, et al. ERS Milan 2017; 181: PA1513
² Seidl E, et al. ERS Milan 2017; 355: PA2962
Transbronchial cryobiopsy (TCB) in ILD diagnosis

Real world experience with TCB¹

- The clinical value of TCB in the context of multidisciplinary ILD team at a tertiary care centre for ILDs was evaluated
- n=115, on average 4 samples were taken, in 70% from 2 lobes
- Complications were pneumothorax in 11%, mild to moderate bleeding in 28%, no acute exacerbations
- 64% of specimens were judged diagnostic, in the context of MDT final diagnoses were possible in 86%

Diagnostic yield of TCB depends on number of samples taken²

- This study showed that diagnostic accuracy of TCB increases when two instead of one sample are taken (see table)
- Increase in diagnostic yield is only statistically significant if the two samples are taken from different segments

<table>
<thead>
<tr>
<th>Number of samples taken</th>
<th>% cases diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
</tr>
<tr>
<td>2 (from same segment)</td>
<td>78</td>
</tr>
<tr>
<td>2 (from different segments)</td>
<td>96</td>
</tr>
</tbody>
</table>

1 Wälscher J. ERS Milan 2017; 525: OA4636
2 Poletti V. ERS Milan 2017; 154: 1392
Diffusing capacity (DL\textsubscript{CO})

- Impairment is more common and stronger in patients with dcSSc and SSc-overlap syndrome than patients with lcSSc
- DL\textsubscript{CO} alone may be a useful marker for diagnosis and monitoring of pulmonary involvement in SSc

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SSc: Systemic sclerosis
dcSSc: diffuse cutaneous systemic sclerosis
lcSSC: limited cutaneous involvement systemic sclerosis

1 Kreuter M, et al. ERS Milan 2017; 115: PA886
Early diagnosis of ILDs

Benefits from a programme for early identification of ILDs in primary care centres¹

**Aim**
To evaluate the efficacy of a programme for early diagnosis of ILDs in primary care centres (PCC)

**Results**
n=62, median time from PCC visit to ILD diagnosis was 6.8 months. Main signs for ILD suspicion were Velcro crackles and finger clubbing, radiological findings and familial history

**Conclusion**
The programme for early ILD identification in PCC leads to a high rate of ILD diagnoses and treatment optimisations. Due to advanced age and comorbidities, a proportion of patients did not benefit from the programme

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Finger clubbing for early diagnosis of ILDs²

**Aim**
Investigate the prevalence of clubbing in patients with ILDs and its association with disease severity and agreement between various assessment methods was evaluated

**Results**
7.41% of the cohort showed clubbing. No correlation between clubbing and disease severity was found. Assessment methods for clubbing showed no to poor agreement

**Conclusion**
As clubbing is one of the early signs for ILD diagnosis there is an unmet need for a robust assessment method for clubbing

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1 Rivera Ortega P. ERS Milan 2017; 525: OA4638
2 van Manen M, et al. ERS Milan 2017; 114: PA870
**Expert comments**

- **DL\textsubscript{CO}** seems to be the most reliable functional biomarker to monitor SSc-ILD disease activity.
- The utility of a multidisciplinary review board to confirm the diagnosis of ILD has also been demonstrated in children.
- The most common ILD diagnosis in children was related to alveolar surfactant disorders.
- Early diagnosis of IPF / ILF is a main unmet need and should be further explored and implemented in primary care centres.
New insights into ILD management

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Rituximab in the management of CTD-ILDs

Rituximab improves interstitial lung disease (ILD) in rheumatoid arthritis (RA) patients

• Rituximab (RTX) was used to treat RA joint and lung manifestations (n=31)
• Female gender, older age, UIP pattern, and longer time between RA diagnosis and ILD were found to be risk factors for progression
• RTX treatment decreases risk of disease progression
• No adverse effects were observed

Rituximab in the management of idiopathic inflammatory myopathies (IIM) complicated by ILD

• Use of RTX to achieve disease stability in patients with IIM-related ILD was investigated
• Clinical and radiological stability was achieved in 5 out of 7 patients at 6 months of RTX treatment
• No significant adverse reactions observed

1 Nieto Barbero A, et al. ERS Milan 2017; 115: PA893
2 Riddell P, et al. ERS Milan 2017; 115: PA898

CTD-ILD: Connective tissue disease associated interstitial lung disease, UILP: Usual interstitial pneumonia
Management of acute exacerbations (AE) in ILDs

Hospital readmission increased short- and long-term mortality in ILD patients who had been hospitalised due to acute respiratory worsening: Hospital readmission is a risk factor for 90-day mortality, 6-month mortality and 1-year mortality (n=74)\(^1\)

Extracorporeal membrane oxygenation (ECMO) for the treatment of AEs of ILDs in patients who received ECMO showed significantly better survival rates compared to mechanical ventilation or non-intubated groups (n=30)\(^2\)

Home-based pulmonary rehabilitation reduced AE-associated hospital admissions, improved quality of life, and increased exercise tolerance in a retrospective evaluation of a cohort (n=90) of patients with COPD, ILD, asthma and bronchiectasis\(^3\)

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1 Barril Farre S, et al. ERS Milan 2017; 355: PA2951
2 Ohshimo S. ERS Milan 2017; 416: OA3396
3 Boral I, et al. ERS Milan 2017; 553: PA4894
Depression and anxiety in patients with idiopathic pulmonary fibrosis (IPF)

Depression in patients with IPF¹

• A prospective study (n=72) found that 39% of patients with IPF showed significant depressive symptoms
• Depression impacts disease severity, quality of life and symptom burden

Anxiety and depression in patients with IPF²

• An outpatient study (n=167) of patients with IPF showed that anxiety and depression were prevalent in the cohort
• Depression and anxiety were associated with quality of life and respiratory function impairment
• There is an unmet need for evaluation and treatment of depression and anxiety in patients with IPF

¹ Tzouvelekis A, et al. ERS Milan 2017; 70: PA357
² Nolan C, et al. ERS Milan 2017; 70: PA848
Fatigue in patients with IPF

Aim

Compare fatigue in patients with IPF receiving pirfenidone vs placebo. Data from the pooled ASCEND and CAPACITY Phase III trials (n=1247)

Conclusions

• Fatigue treatment-emergent adverse events (TEAEs) were more frequent in the pirfenidone group, but shorter in duration

• A history of depression is associated with fatigue TEAEs

• Patients experiencing fatigue TEAEs suffered from GI-related side effects more often

• Fatigue required dose modification more often in patients receiving pirfenidone vs patients in the placebo group

1 Costabel U, et al. ERS Milan 2017; 552: PA4875

<table>
<thead>
<tr>
<th>Grade</th>
<th>Pirfenidone (n=623)</th>
<th>Placebo (n=624)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with ≥1 fatigue TEAE, n (%)</td>
<td>Fatigue TEAEs, n (%)</td>
</tr>
<tr>
<td>All-grade</td>
<td>162 (26.0)</td>
<td>222 (2.9)</td>
</tr>
<tr>
<td>Mild</td>
<td>103 (16.5)</td>
<td>136 (3.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>67 (10.8)</td>
<td>78 (3.0)</td>
</tr>
<tr>
<td>Severe</td>
<td>67 (10.8)</td>
<td>8 (2.2)</td>
</tr>
</tbody>
</table>

TEAEs: Treatment-emergent adverse events
Does enhanced respiratory support affect clinical outcomes in ILD patients with acute respiratory failure?¹

Effect of non-invasive respiratory support on ILD patients with acute respiratory failure (ARF)

- Prognosis for ILD patients in need of non-invasive respiratory support for ARF is generally poor, but depends on the subtype of ILD
- One-year survival is 15% for patients who survive initial admission
- Acute respiratory failure leads to 100% mortality in patients with IPF

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Death during RHCU admission (n)</th>
<th>Death at 60 days (n)</th>
<th>% Overall mortality (incl. 60 day mortality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPF</td>
<td>13</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
<td>4</td>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>Non-specific interstitial pneumonia</td>
<td>3</td>
<td>2</td>
<td>83</td>
</tr>
<tr>
<td>RA-ILD</td>
<td>3</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

¹ Achaiah A, et al. ERS Milan 2017; 114: PA864

RHCU: Respiratory high dependency unit, RA-ILD: Rheumatoid arthritis-associated interstitial lung disease
Strategies used by lung fibrosis patients to relieve dyspnoea

Aim

• Evaluate the self-reported impact of breathlessness members of the Irish Lung Fibrosis Association who suffer from IPF (n=41) and the non-pharmacological interventions they use for relief

Results

• Methods used for relief of dyspnoea included breathing techniques, hand-held fans and relaxation techniques. However, there is no reliable evidence supporting their use

Conclusion

• An assessment of the effects of dyspnoea on the impact on patients’ physical abilities and quality of life should be undertaken. Discussing therapeutic options with patients is important

1 Cassidy N, et al. ERS Milan 2017; 355: PA2957
Treatment adherence in patients with IPF: a nurse’s perspective

- The majority of dropouts of anti-fibrotic treatment happen during the first month after treatment initiation.
- This may be due to delayed follow-up visit, so that patients do not receive sufficient support when they encounter problems.
- In the UK, ILD nurses are the primary contact for patients, especially at commencement of treatment.
- ILD nurses provide advice on management of treatment side-effect and other disease-related issues.
- Shared care should be delayed until treatment routine is established.

Plan of action to improve treatment adherence based on the evaluation of 206 patients with IPF, who received anti-fibrotic treatment of the Heart of England NHS trust:

- Weekly telephone clinic for first 4 weeks
- Delay shared care until patients are established on treatment
- Provide more education at the spoke hospitals
- Provide an in-depth proforma for the spoke hospital
- Titrate the females on pirfenidone more slowly, particularly those who are small

1 Burge G. ERS Milan 2017; 396:OA3235
Further aspects in the management of ILD

Post-transplant morbidity and mortality in patients with pulmonary fibrosis and telomeric shortening — Lung transplantation increases survival in patients with fibrosing ILD, regardless of presence of telomeraseopathy. Patients with telomeraseopathy are, however, more likely to develop complications and require an optimised approach.

Relationship between quality of life (QoL) and clinical features of IPF patients — QoL in patients with IPF is strongly associated with clinical parameters, the most significant correlation was found between QoL, diaphragm mobility and resting dyspnoea.

Japanese guideline for treatment of idiopathic pulmonary fibrosis 2017 — The new guideline was developed to standardise treatment and management of IPF in Japan, and to improve clinical outcome.

1 Garcia Moyano M, et al. ERS Milan 2017; 355: PA2954
2 Bárczi E et al. ERS Milan 2017; 443: PA3813
3 Homma S, et al. ERS Milan 2017; 443: PA3806
Expert comments

- There is further evidence supporting the efficacy of rituximab in stabilising CTD-ILD, especially in rheumatoid arthritis and polymyositis / dermatomyositis.

- Fatigue and depression can affect the burden of respiratory symptoms, especially dyspnoea, and should be regularly assessed in IPF patients.

- Dyspnoea is a major symptom in IPF/ILD. Its relief is crucial for quality of life and treatment acceptance.

- Nurses play a key role in the management of IPF/ILD patients by catching patients’ unmet needs and can help to improve treatment adherence.
Registries in IPF

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Data from the Australian IPF registry

- Decline in FVC% over the previous year does not predict future decline in patients with IPF, but it is associated with mortality on multivariable analysis.
- Male gender, poorer physiology and higher symptom scores are associated with poorer survival (see table).

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.03</td>
<td>1.00–1.06</td>
<td>NS</td>
</tr>
<tr>
<td>Male, gender</td>
<td>2.47</td>
<td>1.21–5.05</td>
<td>0.013</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.96</td>
<td>0.90–1.03</td>
<td>NS</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>1.98</td>
<td>0.99–3.95</td>
<td>0.053</td>
</tr>
<tr>
<td>FVC % pred.</td>
<td>0.69</td>
<td>0.59–0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DLco % pred.</td>
<td>0.60</td>
<td>0.48–0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPI</td>
<td>1.09</td>
<td>1.07–1.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6MWT distance</td>
<td>1.00</td>
<td>0.99–1.00</td>
<td>0.001</td>
</tr>
<tr>
<td>SpO₂ (rest)</td>
<td>0.90</td>
<td>0.82–0.98</td>
<td>0.018</td>
</tr>
<tr>
<td>SpO₂ (nadir)</td>
<td>0.94</td>
<td>0.89–0.98</td>
<td>0.006</td>
</tr>
<tr>
<td>SGRQ</td>
<td>1.03</td>
<td>1.02–1.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>USOB</td>
<td>1.02</td>
<td>1.02–1.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>'Decliner'</td>
<td>1.28</td>
<td>0.74–2.20</td>
<td>NS</td>
</tr>
</tbody>
</table>

6MWT: 6 Minute walk test, BMI: Body mass index, CI: Confidence interval, CPI: Composite physiologic index, HR: Hazard ratio, SGRQ: St. George’s respiratory questionnaire, SpO₂: Peripheral capillary oxygen saturation, USOB: UCSD shortness of breath questionnaire, NS: Not significant.

1 Jo H, et al. ERS Milan 2017; 113: PA852
Long-term safety of pirfenidone in a real-world setting: final results from the prospective, observational PASSPORT registry

- n=1009 total patients included in study; n=741 patients experienced adverse drug reactions (ADRs)
- This study provides valuable long-term data regarding safety and tolerability of pirfenidone in the real-world setting
- Dose adjustments can help to avoid treatment discontinuation in patients who experience ADRs
- Results were consistent with the known safety profile of pirfenidone, no new safety signals were reported

Dose adjustment and patient retention

- Patients with an ADR: n=741 (100%)
  - No dose adjustment: n=383 (52%)
    - Completed: n=100/383 (26%)
    - Discontinued: n=283/383 (74%)
  - Dose adjustment: n=358 (48%)
    - Reduction, n=248
    - Interruption, n=158
    - Completed: n=139/358 (39%)
    - Discontinued: n=219/358 (61%)

ADR: Adverse drug reaction

1 Cottin V, et al. ERS Milan 2017; 317: PA2806
INSIGHTS-IPF registry: gender associated differences in patients with IPF¹

Gender-associated differences in the INSIGHTS-IPF registry population include:

- **DL\textsubscript{CO} % predicted**, $p=0.017$
- **Rate of overweight**, $p<0.001$
- **Time to initial diagnosis**, $p=0.002$
- **Environmental exposures**, $p<0.001$
- **Comorbidities**
  - **Coronary heart disease**, $p<0.001$
  - **Emphysema**, $p=0.047$
  - **Obstructive sleep apnoea**, $p=0.003$
- **Complaints**
  - **Fatigue**, $p=0.001$
  - **Chest pain**, $p=0.027$
- **Rate of hospitalisation due to IPF-related events**, $p=0.032$

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¹ Prasse A, et al. ERS Milan 2017; 525: OA4637
Data from the EMPIRE registry of Eastern and Central European countries

- The EMPIRE registry included 1384 patients with IPF from the Czech Republic (n=669), Poland (n=241), Turkey (n=217), Slovakia (n=115), Hungary (n=96), Serbia (n=31), Croatia (n=15)\(^1\)
- FVC% predicted and percentage of smokers is slightly higher among Polish patients\(^1\)
- 20.6% of patients received pharmacological treatment: Anti-fibrotic treatment was made available Jan 2017\(^1\) (see table)
- Patients with IPF diagnosis within 1 year from onset of symptoms show longer survival than those diagnosed later\(^2\)

### Treatments in the Polish EMPIRE cohort (n=241)\(^1\)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n   (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological treatment</td>
<td>45 (20.6%)</td>
</tr>
<tr>
<td>Clinical study</td>
<td>30 (13.8%)</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td>23 (10.6%)</td>
</tr>
<tr>
<td>Lung transplantation</td>
<td>12 (5.5%)</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>2 (0.9%)</td>
</tr>
</tbody>
</table>

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1 Lewandowska K, et al. ERS Milan 2017; 113: PA855  
2 Vašáková M, et al. ERS Milan 2017; 552: PA4880
Expert comments

Data from registries confirm that only half (or less) of patients with IPF are treated with antifibrotic drugs, which represents a major unmet need for IPF patients.

Long-term observations on pirfenidone indicate that dose discontinuation occurs mainly during the first year of treatment and dose adjustment can be a useful strategy to avoid definitive discontinuation.

Patients who are diagnosed with IPF within 1 year from onset of symptoms have a longer survival time than those diagnosed later.
New data on antifibrotic treatments
Pre-clinical data
New pre-clinical data on anti-fibrotic drugs

Roflumilast N-oxide combined with sildenafil¹
- The combined effect of sildenafil and roflumilast N-oxide (RNO) on epithelial-to-mesenchymal transition (EMT) and fibrocyte to myofibroblast transition were studied in human AECII and fibrocytes
- RNO/sildenafil combination shows synergic activity in reducing mesenchymal marker expression and leads to decreased fibrocyte to myocyte transition, thus improving anti-fibrotic effects in human AECII and fibrocytes

Selective 5-HT2B receptor antagonist AM1125²
- The effect of AM1125 on fibrosis was studied in cell culture and a mouse model
- AM1125 reduces collagen production in human fibroblasts, interferes in TGF-β signalling and reduces fibrosis in the bleomycin-induced fibrosis mouse model

AECII: Type II alveolar epithelial cells

¹ Contreras S, et al. ERS Milan 2017; 546: OA4833
² Wenglen C, et al. ERS Milan 2017; 546: OA4836
# Preclinical data on nintedanib

<table>
<thead>
<tr>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nintedanib inhibits pro-fibrotic mediators from peripheral T cells</td>
<td>• Reductions in immune-stimulating and pro-fibrotic mediators (IFNγ, IL-2, IL-4, IL-5, IL-10, IL12p70, IL-13) might contribute to clinical efficacy of nintedanib in SSc-ILD or RA-ILD</td>
</tr>
<tr>
<td>with relevance to connective tissue disease-associated ILD¹</td>
<td></td>
</tr>
<tr>
<td>Nintedanib relaxes human pulmonary arteries more potently</td>
<td>• In ET-1-pre-contracted pulmonary vessels, nintedanib relaxed human pulmonary arteries (PAs) more potently than murine PAs</td>
</tr>
<tr>
<td>than murine²</td>
<td>• The vasorelaxant properties of nintedanib could potentially provide benefit in treating pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Nintedanib prevents IL-6-mediated secretion of CCL-18 in alternatively</td>
<td>• The anti-fibrotic effect of nintedanib observed in IPF patients may be associated with its effect on reducing CCL-18 release by alternatively activated macrophages</td>
</tr>
<tr>
<td>activated macrophages and transition of fibroblasts to myofibroblasts³</td>
<td></td>
</tr>
</tbody>
</table>

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¹ Wollin L, et al. ERS Milan 2017; 116: PA903  
² Krabbe J, et al. ERS Milan 2017; 293: PA2374  
³ Tandon K, et al. ERS Milan 2017; 424: PA3478  

ET-1: Endothelin-1, IL: Interleukin
Clinical trials
The PRAISE study: Clinical trial data on pamrevlumab in IPF²

Study design
• Pamrevlumab is a monoclonal antibody targeting CTGF
• In a randomised, placebo-controlled, double-blind phase 2 clinical trial pamrevlumab was tested for efficacy in preventing lung function deterioration (dose: 30 mg/kg, every 3 weeks) in patients with idiopathic pulmonary fibrosis (IPF)
• In a sub-study, the safety of pamrevlumab combination therapy with nintedanib or pirfenidone was tested

Results
• Pamrevlumab shows efficacy in preservation of lung function, as measured by:
  1. FVC% predicted
  2. FVC (ml)
  3. FVC% predicted decline of ≥10% or death
• All-cause mortality in pamrevlumab group is reduced by 51%
• Pamrevlumab is well tolerated in mono- and combination therapy with nintedanib or pirfenidone

Conclusion
Results are consistent with prior pamrevlumab Phase 2 data and therefore further investigation of pamrevlumab in IPF is warranted

CTGF: Connective tissue growth factor

¹ Richeldi L. ERS Milan 2017; 416: OA3400
Evaluation of the JNK inhibitor, CC-90001, in a Phase 1b pulmonary fibrosis trial\textsuperscript{1}

\textbf{Aim}

Safety and tolerability of the JNK inhibitor CC-90001 were tested in patients with pulmonary fibrosis in a Phase 1b trial (n=16), study design (see figure).

\textbf{Results}

- CC-90001 was well-tolerated. All treatment-emergent adverse events were mild or moderate, no serious adverse events were observed.
- 83\% of patients in the 200 & 400 mg dose groups showed increased FVC relative to baseline at 12 weeks.
- Plasma tenascin C levels in 200 & 400 mg dose groups decreased from baseline to week 12.

CC-90001 is currently being tested in a Phase 2 trial for efficacy in IPF patients.

\textsuperscript{1} Greenberg S. ERS Milan 2017; 87: OA474
Long-term data

Patterns of pirfenidone discontinuation in the RECAP study¹

- Most frequent cause of discontinuation during the median pirfenidone treatment of 122.4 weeks were non-IPF-related AEs (see figure)
- Discontinuation of pirfenidone was most frequent during the first year of treatment
- Close monitoring of patients during the early stages of treatment is important to reduce risk of discontinuation

![Reasons for discontinuation during RECAP](image)

1 Costabel U. ERS Milan 2017; 416: OA3399
INJOURNEY™ study: nintedanib and pirfenidone combination therapy

- Side-effects during 12-week treatment with nintedanib with add-on pirfenidone were manageable (n=53) and in line with the safety profiles of the individual drugs.
- Plasma trough concentrations of nintedanib were similar when administered alone or with add-on pirfenidone in patients with IPF (see top figure).
- Decline in FVC over 12 weeks was smaller in patients treated with nintedanib and add-on pirfenidone than with nintedanib alone, however these results should be interpreted with caution given the exploratory nature of the analysis (see lower figure).

1 Wuyts W, et al. ERS Milan 2017; 116: PA907
INPULSIS® and INPULSIS®-ON

New data on nintedanib

FVC decline ≥10% predicted in INPULSIS® did not significantly predict subsequent FVC decline in INPULSIS®-ON (p=0.0514), but was associated with higher mortality (p=0.0001)

Nintedanib consistently slowed disease progression in INPULSIS® and INPULSIS®-ON with ~50% reduction in FVC decline regardless of concomitant medication

1 Richele L, et al. ERS Milan 2017; 552: PA4892
2 Kreuter M, et al. ERS Milan 2017; 552: PA4891

FVC is a poor predictor of future decline in FVC

![FVC Proportion Chart](chart.png)

<table>
<thead>
<tr>
<th>FVC Decline</th>
<th>No Absolute Decline</th>
<th>Absolute Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=301</td>
<td>78.6 (n=301)</td>
<td>21.4 (n=82)</td>
</tr>
<tr>
<td>N=47</td>
<td>66.0 (n=31)</td>
<td>34.0 (n=16)</td>
</tr>
</tbody>
</table>

Concomitant medications and efficacy of nintedanib in INPULSIS®-ON

<table>
<thead>
<tr>
<th>Medication</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilator</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Proton pump or histamine-2 receptor inhibitor</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Adjusted annual rate (SE) of decline in FVC over 48 weeks (mL/year)

<table>
<thead>
<tr>
<th>Group</th>
<th>Adjusted Annual Rate (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>-131 (±131)</td>
</tr>
<tr>
<td>Yes</td>
<td>-151 (±131)</td>
</tr>
<tr>
<td>No</td>
<td>-19 (±131)</td>
</tr>
<tr>
<td>Yes</td>
<td>-19 (±131)</td>
</tr>
<tr>
<td>No</td>
<td>-19 (±131)</td>
</tr>
<tr>
<td>Yes</td>
<td>-19 (±131)</td>
</tr>
<tr>
<td>No</td>
<td>-19 (±131)</td>
</tr>
<tr>
<td>Yes</td>
<td>-19 (±131)</td>
</tr>
<tr>
<td>No</td>
<td>-19 (±131)</td>
</tr>
<tr>
<td>Yes</td>
<td>-19 (±131)</td>
</tr>
<tr>
<td>No</td>
<td>-19 (±131)</td>
</tr>
</tbody>
</table>
New data on nintedanib and pirfenidone

Combined treatment with pirfenidone and nintedanib (NCT02598193)¹

- The international, single-arm, open-label Phase IV study showed that combined treatment with pirfenidone and nintedanib for 24 weeks is well tolerated by most patients with IPF.
- The safety profile was similar to that expected with either treatment alone.

Incidence of multiple progression events in patients of the CAPACITY and ASCEND studies²

- **Aim:** To determine the incidence of multiple progression events (decline in forced vital capacity or 6-min walk distance, and respiratory hospitalisation) and the proportion of patients with death subsequent to a progression event in the first 12 months of pirfenidone treatment.
- **Conclusion:** Pirfenidone significantly reduced the incidence of multiple progression events and death subsequent to a progression event at 12 months (see figure).

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¹ Flaherty K. ERS Milan 2017; 317: PA2805
² Nathan S. ERS Milan 2017; 416: OA3401
Real-life data
New data on anti-fibrotics

Effect of 24-month pirfenidone in IPF patients with rapid and slow disease progression

- Pirfenidone significantly reduces the rate of FVC decline in patients with IPF (n=57)
- The effect is stronger and longer-lasting in patients with rapidly progressive disease

Anti-fibrotic treatment improves prognosis for acute exacerbations (AE) in a retrospective, single centre study (n=68)

- Patients who received anti-fibrotic treatment either before AE onset (n=3), or directly following an AE of IPF (n=13) showed improved survival, and delayed time to the next AE (see table)

<table>
<thead>
<tr>
<th>Anti-fibrotic treatment in patients with AE-IPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (OS) following AE-IPF</td>
</tr>
</tbody>
</table>

| Anti-fibrotic treatment | yes (6.6 (0.8-NA)) | no (3.9 (1.7-6.3)) |

| Mortality | 30 days | 31.2% | 25.0% |
| 90 days   | 37.5% | 42.3% |
| 180 days  | 43.8% | 61.5% |

<table>
<thead>
<tr>
<th>Time to recurrence of AE-IPF since first AE-IPF</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Anti-fibrotic treatment</th>
<th>yes</th>
<th>no</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>0%</td>
<td>2.6%</td>
</tr>
<tr>
<td>90 days</td>
<td>9.1%</td>
<td>33.3%</td>
</tr>
<tr>
<td>180 days</td>
<td>9.1%</td>
<td>43.6%</td>
</tr>
</tbody>
</table>

AE-IPF: Acute exacerbation of idiopathic pulmonary fibrosis, CI: confidence interval

1 Biondini D, et al. ERS Milan 2017; 355: PA2966
2 Matsumoto Y, et al. ERS Milan 2017; 552: PA4885
# Observations of nintedanib treatment from smaller cohorts

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Observations</th>
</tr>
</thead>
</table>
| Single-centre study, Siena, Italy<sup>1</sup>                        | 50  | • Patient adherence to nintedanib therapy was good  
                                 • Side effects generally mild, not requiring dose reduction  
                                 • Discontinuation was a rare event and safety profile good |
| Retrospective single centre study, Italy<sup>2</sup>                 | 22  | • Nintedanib treatment was efficient in preventing lung function decline  
                                 • Patients with severe IPF benefited from treatment; adherence and safety profile were good |
| Study in Spain<sup>3</sup>                                           | 79  | • Main side effects were diarrhoea (53%) and weight loss (25%)  
                                 • 39% of patients had a dosage reduction and 18% interrupted treatment, 10% due to side effects |
| Nintedanib compassionate use programme in Estonia<sup>4</sup>       | 17  | • Nintedanib treatment of 17 treatment-naïve IPF patients showed stabilisation of lung function and tolerability in line with previous findings |

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Expert comments

Long-term and real-life data confirm the safety and efficacy profile of the approved anti-fibrotic drugs in IPF. The use of anti-fibrotics seems to reduce mortality from acute exacerbation.

New anti-fibrotic approaches like anti-CTGF and anti-JNK2 molecules have shown promising results in early phase clinical trials. Data on efficacy need to be confirmed.

Data from in vitro and ex vivo models suggest a broader spectrum of action for nintedanib, especially useful for CTD-ILD and perhaps pulmonary hypertension.

Data from clinical trials with anti-fibrotic drugs in combination show promising signals in terms of efficacy, to be confirmed, and confirm safety and tolerability seen in previous studies.
Predictors of disease progression, outcome and survival in ILD

The preparation of the slide kit was sponsored by Boehringer Ingelheim International GmbH and contains personal opinions from leading ILD experts. ERS was neither author nor reviewer of the content. This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).
Environmental risk factors

**NO₂ is associated with IPF incidence¹**

- n=2093 IPF cases, incidence rates from Lombardy with 10 million inhabitants
- Increasing NO₂ concentrations were associated with increased incidence of IPF
- For each 1 µg/m³ increment in the average NO₂ concentration, the incidence rate of IPF increased by 0.64% (95% confidence interval: -0.01-1.29)
- No significant association was found between O₃ and IPF incidence

¹ Conti, S. ERS Milan 2017; 73: PA408
Interstitial lung abnormalities (ILAs) in asymptomatic individuals

**Lung ageing programme**

8% of 500 asymptomatic individuals aged between 60–79 years had ILAs

ILA patients showed:

- Alterations in gas exchange
- MUC5B polymorphism rs35705950 as risk factor (OR 4.48, p=0.014)
- Increased effector T cells (p≤0.001)
- Increased MMP7 biomarker (p=0.0004)
- Altered mRNA profiles (T cell and TGF-β signalling)

Ageing, smoking, and some biomarkers seem to be associated with increased ILA risk

---

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls, n=538</th>
<th>ILA, n=45</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL_{CO} (% predicted)</td>
<td>114 ± 21.7</td>
<td>101 ± 26.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>DL_{CO}/AV</td>
<td>5.5 ± 1.71</td>
<td>4.8 ± 0.9</td>
<td>0.01</td>
</tr>
<tr>
<td>SpO₂ post exercise</td>
<td>92 ± 5</td>
<td>88 ± 8</td>
<td>0.0001</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>95 ± 18</td>
<td>92 ± 15</td>
<td>0.46</td>
</tr>
</tbody>
</table>

DL_{CO}/AV: DL_{CO}/per unit alveolar volume, SpO₂: Peripheral capillary oxygen saturation

---

1 Roldán I, et al. ERS Milan 2017; 262: OA1955
Inflammatory myopathy and ILD

Polymyositis/dermatomyositis (PM/DM) has no effect upon survival of patients with anti-Jo-1 antibody-positive ILD

- Retrospective comparison of survival for 53 patients diagnosed with Jo-1 (positive for anti-histidyl-transfer RNA synthase antibody)-ILD, with or without PM/DM (see table)
- PM/DM did not correlate with long-term survival
- 4 patients with non-PM/DM IPF died of ILD AEs, no PM/DM IPF patients did
- Differentiation between PM/DM positive and negative disease may affect treatments and predicting prognosis

<table>
<thead>
<tr>
<th>Clinical outcomes and treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Follow-up period (months)</td>
</tr>
<tr>
<td>Steroid + IS</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Anti-fibrotic agent</td>
</tr>
<tr>
<td>No treatment</td>
</tr>
<tr>
<td>Death, n (%)</td>
</tr>
<tr>
<td>Causes of death, n</td>
</tr>
<tr>
<td>Number of AEs</td>
</tr>
</tbody>
</table>

AE: Adverse event, IS: Immunosuppressive agents
Inflammatory myopathy and ILD

Extensive ILD is a predictor of mortality in inflammatory myopathy

- n=65; ILD present in 32 patients (49%)
- > 20% ILD total lung involvement was a strong predictor of mortality (HR 14.88, p=0.02)

Assayag D, et al. ERS Milan 2017; 115: PA890
Expert comments

Interstitial lung abnormalities (ILA) should be regarded as a pre-stage of lung fibrosis, and risk factors (e.g. age, smoking, SNPs) have been identified.

There is increasing evidence about the association between environment and incidence of lung fibrosis. Some risk factors, such as nitrogen dioxide, have been confirmed.

The presence of clinical signs of collagen tissue disease in ILD with or without PM/DM does not seem to have an impact on survival but this needs further exploration.
IPF pathobiology and potential biomarkers
Candidate endotype signatures in IPF

Genetic biomarkers in IPF

• Genetic testing revealed that genetic variants rs1800469CC of transforming growth factor beta-1 (TGF-β1), and rs9340799X(G) of oestrogen receptor alpha (ESR1) show promise as prognostic biomarkers of unfavourable IPF outcomes (n=104)

Epigenetic biomarkers in IPF

• A cell free nucleosome epitope combination of HMGB1, 5mC, H3K9Ac, and H3K27Ac found in serum could be used to differentiate between subjects with and without IPF (R²=0.681)

• This might be a potential biomarker for diagnosis and treatment of IPF, and offers a potential non-invasive approach

1 Ultina A. ERS Milan 2017; 349: OA2906
Non-coding RNAs as potential therapeutic targets in IPF

micro RNA (miRNA): Mirtlet7d\(^1\)
- Mirtlet7d negatively regulates transcription of bi-directionally expressed genes as part of the Mirlet7d/EXOSC/SZH2 (MiCEE) complex, downstream of TGF-β1 signalling
- Mirtlet7d-GOF rescued hyperactive wound healing, and reduced cell division in primary cells from patients with IPF

Long non-coding RNA (lncRNA): DNM3OS\(^2\)
- DNM3OS encodes 3 distinct profibrotic miRNAs (miR-199a-5p/3p and miR-214-3p), which modulate lung fibroblast activation in response to TGF-β
  - Silencing of DNM3OS function reduced myofibroblast differentiation
  - Inhibition of miR-199a-5p prevented bleomycin-induced lung fibrosis

LncRNA: FENDRR\(^3\)
- FENDRR is strongly downregulated in IPF lung fibroblasts in a disease-severity dependent manner
- Depletion of FENDRR-induced fibroblast-myofibroblast transition, cellular senescence, increased secretion of collagen and inflammatory mediators, and increased expression of the ROS generating NADPH oxidase 4 (NOX4) in vitro
- siRNA knockdown of NOX4 reversed myofibroblast differentiation

TGF-β: Transforming growth factor-β, GOF: Gain-of-function

1 Barreto G. ERS Milan 2017; 87: OA479
2 Mari B. ERS Milan 2017; 349: OA2908
3 Sakamoto K. ERS Milan 2017; 349: OA2909
Pathogenic mechanisms in IPF

<table>
<thead>
<tr>
<th>Pro-fibrotic signalling(^1)</th>
<th>• Tyrosine phosphatase PTP(\alpha) drives TGF-(\beta)-induced pro-fibrotic signalling, and is required for bleomycin induced pulmonary fibrosis in a mouse IPF model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammosome in IPF derived PBMCs(^2)</td>
<td>• IPF-derived peripheral blood mononuclear cells (PBMCs), treated with NLRP3 and AIM2 activators, release IL-18 upon sole AIM2/caspase activation, whereas activation of AIM2 and NLRP3 induces release of IL-1a in a caspase-1 independent manner</td>
</tr>
<tr>
<td>Neutrophil elastase(^3)</td>
<td>• The use of an inhibitor for neutrophil elastase, alpha1-antitrypsin (AAT), reduced ER stress, secretion of inflammatory cytokines, and improved wound repair in alveolar epithelial cells from IPF patients in vitro</td>
</tr>
</tbody>
</table>

IL: Interleukin, TGF-\(\beta\): Transforming growth factor-\(\beta\), AIM2: Absent in melanoma 2, NLRP3: NLR family pyrin domain containing protein 3, ER: Endoplasmic reticulum

1 Downey G and Aschner Y. ERS Milan 2017; 424: PA3474
2 Sorrentino R, et al. ERS Milan 2017; 269: PA2027
3 Nita I, et al. ERS Milan 2017; 424: PA3483
Pathogenic mechanisms in IPF

RIPK3 regulates necroptosis in AECs¹

- Receptor-interacting serine/threonine-protein kinase 3 (RIPK3) is upregulated in IPF lungs, where cell death of alveolar epithelial cells (AECs) was shown to occur through both apoptosis and necroptosis.
- In both AEC cell culture and a lung fibrosis mouse model using bleomycin treatment, inhibition of RIPK3 or necroptosis reduced lung inflammation and fibrosis.
- Inhibition of necroptosis with necrostatin-1 reduced collagen deposition in bleomycin-treated lung.
- Necroptosis is associated with myofibroblast accumulation and fibrosis pathogenesis, and is a potential target in fibrosis.

IPF fibroblasts secrete pro-inflammatory cytokines²

- The secreted pro-inflammatory cytokines modulate cell adhesion, fibroblast migration in a fibronectin dependent manner, and ITGA5 expression, which are mediated by TNF-α.
- Increased secretion of ITGA5 by both, IPF derived fibroblasts and fibroblastic foci, induce migration of fibroblasts and attachment to fibronectin and thus focal accumulation of fibroblasts.

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¹ Park S, et al. ERS Milan 2017; 499: OA4440

ITGA5: Integrin subunit alpha 5, TNF-α: Tumour necrosis factor-α
IPF and COPD share pathways underlying the progression of phenotypes

- n=105 (control), 212 (COPD), 159 (IPF)
- 13 pathways shared alterations in IPF and COPD, and correlated with disease progression measured by DL\textsubscript{CO}
- The ratio of never smokers was similar for IPF and controls, and higher for COPD

### Modules that correlated with DL\textsubscript{CO} in COPD and IPF patients

<table>
<thead>
<tr>
<th>Biological function of module</th>
<th>Gene expression in subjects with poor DL\textsubscript{CO}</th>
<th># genes in module</th>
<th># genes significant with DL\textsubscript{CO}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune response / viral immune response</td>
<td>down</td>
<td>73</td>
<td>64</td>
</tr>
<tr>
<td>Vesicle localisation</td>
<td>down</td>
<td>97</td>
<td>87</td>
</tr>
<tr>
<td>Regulation of cytoskeleton</td>
<td>down</td>
<td>119</td>
<td>118</td>
</tr>
<tr>
<td>Response to growth factors</td>
<td>down</td>
<td>51</td>
<td>46</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>down</td>
<td>133</td>
<td>128</td>
</tr>
<tr>
<td>WNT pathway</td>
<td>down</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Immune response / myeloid recruitment</td>
<td>up</td>
<td>196</td>
<td>182</td>
</tr>
<tr>
<td>Cadmium ion transport</td>
<td>up</td>
<td>143</td>
<td>117</td>
</tr>
<tr>
<td>Angiostatic</td>
<td>up</td>
<td>49</td>
<td>35</td>
</tr>
<tr>
<td>ECM organisation / cell adhesion</td>
<td>up</td>
<td>93</td>
<td>87</td>
</tr>
<tr>
<td>ECM organisation</td>
<td>up</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>Immune response / lymphocyte activation</td>
<td>up</td>
<td>240</td>
<td>230</td>
</tr>
<tr>
<td>Unfolded protein response</td>
<td>up</td>
<td>194</td>
<td>187</td>
</tr>
</tbody>
</table>

ECM: Extracellular matrix; DL\textsubscript{CO}: Diffusing capacity of the lungs for carbon monoxide

1 Mcdonough J, et al. ERS Milan 2017; 424: PA3484
**Expert comments**

Better knowledge of genetic and epigenetic mechanisms underlying IPF provides new biomarkers with low variability and promising target candidates for new treatments.

Novel genetic biomarkers, like certain SNPs in the TGF-β factor encoding gene, seem to be associated with poor clinical outcome in IPF and could improve diagnosis and follow-up.

New data on the role of the inflammasome, alveolar macrophages and neutrophils in the pathogenesis of IPF represent possible non-primarily fibrotic treatment approaches.

New pathogenic key effectors, related to different accelerated ageing cell and tissue hallmarks, were presented.
Imaging

The preparation of the slide kit was sponsored by Boehringer Ingelheim International GmbH and contains personal opinions from leading ILD experts. ERS was neither author nor reviewer of the content. This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).
ILD patterns are associated with the presence of Velcro crackles

- Fibrosis was significantly associated with Velcro-type crackles on chest auscultation (OR 6.24 (4.5-8-66, p<0.001) in blinded assessment (n=48)
- Multivariate logistic regression shows association between features on HRCT sections with crackles at corresponding recording site (upper), and between HRCT signs of ILD and crackles at corresponding recording site (lower; unilateral crackles not shown, NS)

<table>
<thead>
<tr>
<th>Feature</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground glass opacities</td>
<td>1.74 (1.29–2.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reticulation</td>
<td>2.04 (1.62–2.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Traction bronchiectasis</td>
<td>1.55 (1.03–2.32)</td>
<td>0.034</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>1.88 (1.24–2.83)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HRCT pattern</th>
<th>Bilateral Velcro-type crackles</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>UIP</td>
<td>14.2 (4.14–48.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Possible UIP</td>
<td>11.73 (4.44–31.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inconsistent with UIP</td>
<td>8.87 (2.92–26.94)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Quantitative HRCT fibrosis scores correlate with disease outcome

| Monitoring of structures\(^1\) | Voxel-by-voxel TILD scores on paired HRCT scans 6 months apart allow for monitoring of lung structures over time (n=25)  
- Transitions to worsening lung patterns were observed when symptoms got worse  
- Most traced voxels were either preserved or moved to more severe categories |
| --- | --- |
| Prediction of PFS\(^2\) | At 24 weeks, change in quantitative lung fibrosis (QLF) was a stronger predictor of PFS than change in FVC in an open label Phase 2 trial with 73 patients  
- HR for change in QLF of 4% (3.65); 3% (3.6), and 2% (3.7), all p<0.001  
- HR for change in FVC of 5% was 1.44, 1.51 and 1.64 in these groups (all NS) |
| QLF score at baseline predicts progression\(^3\) | The QLF score from HRCT as a predictor of FVC-based progression free survival (PFS) was investigated in a single-arm trial (n=77)  
- Subjects with mild disease by QLF had longer PFS without rapid declining in lung function |


TILD: Transitional interstitial lung disease,  
Voxel: Represents a value on a regular grid 3D space, PFS: Progression free survival
Prediction of mortality from serial CT

Serial change in lung volumes can predict disease mortality

- Retrospective data from 81 patients with IPF show 58 deaths over 6 months (72%)
- Annual % change in anterior junction distance was a better predictor of mortality than % change in FVC in univariate and multivariable survival analysis

1 Robbie, H, et al. ERS Milan 2017; 526: OA4643
Functional imaging

Hyperpolarised 3-Helium gas MRI demonstrates sub-clinical progression in IPF over 6 months

• The red blood cells (RBC): tissue plasma (T/P) signal (metric of gas exchange) decreased significantly in 12 patients over 6 months, whereas their DL_{CO} did not

18F-FDG PET/CT can predict postoperative acute exacerbation in IPF

• 18F-FDG PET/CT imaging from cancer evaluation was used to predict post-operative complications (incl. AE, n=48)
• SUVR_{TF} ≥1.84 significantly predicted AEs within 30 days of thoracic surgery

1 Weatherley N, et al. ERS Milan 2017; 526: OA4642
2 Ko U, et al. ERS Milan 2017; 113: PA851

18F-FDG PET/CT: Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography, SUVR_{TF}: Lesion-to-liver standardised uptake value ratio, corrected with tissue factor
Functional Respiratory Imaging (FRI)

Assessment of disease progression

FRI offers:
- New insights into the heterogeneity in lung structure and function present in IPF
- Possible novel biomarkers
- Accurate assessment of effects of intervention and treatment efficacy

FRI predicts response to FG3019

- HRCT and 3D segmentation was used to quantify regional manifestation of disease
- Patients who showed stable or improving FVC to 48 weeks of treatment with FG3019 (anti-CTGF monoclonal antibody) could be predicted with an accuracy of 87% (n=66)
- Patients whose fibrosis stabilised or improved could be predicted with an accuracy of 76%

CTGF: Connective tissue growth factor

1 De Backer J. ERS Milan 2017; 262: OA1952
Expert comments

Lung fibrosis can be better quantified by using voxel-based tools and scores, which also allow a comparison of the extent of fibrosis and changes over time.

Preliminary data from new imaging tools are promising as possible future biomarkers in IPF, which will empower assessment to treatment response in future clinical trials once validated.

Dynamic imaging tools could help to better understand lung patterns in early stage disease.
Appendix and acknowledgements

The preparation of the slide kit was sponsored by Boehringer Ingelheim International GmbH and contains personal opinions from leading ILD experts. ERS was neither author nor reviewer of the content. This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).
Abbreviations

6MWD 6-Minute Walk Distance
6MWT 6 Minute Walk Test
ADR Adverse Drug Reaction
AE Acute Exacerbation
ATS American Thoracic Society
ARF Acute Respiratory Failure
BMI Body Mass Index
CCL Chemokine
chILD Children's Interstitial Lung Disease
CI Confidence Interval
cHP Chronic Hypersensitivity Pneumonitis
CPI Composite Physiology Index
CTGF Connective Tissue Growth Factor
dcSSc Diffuse Cutaneous Systemic Sclerosis
DLco Diffusion capacity for Carbon monoxide
DLco/AV DLco per unit Alveolar Volume
DM Dermatomyositis
ECM Extracellular Matrix
ECMO Extracorporeal Membrane Oxygenation
EU European Union
ENA Extractable Nuclear Antigens
EMT Epithelial-to-Mesenchymal Transition
ERS European Respiratory Society
FEV1 Forced Expiratory Volume in 1 second
FVC Forced Vital Capacity
FRI Functional Respiratory Imaging
GAP Gender, Age, and Physiology index
GER Gastroesophageal Reflex
HR Hazard Ratio
HRCT High Resolution Computed Tomography
HRQoL Health-Related Quality of Life
HRT Interferon gamma
Idiopathic Interstitial Pneumonia
Interleukin
Interstitial Lung Disease
Inflammatory Myopathies
Idiopathic Pulmonary Fibrosis
Integrin Subunit Alpha 5
limited Cutaneous Involvement Systemic Sclerosis
MultiDisciplinary Discussion
Multidisciplinary Team
Not Significant
Peripheral Blood Mononuclear Cell
Primary Care Centres (PCC)
Progression Free Survival
PFS Pulmonary Fibrosis
QoL Quality of Life
RA Rheumatoid Arthritis
RHCU Respiratory High Dependency Unit
RNO Rollferulast N-Oxide
RTX Rituximab
SGRQ St George's Respiratory Questionnaire
SNP Single Nucleotide Polymorphism
SpO2 Peripheral Capillary Oxygen Saturation
SSc Systemic Sclerosis
T1DM Transbronchial Cyrobiopsy
TAE Treatment Emergent Adverse Event
TILD Transitional interstitial lung disease (TILD)
TGF Transforming Growth Factor
TNF-alpha Tumour Necrosis Factor-alpha
UAP Usual Interstitial Pneumonia
UK United Kingdom
USOB UCSD Shortness Of Breath Questionnaire
UCSD UCSD Shortness Of Breath Questionnaire
VAS Visual Analog Scale
PH Pulmonary Hypertension
PM Polymyositis
PFS Primary Fibrosis Survival
Summary of product characteristics

To view the full summary of product characteristics please click on the PDF icon below or visit www.Global.OFEV.com.
Acknowledgments

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