ILD highlights from the ERS 2018 congress
September 15 – September 19 / Paris, France

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Objective and focus of this report

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OBJECTIVE AND FOCUS

European Respiratory Society Congress (ERS) 2018
The congress programme 2018 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 healthcare professionals in research and daily practice with an overview and expert perspectives on the clinical importance of the new data and novelties in the field of ILDs and IPF reported at the ERS 2018 congress.

Focus of this report
Up-to-date developments, main topics of discussion and highlights on IPF and ILDs presented in numerous oral and poster sessions at the ERS 2018 are summarised in this report.

In the “Breakthroughs” section, our experts provide their personal picks of the most important and exciting topics discussed at the congress.

At the end of each chapter, the experts have provided their comments and opinions concerning the respective topic.

Please note that these slides report the data presented during the ERS 2018 in Paris, France.

We have reported on posters and oral presentations. These are marked OAXXXX for an oral presentation, and PAXXXX for a poster presentation. Oral presentations from the congress that have been published have bibliographic references.

If you wish to view the abstracts, they are available under this link.

Please check your local regulations and guidelines when prescribing treatment and managing patients with ILD.
TOPIC OVERVIEW

► Breakthrough: the experts’ picks

★ Deep learning in the classification of fibrotic lung disease
★ INSTAGE® trial: Nintedanib with add-on sildenafil
★ Palliative care and nurse support in ILD
★ Emerging MALDI-FTICR imaging in IPF diagnosis
★ Mitochondrial dysfunction in ILD

► New insights into ILD pathobiology

• Immune findings in IPF
• Novel murine models of IPF
• Biomarkers in ILD / IPF diagnosis

► Non-pharmacological support in ILDs

• Physical training in IPF
• Pulmonary rehabilitation
• Palliative care and nurse support

► New insights into ILD diagnosis and management

• Novel diagnostic biomarkers
• New imaging tools in diagnostics
• Updates in ATS / ERS / JRS / ALAT guidelines

► Real world data: registries

• International registries

► Non-IPF ILDs

• Hypersensitivity pneumonitis
• Connective-tissue disease associated ILDs
• Systemic sclerosis

► Appendix and acknowledgements

• Abbreviations
• Prescribing information
• Acknowledgements
Method
The algorithm “learned” to detect IPF by analysis of 1157 HRCTs showing evidence of fibrotic lung disease.

Results
Algorithm gave equal prognostic discrimination to a new set of 150 HRCTs classifying “UIP vs not UIP” vs radiologists.

Conclusion
This algorithm could provide low cost, virtually instantaneous decision support, and be used to predict disease behaviour for future studies – but is not an attempt to replace radiologists.

Summary: “Deep learning” is a computer learning method that uses an algorithm to identify and map intricate patterns of fibrotic lung disease on HRCT to classification according to IPF guidelines.

HRCT: High-resolution computed tomography
UIP: Usual interstitial pneumonia

Figure: Algorithm compared to experts

To find out more about these exciting developments, follow the link to the “New insights into ILD diagnosis and management...” chapter of this report.
INSTAGE® TRIAL: NINTEDANIB WITH ADD-ON SILDENAFIL

Summary: INSTAGE® compared whether an active combination of nintedanib with sildenafil treatment provides additional benefits compared to nintedanib alone in patients with IPF and severely impaired gas exchange (DLCO ≤35%).

The addition of sildenafil to nintedanib did not show significant improvement vs nintedanib alone (SGRQ score) over a period of 24 weeks. No new safety signals were identified.

Patients were treated with nintedanib 150 mg bid plus placebo (n=137), and nintedanib 150 mg bid plus sildenafil 20 mg tid (n=136)

Primary endpoint
No significant difference in adjusted mean change from baseline in SGRQ score at week 12 between nintedanib plus sildenafil vs nintedanib alone
- -0.77 and -1.28 in patients who received nintedanib alone and nintedanib plus sildenafil, respectively (p=0.72, 95% CI -3.33, 2.30)

Secondary endpoints
No significant difference in adjusted mean change from baseline in SGRQ score at week 24 between nintedanib plus sildenafil vs nintedanib alone
- 2.42 and 0.23 in patients who received nintedanib alone and nintedanib plus sildenafil, respectively (p=0.18, 95% CI -5.40, 1.02)

Decline in FVC was numerically lower in patients treated with nintedanib plus sildenafil vs nintedanib alone
- Difference 37.4 mL (p=0.18, 95% CI -17.4, 92.3)

Nintedanib plus sildenafil was associated with a reduction in risk of an absolute FVC decline ≥5% predicted or death vs nintedanib alone
- HR: 0.56 (p=0.003)
- Nintedanib plus sildenafil had a manageable safety and tolerability profile
- The safety and efficacy of nintedanib alone was consistent with that observed in patients with IPF and milder lung function impairment

To find out more about these exciting developments, follow the link to the “New results from clinical studies …” chapter of this report.

1. Kolb M. ERS Paris 2018; 82: OA546

PDE: Phosphodiesterase; DLCO: Diffusing capacity of the lungs for carbon monoxide (% predicted)
FVC: Forced vital capacity; SGRQ: St. George's Respiratory Questionnaire
Bid: Twice daily; Tid: Three times daily
**PALLIATIVE CARE AND NURSE SUPPORT IN ILD**

**Objective:** To evaluate how the nurse support in ILD affects compliance to anti-fibrotic medication and hospitalisation admissions. To analyse the impact of diagnosis on patients with IPF and caregivers; and to provide an overview of care in patients with ILD with advanced disease.

**Compliance to anti-fibrotic medication**

- Hiring of an ILD nurse significantly improved compliance (to 90% above standard rates of ~80%) and reduced discontinuation rates due to adverse events.

**Effect on hospital admissions**

- Comparing visit rates for 74 IPF patients over the 20 months before and after an ILD nurse was hired, the presence of a specialist nurse tended to have a positive effect upon hospital admissions and emergency department visit rates.

**Impact of diagnosis on IPF patients and caregivers**

Semi-structured clinical interviews with 24 IPF patients and 15 caregivers suggested that:

- Preparatory grief is experienced at time of diagnosis and possibly during accelerated lung function decline.
- A perceived lack or absence of psychological support exacerbated distress.
- 38% of IPF patients reported grief, yet 68% reported that distressing emotions came in waves, indicating a lack or grief recognition.

**Care for ILD patients with advanced disease**

- A retrospective audit of 67 end-of-life patients with ILD showed that referral to palliative care and use of palliative medication occurred just prior to death, with only a minority given access to symptom palliation at an earlier disease stage.
- Systematic review of 12 trials for holistic breathlessness programs reported improvements in psychological aspects of breathlessness and health for some of the studies.

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5. Miller S, et al. ERS Paris 2018; 228; PA2045

To find out more about these exciting developments, follow the link to the “Non-pharmacological support in ILDs” chapter of this report.
NOVEL MALDI-FTICR IMAGING IN FOLLOWING PULMONARY ANTI-FIBROTIC TREATMENT

Summary: MALDI-FTICR imaging was used to quantify pharmacometabolic response to pirfenidone, and detect specific alterations in metabolic pathways in lung tissue following anti-fibrotic treatment\(^1\)

This study highlights the \textit{in situ} pharmacometabolic effect of pirfenidone in fibrotic tissue\(^1\)

Objective
To evaluate how novel high resolution MALDI imaging coupled with FTICR could be used in order to follow pulmonary changes post anti-fibrotic treatment\(^1\)

Findings
- Breakdown of pirfenidone into its metabolites was followed over time in normal mouse lung tissue, in a study from 2016\(^2\)
- In a mouse model of lung fibrosis, pirfenidone preferentially localises to region of lesser fibrosis\(^1\)
- In human lung samples, MALDI-FTICR could quantify changes in metabolites in IPF lung, and any modulatory effect of pirfenidone\(^1\)

Conclusion
- MALDI-FTICR allows the characterisation of the pharmacometabolomic effects of a compound in both research models’ and human subjects’ lungs. It highlights the suitability of this technique furthering advancement of currently used therapies for IPF\(^1\)

MALDI imaging: Matrix-assisted laser desorption/ionisation (a type of mass spectrometry whereby the distribution of molecules can be mapped without molecular tags or labels);

FTICR: Fourier-transform ion cyclotron resonance

To find out more about these exciting developments, follow the link to the “\textit{New insights into ILD diagnosis and management …}” chapter of this report

MITOCHONDRIAL DYSFUNCTION IN ILD

**Summary:** Novel findings which demonstrate the involvement of mitochondria and plasma mitochondrial DNA in lung disease

Mitochondrial dysfunction is a driver of lung disease

- Through the release of DAMPs, mitochondria are involved in apoptosis, immune response and lipid biosynthesis
- Infection, inflammation, oxidative stress and ageing can damage mitochondria, leading to apoptosis, inflammatory and fibrotic signalling that can cause lung diseases including IPF
- Increased extracellular mtDNA concentrations from BAL are a strong, significant predictor of mortality in IPF

Impaired repair of mitochondria and ageing in fibrosis – a vicious circle

- Mitochondrial dysfunction can induce lung ageing by reduced autophagy, altered proteostasis, DNA damage, telomere shortening
- Mitochondrial homeostasis is impaired in IPF lung Dysfunctional/dysmorphic mitochondria and mtDNA accumulate in IPF lung and are drivers of lung fibrosis
- Plasma mtDNA as a potential biomarker for IPF progression
  - In a study of 363 IPF patients, mtDNA plasma levels were significantly correlated with baseline DLCO (r=0.203, p<0.001), and changes in DLCO over 6 months (r=-0.224, p<0.001)
  - mtDNA levels could therefore be a marker for disease progression

To find out more about these exciting developments, follow the link to the "New insights into ILD pathobiology: ..." chapter of this report

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1. Meiners S. ERS Paris 2018; 173: OA1629

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BAL: Bronchiolar lavage; DAMPs: Damage-associated molecular patterns; mtDNA: mitochondrial DNA; DLCO: Diffusing capacity of the lungs for carbon monoxide (% predicted)
New insights into ILD pathobiology
MESENCHYMAL STROMAL EXOSOMES TO TREAT FIBROSIS IN A MURINE MODEL

MSCs are proposed as treatment for IPF

Purified MSC exosomes (MEx) have been previously used in respiratory disease

Using MEx to treat fibrosis in a murine IPF model

- Exosomes were isolated from media conditioned by human bone marrow MSCs using iodixanol density floatation as described by Willis et al

- Adult C57BL/6 treated mice and controls were assessed at day 7 and/or 14 for histology, flow cytometry, RNA and protein expression levels

- Bleomycin induced lung fibrosis 14 days post injection, and a single dose of MEx treatment significantly reduced fibrosis on day 1

- On day 7 MEx treatment reverted fibrosis and restored lung and alveolar Mϕ numbers

- Transplantation of MEx-preconditioned BMDMϕ prevented bleomycin-induced fibrosis

Conclusion

MEx treatment alleviated core features of pulmonary fibrosis and reduced collagen deposition by modulation of myeloid cell phenotype

- The proportion of lung classical proinflammatory monocytes, regulatory monocytes and alveolar macrophages was shifted to favor the monocyte/macrophage profiles of untreated (control) mice

- Second, MEx treatment further reduced lung fibrosis via a pro-homeotic effect upon bone marrow-derived monocytes that were preconditioned with MEx

MSC: Mesenchymal stromal cells
Mϕ: Macrophage; BMD: Bone marrow derived

1. Mansouri N. ERS Paris 2018; 46: OA261
CELLULAR REGULATION AND FUNCTION IN PULMONARY FIBROSIS

The role of myeloid-derived suppressor cells (MDSCs) in IPF progression

- MDSC levels were significantly increased in 69 IPF patients vs 22 controls, and correlated with FVC
- MDSC levels correlate with GAP index; and IPF patients with circulating levels of MDSC >25 showed significantly reduced transplant-free survival

Possible mechanism?

- Patients with increased levels of MDSCs have deregulated co-stimulatory T-cell signals
- IPF-MDSCs have an altered ligand profile where they express pro-fibrotic molecules like MMP1 and TGF\(\beta\)1, and suppress the autologous proliferation of T-cells

Future perspectives

The importance of MDSCs in the modulation of T-cells and fibrosis / fibrogenesis remains to be elucidated – as well as the clinical relevance

Senescence of alveolar epithelial cells (AECs) as a driver of fibrosis

- Bleomycin induced AEC senescence, activated PTEN/NF-\(\kappa\)B pathway, and induced a senescence-associated secretory phenotype (SASP)
- SASP increased collagen expression in fibroblasts
- Staining of senescent AECs and IPF lung tissue showed decreased PTEN (originally characterised as a tumour suppressor) and increased NF-\(\kappa\)B activation – confirming disease relevance
- NF-\(\kappa\)B silencing rescued AEC from senescence, and fibroblasts from collagen deposition, whereas PTEN deletion accelerated these processes
- As NF-\(\kappa\)B silencing rescued AECs from senescence and fibroblast collagen deposition, this pathway could be a candidate for therapeutic intervention in IPF and development of IPF

Conclusion

This study suggests that interactions between the epithelial cells and fibroblasts may promote the genesis of fibrosis

GAP: Gender, age, physiology; FVC: Forced volume vital capacity
MMP1: Matrix metalloproteinase 1; TGF\(\beta\)1: Transforming growth factor \(\beta\)1

1. Fernandez I. ERS Paris 2018; 495: OA4926
**PREVALENCE OF ANTINUCLEAR ANTIBODY (ANA) IN IPF PATIENTS (ESTAIR TRIAL)**

1. Wung P. ERS Paris 2018; 82: OA540
2. ClinicalTrials.gov Identifier: NCT02345070

**Rationale and patient selection**
- ANA is used in the evaluation of patients with suspected IPF to exclude underlying collagen vascular disease
- In patients with low ANA titres, it is unclear whether this is an epiphenomenon of the fibrosis
- A subgroup analysis of the phase 2b ESTAIR trial data* examined patients with confirmed diagnosis of IPF and ANA levels recorded at baseline (n=325)

**Results**
- In the intent-to-treat population, patients were stratified into ANA negative (<1:40) (n=171, 52.6%), ANA low positive (1:40, 1:80) (n=105, 47.1%), and ANA high positive (≥1:160) (n=48, 14.8%)
- High positive ANA vs ANA negative was significantly associated with the following characteristics: Caucasian, female, never smoker, greater history of acute exacerbation, requiring supplemental O₂ (all p<0.05)

**Conclusion**
- Circulating ANA was found in a subset of the IPF population, which likely represent a unique subset of the IPF patients
- The clinical significance of ANA remains to be elucidated and further studies are needed to verify these findings and identify diagnostic and treatment algorithms

*ESTAIR tested the safety and efficiency of SAR156597, but the primary endpoint was not reached
**MITOCHONDRIAL DYSFUNCTION IN ILD**

**Mitochondrial dysfunction is a driver of lung disease**¹
- Mitochondria are involved in multiple functions aside from energy production, such as lipid biosynthesis, signalling, cell death and the innate immune response, through the release of DAMPs
- Infection, inflammation, oxidative stress and ageing can damage mitochondria, leading to cell death and pro-inflammatory and fibrotic signalling that can cause lung diseases including IPF
- Increased extracellular mtDNA concentrations from BAL are a strong, significant predictor of mortality in IPF²

**Impaired repair of mitochondria and ageing in fibrosis – a vicious circle**³
- Mitochondrial dysfunction can drive ageing by reduced autophagy, altered proteostasis, DNA damage / instability and telomere shortening
- Mitochondrial homeostasis is impaired in IPF lung. Dysfunctional / dysmorphic mitochondria and mtDNA accumulate in IPF lung and drive lung fibrosis³⁴

**Plasma mtDNA as a potential biomarker for IPF progression**⁵
- In a study of 363 IPF patients, mtDNA plasma levels were significantly correlated with baseline DLCO (r=0.203, \( p<0.001 \)), and changes in DLCO over 6 months (r=-0.224, \( p<0.001 \))
- mtDNA levels could therefore be a marker for disease progression

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1. Meiners S. ERS Paris 2018; 173: OA1629
5. Yoon H. ERS Paris 2018; 391: PA3722

BAL: Bronchiolar lavage; DAMPs: Mitochondrial damage-associated molecular patterns
mtDNA: mitochondrial DNA; DLCO: Diffusing capacity of the lungs for carbon monoxide (% predicted)
**Sporadic and familial pulmonary fibrosis: \( I^{ER-SP-C}_{73T} \) expressing mice develop polyclonal alveolitis**¹

- Alveolar type 2 (AT2) cell-specific surfactant protein C (\( SFTPC \) gene) known to be involved in fibrotic lung remodeling was studied by construction of \( SFTPC^{{I73T}} \) allele under the control of a tamoxifen (TAM)-inducible promoter
- RNA-Seq analyses of AT2 cells revealed that compared to controls, \( SP-C^{{I73T}} \) cells exhibited 3,768, 3,738 and 666 differentially expressed inflammatory, matrisome-associated and profibrotic-signalling genes at 3, 14 and 42 days post TAM-induced mutation, respectively (\( p<0.01 \))

**Conclusion**

The fibrotic phenotype in the mouse model of sporadic and familial pulmonary fibrosis is controlled by \( SFTPC \) by altering the transcriptomic profile of AT2 cells

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**Development of a chronic pulmonary fibrosis model in the BALB/c genetic background**²

- In this study 5 U/mL of bleomycin treatment of BALB/c mice was evaluated in order to develop an experimental model with a milder but extended inflammatory response
- Inflammation was observed 5 days post treatment, and collagen deposits and fibrosis developed after 15 and 30 days post treatment, respectively
- mRNA expression and cytokine levels were consistent with the fibrotic profile, and the ventilatory mechanics were in line with the histological findings

**Conclusion**

This study suggests that BALB/c mice treated with bleomycin show chronic progressive decay of respiratory functions resembling chronic pulmonary fibrosis

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¹ Katzen J, et al. ERS Paris 2018; 110: PA988
**HUMANISED MOUSE MODEL FOR STUDYING IPF**

### Generation of the model
Addition of human ABCs from IPF patients (but not healthy control ABCs) to Rag2⁻/⁻ mice pre-treated with bleomycin promotes fibrosis, aberrant bronchiolisation, and cystic lesions.

### Treatment of bleomycin-treated humanised Rag2⁻/⁻ model with nintedanib
- Reduced the fibrosis Ashcroft score ($p=0.019$)
- Reduced hydroxyproline levels in a collagen assay ($p=0.039$)
- Reduced BAL neutrophil counts ($p=0.053$)

### Conclusion
Expression levels of ABC derived genes in BAL strongly correlates with mortality in IPF patients, so the model makes use of a clinically relevant cell type to promote IPF-like phenotypes that respond to a well characterised anti-fibrotic agent.

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**ABCs**: Airway basal cells; **RAG**: Recombinase activating gene

**Hydroxyproline**: Component of collagen; **BAL**: Bronchiolar lavage
SPUTUM-DERIVED EXOSOMES IN PATIENTS WITH IPF

Aim
To isolate and characterise sputum-derived exosomes and exosomal miRNAs in patients with IPF.

Method
• Isolation of exosomes from sputum supernatant of healthy subjects (HS) and IPF patients, followed by pre-clearing of the supernatant by ultracentrifugation and precipitation
• Isolation of total exosomal RNA, followed by miRNA array and quantitative RT PCR assays

Results
• miRNAs miR-142-3p and miR-33a-5p expression in exosomes of IPF patients is increased compared to HS (p<0.0001 and p=0.006, respectively)
• miRNA Let-7d-5p expression in exosomes of IPF patients is decreased compared to HS (p=0.006)
• miRNAs miR-142-3p and Let-7d-5p expression correlates with DLCO/VA (%) (r=-0.68, p=0.010 and r=0.55, p=0.048, respectively)

Conclusion
• New potential biomarkers of disease identified from sputum-derived exosomes of IPF patients
• Different expression levels of Let-7d-5p, miR142-3p and miR-33a-5pmiRNAs are found in the exosomes derived from IPF patients sputum and not in HS
• The correlation between the miR142-3p and Let-7d-5p and DLCO/VA suggests these miRNAs are indicative of IPF pathophysiology

1. Guiot J. ERS Paris 2018; 243: OA2119
2. Guiot J, et al. Thorax 2018, manuscript accepted

DLCO: Diffusing capacity of the lungs for carbon monoxide (% predicted)
VA: Alveolar volume; miRNA: microRNA; RT PCR: real-time polymerase chain reaction
Serum AGE / RAGEs allow differential diagnosis of ILDs

AGE/sRAGE ratios from serum samples taken from 12 control, 48 IPF, 15 cHP, and 15 fNSIP subjects were compared to PFT data.

Results
- IPF and cHP patients had low sRAGE levels and increased AGE concentration vs controls (both p<0.01).
- This imbalance of AGE/sRAGE could differentiate IPF and cHP from NSIP.
- Reduced sRAGE concentration correlated with reduced FVC pred. % and DLCO, thus reflecting the severity of the disease.

Conclusion
Serum AGE/sRAGE levels allowed differential diagnosis of ILD forms, and correlated with pulmonary function data to reflect disease severity.

Prognostic biomarker of IPF: CXCL13

Rationale
To characterise the expression of CXCL13 (chemokine ligand 13) in macrophages of patients with IPF and confirm CXCL13 role as a prognostic biomarker, this study focused on a large cohort of 121 patients with IPF.

Results
CXCL13 levels are increased in patients with IPF, and plasma levels are associated with the severity of the disease:
- IPF patients with serum levels of CXCL13 >53.1 pg/mL had reduced DLCO, decreased exacerbation-free survival and lower overall survival.
- CXCL13 levels in plasma of IPF patients is controlled by TNF-α and IL-10 in human macrophages.

Conclusion
CXCL13 is confirmed as a prognostic biomarker of IPF, and its expression is suggested to be regulated by TNF-α and IL-10 axis in IPF patients.


cHP: Chronic hypersensitivity pneumonitis; fNSIP: fibrotic nonspecific interstitial pneumonia
AGE: Advanced glycation end products; FVC: Forced vital capacity
(s)-RAGE: (soluble) Receptor for advanced glycation end-products; PFT: Pulmonary function tests
IL: Interleukin; DLCO: Diffusing capacity of the lungs for carbon monoxide (% predicted)
ALTERATIONS IN ECM AND MOLECULAR DRIVERS OF PATHOGENESIS IN PATIENTS WITH IPF

Correlating cellular and extracellular matrix (ECM) changes to IPF pathology

Analyses of lung scaffolds (decellularised tissue) and lung cell cultures from 4 healthy and 4 subjects with IPF

- Histology, mass spectrometry, scanning electron microscopy, DNA content, tissue density and tensile strength were used to assay tissue and cellular differences
- IPF-derived scaffolds showed denser morphology and higher ECM stiffness compared to healthy scaffolds
- Mass spectrometry analyses revealed increased fibroblast proliferation and tissue stiffness

Conclusion
- Alterations in ECM structure and cellular responses correlate with IPF disease pathology

Identifying molecular drivers of pathogenesis in patients with IPF and non-IPF UIP

Determining if IPF and non-IPF UIP lungs share common molecular signals, from ILD patients identified from an ongoing longitudinal prospective cohort (57 non-IPF UIP, 169 IPF) with SLB/explant tissue available for analyses

Identification of shared molecular markers

- Telomeres were shortened in AECs from IPF and non-IPF UIP lungs vs healthy age-matched controls
- p16 and p21 levels were elevated in UIP/non-IPF UID lung lysate, and immunostaining localised the proteins in AEC II cells

Conclusion
- Molecular markers for senescence and telomere dysfunction were identified in both
- UIP and non-IPF UID lung, suggesting that common molecular drivers contribute to pathogenesis in both forms of pulmonary fibrosis

2. Lee J. ERS Paris 2018; 550: OA5362

UIP: Usual interstitial pneumonia; SLB: Surgical lung biopsy; AECs: Alveolar epithelial cells

ERS Highlights 2018 Slide Kit. Sponsored by Boehringer Ingelheim; not reviewed or approved by ERS
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).
**EXPERT COMMENTS**

New *in vivo* models that better mimic human pulmonary fibrotic processes are under development.

Better understanding of the role of genotype in therapeutic response should be highlighted for future clinical trials.

Exosomes from MSCs demonstrate anti-fibrotic effects in a murine model of lung fibrosis. Exosomes may be evaluated from patients’ sputum.

New serum biomarkers to identify different subgroups of IPF patients with specific features have been found. Further prospective multicentric studies are required for the validation and better understanding of these biomarkers. The role of global IPF biobanks is essential to accomplish this aim.

Different drivers and players in the processes of cell senescence and mitochondria dysfunction are implicated in pulmonary fibrosis.

Working together in global IPF biobanks represents a milestone to be achieved in order to have reliable and useful biomarkers in IPF.
Non-pharmacological support in ILDs
### Home testing of IPF symptoms

**Aim**
To test the feasibility of 'IPF-online' home monitoring programme incorporating daily home spirometry, weekly online patient-reported outcomes, and automatic email alerts in response to changes in 10 patients

**Results**
- Adherence to daily spirometry was 98.8%
- 80% found the spirometer easy to use: all patients considered home monitoring useful, and no significant increase in anxiety was reported
- Home and hospital FVC readings highly correlated (r=0.94), with a mean difference of 0.14 L
- Median relative variability for home FVC was only 3.76%

**Conclusion**
Home monitoring of changes to FVC and patient-reported outcomes was shown to be feasible in this Netherlands-based study. Usage of new eHealth technologies is feasible and appreciated by patients with IPF

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### Non-invasive airway testing

**Rationale**
IPF affects the parenchyma of the lungs, and reduces elasticity and lung volume. This study sought to test whether lung elasticity measurements using impulse oscillometric (IOS) airways testing in 22 IPF patients would correlate with PFT data

**Results**
- Elasticity throughout the conductive airway system was measured at 5 Hz (X5)
- Reactance at 5 Hz (X5) was significantly correlated with FEV₁, FEV and TLC (p<0.05)

**Conclusion**
Where patients are unable to undergo traditional PFTs, IOS could be used to evaluate lung elasticity, indicating the reduction of lung volume caused by the disease

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2. Flensborg E, et al. ERS Paris 2018; 296: PA2974

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PFT: Pulmonary function tests; FEV₁: forced expiratory volume in one second
FVC: Forced vital capacity; Hz: Hertz; TLC: total lung capacity
PHYSICAL TRAINING IN IPF

Whole body vibration training (WBVT)¹

3-month WBVT programme in 3 centres, explored the effect of training on clinical effectiveness and biomarkers: 11 patients were assigned to WBVT and 15 to sham training

Results
- Significantly higher 6MWD ($\Delta_{\text{training}}$=34.82 m, $p=0.024$). The 6MWD MID has been estimated at 28 m, although estimates differ²
- Significant reduction in IL-6, a proposed factor for sarcopenia, and myostatin, which could explain the improved performance in the 6MWD
- Although no changes were seen in other physical parameters including FEV₁ and VCₘₐₓ, chair raising test, or in quality of life questionnaires, this study represents the first proof of WBVT clinical benefits

Conclusion
These findings add clinical value to previous studies that have shown improvements in physical capability, although previous findings of improved HRQoL and lung function were not studied here

Supervised physical training (sPT)³

16 patients completed sPT (n=6 for one year; n=10 for 12 weeks – both followed by 9 months of nsPT). 14 IPF patients performed nsPT, with evaluation at baseline, 12 weeks and 1 year³

Results
- The observational group displayed a clinically relevant decrease to 6MWD of 33 m, whereas the sPT group did not change from the baseline value
- No group showed benefits in FVC, TLC or DLCO at 12 weeks or 1 year
- The sPT group showed a trend towards improved HRQoL and health status, but these did not reach significance

Conclusion
sPT led to benefits in HRQoL and 6MWD, but further research and randomised clinical trials are needed to identify effective training interventions


MID: Minimally important distance; FVC: Forced vital capacity; DLCO: Diffusing capacity of the lungs for carbon monoxide
IL: Interleukin; TLC: Total lung capacity; 6MWD: 6-minute walking distance; $V_{c_{\max}}$: Maximum vital capacity
HRQoL: Health related quality of life; nsPT: non-supervised physical training
PULMONARY REHABILITATION IN ILD

An effective rehabilitation programme
- A 2-3 times daily, 4-week pulmonary rehabilitation (PR) programme combining exercise and breathing technique training benefited both ILD (n=30) and IPF (n=23) patients, significantly improving 6MWD, FVC, and other functional markers.

PR in unstable in patients with ILD
- A retrospective, two-centre study (n=103) found that patients with poor general condition and motor function experienced a delay to PR initiation.
- Low CRP levels and walking ability before hospitalisation were significant predictors for early PR initiation.

Systematic review and meta analyses: PR in 27 ILD studies
- Significant increase in 6MWD immediately following intervention compared to control (MD 45.9 m ± 23.3 m).
- No significant difference seen at 3 or 6 months (MD 5.3 m ± 18.1 m).
- No consistent change in dyspnoea immediately following the intervention.
- No significant difference to QoL seen, either long-term or short-term.
- Lack of support for positive outcomes in exertional dyspnoea or QoL contrasts findings of the Cochrane review: further research is therefore needed to clarify the usefulness of PR.

References:

PR: Pulmonary rehabilitation; 6MWD: 6-minute walking distance; FVC: Forced vital capacity; CRP: C-reactive protein; QoL: Quality of life.
## Palliative Care and Nurse Support in ILD

### Compliance to anti-fibrotic medication

- Hiring of an ILD nurse significantly improved compliance (to 90% – above standard rates of ~80%) and reduced discontinuation rates due to AEs (n=59 IPF patients)

### Effect on hospital admissions

- Comparing visit rates for 74 IPF patients over the 20 months before and after an ILD nurse was hired, the presence of a specialist nurse tended to have a positive effect upon hospital admissions and emergency department visit rates

### Impact of diagnosis on IPF patients and caregivers

Semi-structured clinical interviews with 24 IPF patients and 15 caregivers suggested that:

- Preparatory grief is experienced at time of diagnosis and possibly during accelerated lung function decline
- A perceived lack or absence of psychological support exacerbated distress
- 38% of IPF participants reported “grief”, yet 68% reported that distressing emotions came in waves, indicating a lack or grief recognition

### Care for patients with ILD and advanced disease

- A retrospective audit of 67 end-of-life ILD patients showed that referral to palliative care and use of palliative medication occurred just prior to death, with only a minority given access to symptom palliation at an earlier disease stage
- Systematic review of 12 trials for holistic breathlessness programs reported improvements in psychological aspects of breathlessness and health for some of the studies

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3. Reynolds-Sanford D, et al. ERS Paris 2018. 430; PA4106
5. Miller S, et al. ERS Paris 2018; 228; PA2045

AEs: Adverse events
EXPERT COMMENTS

To further advancement in palliative care in ILD patients, it is essential that international consensus is reached on statements for research, selection of population baseline characteristics and putative outcomes.

There is a high demand for a more comprehensive approach to understand disease behaviour in palliative care in ILD.

Delivery of palliative care to ILD patients and the palliation of symptoms should be started as early as possible, rather than waiting until an advanced stage.

As many ILD specialist doctors can attest, the value of a specialist ILD nurse is hard to overstate.

Pulmonary health care providers often lack specific palliative expertise, while palliative care specialist often lack knowledge on ILD, more cross-fertilisation is needed.
New insights into ILD diagnosis and management
NEW CONFOCAL ENDOMICROSCOPY-BASED IMAGING IN ILD DIAGNOSIS

Probe-based confocal laser endomicroscopy (pCLE)\(^1\)
- A novel method for imaging of bronchial walls using real-time microscopy, Cellvizio system (488 nm excitation laser and 1.4 mm Alveoflex probe) was studied in 20 patients with bilateral pulmonary infiltrates shown on patient chest CTs, confirmed by lung biopsy
- Septal wall thickness, architecture, diameter of alveoli and presence of inflammatory cells were detected
- pCLE technique showed most sensitivity in patients with metabolic lung diseases, then in IPF and COPD, needing further validation for differential diagnosis in ILD

Confocal laser endomicroscopy (CLE) in ILD patients\(^2\)
- To distinguish between the partially filled alveoli or fine fibrosis of ground glass opacities (GGO) on the HRCT scan, a pilot study was performed in 20 non/former smokers with ILD scheduled for lung biopsies
- Real-time microscopy CLE is a novel method that differentiates between the two commonly inconclusive histological patterns, reducing the need for lung biopsies
- Although no adverse events occurred, further studies are needed to validate the technique

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**NOVEL IMAGING AND ANALYSIS TOOLS IN ILD DIAGNOSIS**

**R-EBUS-guided transbronchial lung biopsy (TBLB) in diffuse lung lesions**
- Retrospective analyses of 50 patients (32 in R-EBUS and 20 in the blinded group) who underwent TBLB and those who underwent R-EBUS-guided TBLB
- There was no difference in the diagnostic yield between the TBLB and R-EBUS guided TBLB, but the incidence of pneumothorax complication was significantly lower in the R-EBUS-guided group ($p=0.024$)
- Further studies are needed to validate these findings in other settings

**Lung Fibrosis quantification Tool (LUFIT) in acute exacerbations of IPF (AE-IPF)**
- To evaluate the differences between visual scoring and automated computer-aided quantification of CT scans, LUFIT was developed to circumvent limited reproducibility between the readers of the scans
- In 49 patients with IPF (30 with AE-IPF and 19 without AE-IPF), longitudinal visual scoring was performed on 98 paired CT data-sets by an experienced chest radiologist and compared to automated CT analyses using LUFIT
- LUFIT automated quantification identified changes present during AE-IPF (acute inflammation (GGO) and fibrosis), supporting its further use in the clinic


AE-IPF: Acute exacerbations of IPF
EMERGING MRI AND MALDI-FTICR IMAGING IN IPF DIAGNOSIS

Using hyperpolarised gases-MRI to quantify gas exchange in patients with IPF\(^1,2\):
- Multinuclear MRI using hyperpolarised (HP) \(^{129}\)Xe and \(^{3}\)He can assess the structure and function of capillary perfusion in patients with IPF\(^1\)

Dynamic contrast-enhanced (DCE) perfusion MRI:
HP gas ventilation features from MRI in patients with IPF are similar to those read on CT\(^2\):
- Assessing \(^{129}\)Xe longitudinal sensitivity by quantifying acinar microstructure, gas exchange and perfusion over 12 months
- Quantitative parameters correlate with DLCO, are reproducible over time and relate to regions of fibrosis\(^2\)
- Sensitivity to changes over 12 months was better than in pulmonary function tests\(^2\)

Conclusion
Novel MRI imaging techniques could add value for patient care and in clinical trials – deep learning could affect how IPF is diagnosed\(^3\):
- Sensitive to early changes\(^2\)
- Validated and reproducible over time\(^2\)

Further scientific evidence could lead to changes in guidelines\(^3\)

MALDI-FTICR imaging was used to quantify pharmacometabolic response to pirfenidone, and alterations in metabolic pathways in lung tissue\(^4\):
- Breakdown of pirfenidone into its metabolites was followed over time in normal mouse lung tissue, in a study from 2016\(^5\)
- In a model of lung fibrosis, pirfenidone preferentially localises to a region of lesser fibrosis\(^4\)
- In human lung samples, MALDI-FTICR could quantify changes in metabolites in IPF lung, and any modulatory effect of pirfenidone\(^4\)

Conclusion
MALDI-FTICR allows the characterisation of the pharmaco-metabolomic effects of a compound in both research models’ and human subjects’ lungs. It highlights the suitability of this technique furthering advancement of currently used therapies for IPF\(^4\)

2. Wild J, ERS Paris 2018; 546: OA5338
3. Vogel-Claussen J, ERS Paris 2018; 334: OA3244
**Nutrition and Metabolism**

**Rationale**
To evaluate the diagnostic yield and risk / benefit of TBLC in 699 patients with diffuse parenchymal lung disease (assessed on HRCT)

**Results**
- Diagnostic yield is significantly higher when the number of samples increases ($p<0.0001$) and when the biopsies are performed in different segments (88% for one vs 94% for different segments, $p<0.0001$)
- Pneumothorax is influenced by the number of samples ($p=0.008$), the site of sampling ($p=0.0009$), and the baseline FVC ($p=0.008$)
- Incidence of pneumothorax is significantly lower when a 1.9 probe is used ($p=0.0001$), while the bleeding is not affected by the probe size
- Mortality due to the procedure occurred in 2 patients

**Conclusion**
Cryobiopsy is a safe and effective approach for diagnosis in patients with suspected diffuse parenchymal lung diseases

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**Multidisciplinary team (MDT) in diagnosis of genetic ILD**

**Rationale**
To evaluate feasibility of monthly MDT meetings* in indication and interpretation of genetic testing in ILD (n=70: 37M, 33F, mean age 46.4; 3 patients <15 years) in 31 centres in 7 countries

**Results**
- HRCT showed UIP in 10, possible UIP in 11, inconsistent with UIP and no ILD in 4 patients
- Rare genetic variants were detected and considered pathogenic in 43 patients: TERT (n=18), TERC (n=4), RTEL1 (n=1), PARN (n=1), SFTPC (n=8), SFTPAl (n=2), SFTPA2 (n=2), NKX2-1 (n=3), ABCA3 (n=3), GATA2 (n=1)
- Antifibrotics were recommended in 23, supportive care in 4, surgical lung biopsy in 2, steroids in 7, lung transplantation in 16 and watch and wait in 9 patients

**Conclusion**
MDT dedicated to genetic analyses is feasible and provides opportunity for more effective diagnosis and management of patients with suspected ILD

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*included pneumologist experts in ILD for adults and children, geneticists, radiologists
DEEP LEARNING IN THE CLASSIFICATION OF FIBROTIC LUNG DISEASE

Aim
Use “deep learning” – a computer learning method that can identify and map intricate patterns in high dimensional data to simple classifications – to classify HRCT scans, according to IPF guidelines.

Method
The algorithm “learned” to detect IPF by analysis of 1157 HRCTs showing evidence of fibrotic lung disease.

Results
Algorithm gave equal prognostic discrimination to a new set of 150 HRCTs classifying “UIP vs not UIP” vs radiologists.

Conclusion
This algorithm could provide low cost, virtually instantaneous decision support, and be used to predict disease behaviour for future studies – but is not an attempt to replace radiologists.

Figure: Algorithm compared to experts

Comparison of accuracy for algorithm vs radiologists in the diagnosis of UIP vs not UIP

1. Walsh, S. ERS Paris 2018; 46: OA262
### The Most Important Changes in the ATS/ERS/JRS/ALAT 2018 IPF Diagnosis Guidelines

| 2018: In patients with newly detected probable or indeterminate UIP on HRCT, or an alternative diagnosis | **• Conditional recommendations were made for performing BAL and surgical lung biopsy**  
**• No recommendation was made for or against performing transbronchial lung biopsy**  
**• Experienced centres and experts with a safe track record can reasonably continue to use lung cryobiopsy** |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined patterns of Usual Interstitial Pneumonia (UIP) according to 2011 and 2013 guidelines</td>
<td><strong>• UIP, probable UIP, indeterminate UIP, and alternative diagnosis (assigned to both histopathology and HRCT results)</strong></td>
</tr>
</tbody>
</table>
| 2018: In patients with newly detected UIP pattern on HRCT | **• Strong recommendations were made against performing lung cryobiopsy, surgical lung biopsy, or transbronchial lung biopsy**  
**• Conditional recommendation against performing BAL** |
| 2018: Further recommendations | **• Conditional recommendation for multidisciplinary discussion**  
**• Strong recommendation against measurement of serum biomarkers for the sole purpose of distinguishing IPF from other ILDs** |

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HRCT: High resolution computed tomography; BAL: Bronchoalveolar lavage


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IPF DIAGNOSTIC CRITERIA: STATE OF THE ART

Updated approach for accurate diagnosis of IPF, established by members of the Fleischner Society, presented at the ERS 2018\(^1,2\)
Main updates include:

- A highly probable, but not a definite working IPF diagnosis can be achieved using a multidisciplinary approach by combining existing evidence with clinical reasoning
- A working diagnosis of IPF can be made in the presence of progressive fibrosing interstitial pneumonia in the absence of an alternative explanation
- The role of CT in patients with suspected IPF is extended in diagnosis of IPF if surgical biopsy is not available
- The guidance provided by the Fleischner Society statement will likely yield the same diagnosis as the algorithm provided in ATS/ERS/JRS/ALAT guidelines\(^3\)

Conclusion
Criteria to establish a confident and working multidisciplinary diagnosis of IPF are presented at ERS 2018\(^1,2\)

Differences between the Fleischner Society White Paper and the ATS/ERS/JRS/ALAT IPF Clinical Practice Guideline\(^3,4,5\)

- Four grade HRCT system broadly adopted in 2018 guidelines, with a focus on probable UIP and biopsy
- IPF-specific treatment in patients with probable UIP on HRCT without surgical lung biopsy data
- Experts encouraged to use TBLC

Conclusion
IPF diagnosis can be definite or confident working diagnosis, and their management is likely the same, therefore acrimony of the statements should be avoided\(^5\)


HRCT: High resolution computed tomography; MDD: Multidisciplinary discussion
UIP: Usual interstitial pneumonia; TBLC: Transbronchial lung cryobiopsy
AN UNMET NEED: GUIDANCE ON DIAGNOSIS AND TREATMENT OF AE-IPF

509 ILD specialists in 66 countries were surveyed about their handling of acute exacerbations in IPF (AE-IPF)¹

Results

- Significant differences were found in the approach to diagnostic procedures, treatments, ICU and palliative care, and prevention of AE-IPF across continents; within continents, methods were highly variable
- While HRCT is used by 91% of specialists in Asia to diagnose AE-IPF, & 67% in Europe. Likewise, BAL is always used in the diagnosis of AE-ILD in 9% of cases in Asia – in Europe, only 4%
- Treatment methods also widely differed (Table)
- Assessment of strategies within German pneumology departments confirmed that strategies for prevention, diagnosis and treatment of AE-IPF can show strong differences within a single country²

Conclusion

There is a strong, unmet need for international consensus recommendations for the handling of AE-IPF and AE-ILDs

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¹ Kreuter M. ERS Paris 2018; 82: OA542
² Polke M, et al. ERS Paris 2018; 293: PA2903

### Treatments of AE-IPF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total (n=509)</th>
<th>Europe (n=238)</th>
<th>North-America (n=56)</th>
<th>South-America (n=51)</th>
<th>Asia (n=115)</th>
<th>Australia (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone ≥500 mg with tapering</td>
<td>62</td>
<td>59</td>
<td>56</td>
<td>67</td>
<td>69</td>
<td>60</td>
</tr>
<tr>
<td>Methylprednisolone ≥500 mg pulsed (w/o tapering)</td>
<td>11</td>
<td>17</td>
<td>4</td>
<td>9</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Prednisolone 100 mg</td>
<td>32</td>
<td>25</td>
<td>47</td>
<td>37</td>
<td>28</td>
<td>45</td>
</tr>
<tr>
<td>No immunosuppression</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Cyclophosphamide i.v.</td>
<td>18</td>
<td>18</td>
<td>0</td>
<td>9</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Rituximab</td>
<td>4</td>
<td>3</td>
<td>10</td>
<td>11</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Differences between continents: p<0.0001

AE-IPF: Acute exacerbation of IPF is characterised by an acute, clinically significant respiratory deterioration; AE-ILD: Acute exacerbation of interstitial lung disease

BAL: Bronchoalveolar lavage; ICU: Intensive care unit; w/o: without; i.v.: intravenous
EXPERT COMMENTS

The expert MDD evaluating clinical and HRCT data may avoid SLB in some cases. The MDD is the “gold standard” for IPF diagnosis.

There are 4 HRCT patterns that help us discriminate the probability of IPF:

- **Confident UIP + appropriate clinical context:** IPF
- **Probable UIP + appropriate clinical context:** high probability of IPF (MDD and patient priorities are mandatory for deciding if lung biopsy, BAL or TBLC are required)
- **Indeterminate UIP + appropriate clinical context:** less probable but not impossible IPF (MDD and patient priorities are mandatory for deciding if lung biopsy, BAL or TBLC are required)
- **Inconsistent UIP or Alternative diagnosis:** almost impossible IPF

In case of suspected IPF/probable UIP on HRCT, and MDD should always weigh the confidence in an IPF diagnosis and whether or not anti-fibrotic therapy will be started if there will be no surgical lung biopsy. This should be discussed with the patient, to frankly weigh the risk-benefits of the potential surgical biopsy.

New techniques – such as deep learning, will speed up the diagnostic process for patients and facilitate access to the right care and treatment.
New results from clinical studies: antifibrotics in ILD / IPF
PROFILING TREATMENT PATTERNS WITH ANTIFIBROTICS

Aim
To understand the extent of availability of pirfenidone and nintedanib to patients, and therapeutic practices on a country by country basis (see region-based summaries in Figure)\(^1\)

Method
330 physicians treating IPF from 39 countries, where both nintedanib and pirfenidone are approved completed 2 questionnaires

Results
Over 12 months, 57.2% of 24,923 patients were treated with antifibrotics (on average, 30.92% were on pirfenidone and 26.33% on nintedanib), 13% had been previously treated, and 29% were never treated 42.7% were not taking any of the two antifibrotics

Conclusion
Many patients still continue to have restricted access to antifibrotic therapies (these restrictions vary differently, by region). Analyses of profiling patterns of antifibrotic treatment indicate that differences in access to antifibrotics can impact health outcomes, and the design / analysis of clinical studies of add-on therapies\(^1\)

Figure: Regional differences in patient treatment levels

\(^{1}\) Wijsenbeek M. ERS Paris 2018; 46: OA263
CHOICE OF ANTIFIBROTIC THERAPY IN IPF

Rationale
To examine whether choice of antifibrotic therapy in IPF is patient or physician-led, and the reasons behind these decisions

Results
• Out of 51 patients who were started on antifibrotic therapy, 27 were prescribed nintedanib and 24 pirfenidone
Where physicians led the selection of antifibrotic therapy (n=22)
• Pirfenidone was selected in 13 cases, and nintedanib in 9
Choices were primarily based upon relative contraindications
Where patients drove the selection of antifibrotic therapy (n=29):
• Pirfenidone was chosen in 11 cases over nintedanib to avoid diarrhoea
• Nintedanib was chosen over pirfenidone in 18 cases due to reluctance to apply sunscreen (44.5%), the pill burden (27.8%), constipation (16.7%), photosensitivity (5.5%), and indigestion (5.5%)
There were no differences in discontinuation rates in cases of patient- and physician-led therapy choices

Conclusion
In their discussions with physicians:
• 56.9% of the patients (39 cases out of 51) made the decision regarding which antifibrotic therapy they want to use
• Patients selected specific therapies mainly to avoid undesired side effects, whereas physician-led choice for antifibrotic therapy was based upon contraindications

INPULSIS®-ON: LONG-TERM NINTEDANIB TREATMENT IN IPF

Rationale
Long-term safety and efficacy of nintedanib treatment was assessed in patients with IPF who completed one of the INPULSIS® trials

Methods
• From July 2012 to September 2017, 734 patients from the INPULSIS® trials were enrolled in the INPULSIS®-ON trial with permanent or temporary dose reductions from 150 mg to 100 mg bid nintedanib

Results
• The rates of decline in FVC were -145.0 (7.4) and -119.7 (9.2) mL/year in patients who continued and initiated nintedanib, respectively (Figure)
• Incidence rate of acute exacerbations in all patients was similar to that of nintedanib-treated patients in INPULSIS®
• Most common adverse event was diarrhoea, and discontinuations of nintedanib occurred in 4.7 % and 10.2% of patients who continued and initiated nintedanib, respectively

Conclusion
The final data from INPULSIS®-ON suggest that the effect of nintedanib on slowing disease progression in patients with IPF persists beyond 4 years. Continued treatment with nintedanib for up to 68 months had an acceptable safety and tolerability profile, with no new signals identified


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**INSTAGE® TRIAL: NINTEDANIB WITH ADD-ON SILDENAFIL**

| Aim / rationale | • To evaluate if combining nintedanib and sildenafil is more beneficial than nintedanib alone in 247 patients with IPF and severely impaired gas exchange, over the course of 24 weeks  
• Patients were randomised 1:1 to receive nintedanib plus placebo (N) or nintedanib plus sildenafil (N+S) |
|---|---|
| Primary endpoint | • No significant difference in adjusted mean change from baseline in SGRQ score at week 12 between nintedanib plus sildenafil vs nintedanib alone  
  -0.77 and -1.28 in patients who received N alone and N+S, respectively (p=0.72, 95% CI -3.33, 2.30) |
| Secondary endpoints | • No significant difference in adjusted mean change from baseline in SGRQ score at week 24 between N+S vs N alone  
  2.42 and 0.23 in patients who received N alone and N+S, respectively (p=0.18, 95% CI -5.40, 1.02)  
• Decline in FVC was numerically lower in patients treated with N+S vs N alone  
  Difference 37.4 mL (p=0.18, 95% CI -17.4, 92.3)  
• N+S was associated with a reduction in risk of an absolute FVC decline ≥5% predicted or death vs N alone  
  HR: 0.56 (p=0.003) |
| Safety | • Nintedanib plus sildenafil had a manageable safety and tolerability profile  
• The safety and efficacy of nintedanib alone was consistent with that observed in patients with IPF and milder lung function impairment |

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1. Kolb M. ERS Paris 2018; 82: OA546
[Epub ahead of print]

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**DLCO**: Diffusing capacity of the lungs for carbon monoxide (% predicted)  
**FVC**: Forced vital capacity; **SGRQ**: St. George’s Respiratory Questionnaire
NEW DEVELOPMENTS IN ANTIFIBROTICS: PIRFENIDONE

**Phase 1 trial of aerosolised pirfenidone**

**Rationale:** Systemic toxicity of oral pirfenidone limits drug dosing. Aerosol administration with a nebuliser increases lung concentration and potential efficacy while minimising systemic exposure and AEs.

**Phase 1 dose safety and PK results:**

- Aerosolised pirfenidone was well tolerated (transient / mild AEs and one case of dizziness reported).
- 100 mg nebuliser dose had <10 fold systemic exposure of a 801 mg oral dose.
- The area under the curve (μg hr/ml) for epithelial lining fluid was 180% the oral dose.

**Pirfenidone in the treatment of lung fibrosis in asbestos exposed individuals**

**Rationale:** In some patients with definitive or possible UIP-pattern exposed to asbestos, disease course resembles that of IPF, implicating “IPF with asbestos exposure”, rather than asbestos associated progressive lung fibrosis. As pirfenidone has anti-inflammatory and anti-fibrotic effects, it was used to treat 4 such patients.

**Retrospective analysis of efficacy:**

- FVC had declined in all 4 patients in the 6 months prior to treatment.
- Following 3-6 months of treatment, FVC either stabilised or improved.
- Pirfenidone was well tolerated in these patients.
- As no treatment has been approved for this disease, RCTs are needed.

1. Montgomery A. ERS Paris 2018; 46: OA266

PK: Pharmacokinetics; FVC: Forced vital capacity

AEs: Adverse events; UIP: Usual interstitial pneumonia; RCT: Randomised controlled trial
CLINICAL TRIALS INVESTIGATING POSSIBLE FUTURE IPF TREATMENTS

Rationale: The mAb against connective tissue growth factor pamrevlumab showed favourable safety, efficacy and QoL (SGRQ) results in PRAISE, in comparison to placebo. 22 patients receiving pamrevlumab, and 20 patients on placebo completed the USCD-SOBQ to monitor progression of dyspnoea.

Phase 2 USCD-SOBQ results:
• At week 48, there was a statistically significant absolute difference between the total score change from baseline of -13.32 (SE 6.46) in favour of pamrevlumab (p<0.05)

Rationale: CHIT1 has been implicated in the pathology of multiple inflammatory and fibrotic diseases (IPF, COPD, sarcoidosis), and is significantly upregulated in IPF lung.

Preclinical data, and phase 1a safety and PK results:
• Mouse studies confirmed OATD-01 inhibition of chitinolytic activity
• In the bleomycin-induced mouse model of pulmonary fibrosis, OATD-01 demonstrated roughly equivalent antifibrotic activity to pirfenidone and nintedanib
• OATD-01 has successfully completed phase 1a clinical studies in healthy volunteers, with no sAEs or withdrawals due to AEs reported, and the PK profile indicates that inhibition of chitinolytic activity in plasma is achievable with once-a-day oral dosing

USCD-SOBQ results from the PRAISE phase 2 study of pamrevlumab in IPF

Phase 1b trial of the small molecule inhibitor of CHIT1, OATD-01

2. Dynek B. ERS Paris; 550: OA5361
3. Pikul S. ERS Paris 2018; 535: PAS228

mAb: Monoclonal antibody; SGRQ: St. George’s Respiratory Questionnaire; UCSD-SOBQ: University of California San Diego – Shortness of Breath Questionnaire; (s)AE: (Serious) adverse event; PK: Pharmacokinetics; CHIT1: Chitinase 1; COPD: Chronic obstructive pulmonary disease; OATD-01: A selective chitinase inhibitor

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EXPERT COMMENTS

Differing management strategies of AE-IPF between continents underline the need for consensus and evidence-based guidance

Patient-led choice is observed in majority of cases. Their choice of antifibrotic is based on the side-effects of the drug

Patients with advanced IPF, with DLCO<35%, may benefit from nintedanib treatment. However, the combination with sildenafil doesn’t demonstrate additional benefit

Nintedanib treatment of patients with advanced IPF in the INSTAGE® trial showed a decline in FVC similar to that observed in patients less advanced IPF from the INPULSIS® trials

New drugs targeting different pathways than pirfenidone and nintedanib show promising results in clinical trials

Exploring safety and beneficial effects of the current anti-fibrotic drugs in IPF for other progressive and non-IPF ILDs represents a new hope for these patients
Real world data: registries

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).
**European IPF registry** (n=525 IPF patients)¹
- Between 2014-2016: cryobiopsy became the most commonly used bioptic procedure. While standard lung biopsy continued to be used in this period, forceps biopsy usage reduced to 0
- Significantly increased survival (p=0.001) was seen for patients treated with antifibrotic therapy, compared to those not treated with antifibrotics (taking into consideration different approval times for antifibrotics, in this registry it is noted that 43% of patients received pirfenidone and 8.7% received nintedanib)

**Outcome differences from the EXCITING™ registry**²
- Multi-centre German ILD registry with 601 patients: 151 of these had IPF
- Baseline physiology of IPF patients: 76% male, av. 74 y/o, (ex)-smokers 58% with FVC of 69%, GAP-ILD 0-1 0.5%, 2-3 16%, 4-5 44%, 6-8 40%
- Comorbidities in IPF patients: 25% GERD, 15% Emphysema, 12% PH
- Time to death was 101 months for IPF vs 229 months for non-IPF ILDs (p<0.001)
- PFS (time from diagnosis to >10% decrease in FVC, hospitalisation due to respiratory-related event, or death) was 62 months for IPF vs 113 months for non IPF (p=0.006)
- IPF showed more rapid progression and worse mortality compared to other ILDs

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¹ Guenther A, et al. ERS Paris 2018; 252: PA2198
² Kreuter M, et al. ERS Paris 2018; 252: PA2197

GERD: Gastroesophageal Reflux Disease; PH: Pulmonary hypertension
FVC: Forced vital capacity; GAP: Gender, age, physiology
EMPIRE (EUROPEAN MULTIPARTNER IPF) REGISTRY: BASELINE CHARACTERISTICS AND OUTCOMES

Aim
Use the EMPIRE registry to analyse baseline differences in 2048 patients (626 F, 1422 M) from 8 countries in Central and Eastern Europe; profile access to pharmacological treatments and outcomes.

Patient characteristics
- Significant differences in age, smoking history, and FVC (%) pred. between EMPIRE countries.
- Rate of typical UIP diagnosis from HRCT ranged from 96.4% (Turkey) to 57.1% (Serbia) (with an average of 75.4%).
- Median FVC was 76.2%, and median transfer factor was 47%.
- Survival was significantly better in females ($p<0.001$), patients with better initial FVC and TLCO ($p<0.001$), non-smokers ($p=0.021$) and patients with atypical HRCT ($p=0.011$).

Conclusion
The EMPIRE registry shows IPF in real world, demonstrating the effectiveness of antifibrotics across the diversity of IPF compared to the randomized clinical trials. The data showed better outcome in patients on antifibrotic therapy, in females, and in those with better initial FVC and TLCO, with atypical HRCT pattern.

Antifibrotic treatment
- Pirfenidone ($p=0.033$) and nintedanib ($p<0.001$) treatment showed survival advantage compared to any other or no therapy (Figure).

Figure: Long-term survival according to treatment

HRCT: High-resolution computed tomography
TLCO: Carbon monoxide transfer factor
FVC: Forced vital capacity
UIP: Usual interstitial pneumonia

EXPERT COMMENTS

There were several examples of successful international collaborations, resulting in the availability of international, large scale datasets of real world data.

International registries allow us to see in real-life, how the patient characteristics, diagnostic procedures, and access to treatment, differ by region – and confirm clinical trial data.

Extensive variation in patient characteristics at baseline and access to antifibrotics were seen. That significant survival advantage with antifibrotic treatment in the European IPF registry was seen underlines the importance of making treatment widely available.

Going forwards, the standardisation of inclusion criteria and parameters registries would make comparison of datasets more straightforward.
Non-IPF ILDs
Shortened telomeres are detectable in diverse fibrotic ILDs

- Significantly shortened telomere length was detected in CPFE (n=10), CTD-ILD (n=7) and in both IPF patients with stable disease (n=24) and those who had displayed exacerbations (18), vs 25 healthy controls (p<0.001)
- No significant differences were detected in telomere lengths between ILD groups
- Acute exacerbation of IPF was not found to be associated with a further shortening of telomere length

Prognostic impact of comorbidities for cHP patients

- 211 cHP patients with on average 3 comorbidities were followed up for 32 months
- Deceased patients had more comorbidities than survivors (p=0.005)
- PH, diastolic dysfunction and diabetes were significantly associated with impaired survival (all p<0.05)

Identification of genotypic effects upon disease course in HP-ILD patients with dominant lung fibrosis

- A prospective observational study genotyped and followed progression (reduction of FVC >10% / drop of DLCO >15% / acute exacerbations / death) in 19 HP patients with dominant fibrotic lung involvement over 18 months
- Three gene polymorphisms within the TOLLIP gene were identified as significantly modifying the risk of progression, with both protective and risk alleles identified
- Confirmation of these results could allow the identification of patients at increased risk of progression, who would be prioritised for lung transplantation

<table>
<thead>
<tr>
<th>HP: Hypersensitivity pneumonitis</th>
<th>CPFE: Combined pulmonary fibrosis and emphysema</th>
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<tbody>
<tr>
<td>cHP: Chronic hypersensitivity pneumonitis</td>
<td>CVD: Collagen vascular disease (aka connective tissue disease(CTD))</td>
</tr>
<tr>
<td>PH: Pulmonary hypertension</td>
<td>CTD-ILD: CVD-associated-ILD</td>
</tr>
<tr>
<td>DLCO: Diffusing capacity of the lungs for carbon monoxide (% predicted)</td>
<td>TOLLIP: Toll-interacting protein</td>
</tr>
<tr>
<td>FVC: Forced vital capacity</td>
<td></td>
</tr>
</tbody>
</table>

1. Šterclová M, et al. ERS Paris 2018; 388: PA3665
**DIAGNOSIS OF HYPERSENSITIVITY PNEUMONITIS**

**Hypersensitivity pneumonitis (HP)**

No consensus in diagnosis of HP¹

Identification of a causative antigen and antigen source is crucial for diagnosis: criteria and algorithms to separate acute from chronic clinical HP²

- Evaluating the environment and antigen exposure, clinical symptoms, specific IgG antibodies, BAL, HRCT and histopathology patterns¹

Pulmonary function tests: change in FVC and survival in chronic HP³

**Radiology predictors for HP¹,⁴**

- Extent of MA-AT > reticulation (OR 6.20; p<0.0001)
- Diffuse axial disease distribution (OR 2.33; p=0.004)
- Model-based score >2 points (1 point for axial distribution, 2 points for MA-AT > reticulation) has:
  - Specificity 90% and PPV 74% in the derivation cohort
  - Specificity 96% and PPV 44% in the validation cohort

**Conclusion¹**

- Antigen avoidance is crucial in management of HP
- Corticosteroids and cytotoxic drugs can be used in inflammation while the use of antifibrotic agents needs further studies¹,²

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1. Koschel D, ERS Paris 2018; 490: OA4902

MA-AT: Mosaic attenuation or air trapping; PPV: Positive predictive value
FVC: Forced vital capacity; BAL: Bronchoalveolar lavage
HRCT: High-resolution computed tomography; Ig: Immunoglobulin

ERS Highlights 2018 Slide Kit. Sponsored by Boehringer Ingelheim; not reviewed or approved by ERS
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).
## CONNECTIVE TISSUE DISEASE-ASSOCIATED INTERSTITIAL LUNG DISEASE (CTD-ILD)

###Pathophysiology
- Shared genetic susceptibility in IPF and rheumatoid arthritis-associated ILD (RA-ILD)
- ILD may precede CTD (Japanese retrospective series)

###Diagnosis: emphasis on MDD and international collaboration
- Confident CTD-ILD diagnosis should include a multidisciplinary discussion (MDD) including rheumatologists and internal medicine
- International collaborations are essential for confident diagnosis: valuable results stem from 2016 study of 70 patients between 7 different MDD teams from 7 countries
- Rheumatological evaluation is crucial for ILD diagnosis
  - 40% had RA-ILD and 21% of CTD-ILD patients were correctly diagnosed only after rheumatology assessment

###Emerging therapeutic strategies
- Targeted immunotherapy: rituximab (α-CD-20) in NCT01862926, abatacept (α-CTLA-4), TNF inhibitors
- Autoimmunity suppressants: cyclophosphamide
- Ongoing trials with anti-fibrotics:
  - pirfenidone for RA-ILD in TRAIL-1 (NCT02808871), nintedanib in progressive fibrosis (including CTD) in INBUILD (NCT02999178), and nintedanib in SSc-ILD in SENSCIS (NCT02597933)
- Combination therapies: targeted immunotherapy and anti-fibrotics

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TREATING LUNG INVOLVEMENT IN SYSTEMIC SCLEROSIS-ILD (SSC-ILD)¹

**Involvement of ILD in SSc¹**

- Most SSc patients have ILD at autopsy (NSIP 78%, UIP 15%)
- ILD progression risk is highest in the first 2-4 years, and ILD is the commonest cause of death in SSc

**SSc-ILD treatment options: available and in the pipeline**

- A treatment algorithm for SSc-ILD has been published with three lines of treatment (MMF, i.v. CYC, and rituximab, respectively)²
- Several clinical trials for the treatment of SSc-ILD are running, including phase 3 trials for nintedanib (NCT02597933)³ and tadalafil (NCT01553981)⁴

**Mesenchymal stromal cells (MSC) in the treatment of SSc³**

**Rationale:** Ablate immune and haematopoietic system, replace with transplanted, autologous MSCs, “reset” auto-aggressive immune system. MSCs home to inflamed tissue and have an anti-inflammatory / anti-proliferative effect

**Evidence:** Two randomised phase 3 trials in SSc comparing autologous HSCT and i.v. pulse cyclophosphamide found a significant survival advantage for HSCT, although both trials saw treatment-related mortality⁵,⁶

**EULAR SSc recommendation for use:** HSCT has a strong recommendation for use in selected patients with rapidly progressive SSc at risk of organ failure⁷

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1. Tyndall A. ERS Paris 2018; 523: OA5143
3. ClinicalTrials.gov Identifier: NCT02597933
4. ClinicalTrials.gov Identifier: NCT01553981

NSIP: Nonspecific interstitial pneumonia
CYC: Cyclophosphamide; MMF: Mycophenolate mofetil
HSCT: Haematopoietic stem cell transplantation
The Importance of ILA Patterns in a Lung Cancer Screening Protocol

3559 smokers / former smokers (≥40YO, >10PY, asymptomatic for lung cancer) were screened for ILAs and emphysema with low dose CT, evaluated with PFT, and monitored for lung cancer development.

At baseline, ILA/ILD patterns were associated with:
- Decreased pulmonary function (FVC % pred. 107.1 vs 103.8, \(p=0.018\); TLC % pred. 96.45% vs 101.1%, \(p=0.001\); DLCO 74.2% vs 84.0%, \(p<0.001\))
- Increased incidence of emphysema (62.5% vs 32.5%, \(p<0.001\))

Over the screening period, ILA increased risk for lung cancer 5 fold, while in emphysema and emphysema / ILD, the risk increased to around 20 fold.

Conclusion

Findings of ILA in CT may identify patients at a higher risk for lung cancer. Further studies are needed to characterise the risk for progression of ILA to ILD, and the development of cancer in ILA/ILD patients.

1. As part of the P-IELCAP cancer screening programme in Pamplona

FVC: Forced vital capacity; DLCO: Diffusing capacity of the lungs for carbon monoxide
TLC: Total lung capacity; ILA: Interstitial lung abnormalities
ILD: Interstitial lung disease; PFT: Pulmonary function tests
PY: Pack years; YO: Years old
In order to ameliorate the future studies that will be conducted and allow for more advantageous outcomes, an international consensus on diagnostic criteria for HP should be reached.

Standardised treatment algorithms for SSc-ILD treatment have been published to improve the patient management.

Autologous MSC bone marrow transplantation has demonstrated improvements in disease survival in rapidly progressive SSc, although the number of patients is limited and severe side effects have been observed.

ILD is the main cause of death in SSc. The role of anti-fibrotic therapy in patients with collagen vascular disease-related pulmonary fibrosis in SSc is currently being investigated.
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).
SUMMARY OF PRODUCT CHARACTERISTICS

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