ILD highlights from the ATS 2018 congress

May 18 – May 23 / San Diego, CA

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Objective and focus of this report

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OBJECTIVE AND FOCUS

ATS congress 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 ATS 2018 congress.

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 oral and poster sessions at the ATS 2018 are summarized 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 ATS 2018 in San Diego, CA.

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 since 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**
  - Successful phase II clinical drug trials
  - WRAP-IPF and anti-reflux treatment in patients with IPF
  - Single-cell sequencing as a tool in IPF research
  - Mitochondria and IPF pathogenesis
  - Interstitial lung abnormalities (ILA): meaning and management

- **New insights into ILD diagnosis and management**
  - New clinical guidelines for IPF diagnosis
  - Genetic testing in patients with idiopathic interstitial pneumonia (IIP)
  - Cardiovascular risk in patients with IPF
  - Health-related quality of life in patients with IPF
  - Lung transplantation in patients with IPF

- **Non-IPF ILDs**
  - Lymphangioleiomyomatosis (LAM)
  - Hypersensitivity pneumonitis (HP) & IPF outcome predictors: radiologic phenotype vs clinical diagnosis
  - Nintedanib attenuates histopathology of interstitial pneumonia in a transgenic mouse model of arthritis
  - New insights on systemic sclerosis (SSc) related to interstitial lung disease (ILD)

- **New data on antifibrotic treatment and results from new clinical trials**
  - New data on nintedanib and pirfenidone
  - Data on new anti-fibrotic drugs in IPF
  - Insights from pre-clinical studies

- **IPF pathobiology**
  - Novel immunological aspects of lung fibrosis
  - Novel genetics aspects
  - Pathobiology of fibrosis: new targets

- **Appendix and acknowledgements**
  - Abbreviations
  - Prescribing information
  - Acknowledgements

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Breakthroughs: the experts’ picks

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SUCCESSFUL PHASE II CLINICAL TRIALS

Background: Since the approval of the anti-fibrotic drugs nintedanib and pirfenidone for IPF, the disease remains incurable to this day\(^1\). In the light of the progressive nature and poor prognosis of IPF\(^2\), development of new treatments is of particular importance.

At the American Thoracic Society (ATS) congress 2018, promising results were presented for many ongoing clinical studies with new anti-fibrotic drugs, such as:

- Autotaxin inhibitor GLPG1690
- Recombinant human pentraxin-2
- PBI-4050
- mTor inhibitor sirolimus
- Anti-αvβ6 IgG1 monoclonal antibody BG00011
- MK2 inhibitor MMI-0100
- AT2-receptor antagonist C21

Besides results from clinical trials, challenges in the design of clinical trials in IPF were also discussed at the congress, e.g.:

- Determining endpoints that are meaningful, feasible and reliable in IPF\(^3\)
- Should new drugs be tested head-to-head with the standard of care, or in combination with established anti-fibrotic drugs?\(^3\)
- Should patients with non-IPF progressive fibrotic lung diseases be included in clinical trials?\(^3\)

To find out more about these exciting developments, follow the link to the "New data on antifibrotic treatment" chapter of this report.

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3. Richeldi L, ATS San Diego 2018; D83: Feels, function, survives: Are clinically meaning endpoints feasible in IPF clinical trials?
WRAP-IPF AND ANTI-REFLUX TREATMENT IN PATIENTS WITH IPF

Background: Incidence of GERD (gastroesophageal reflux disease) is higher in patients with IPF compared with the general population and significantly affects symptoms and survival. Current treatment guidelines give a conditional recommendation for AAT (antacid treatment) in patients with IPF, however increasing evidence suggests that AAT may not be effective and have adverse effects on patients with IPF.

At the ATS 2018, the results of the phase II trial Weighing Risks and benefits of laparoscopic Anti-reflux surgery in Patients with IPF (WRAP-IPF) was presented. The trial failed to meet its primary endpoint (defined as change in FVC over 48 weeks).

Additionally, another presentation at the ATS 2018 concluded that AAT significantly increases risk of death or transplant at one year and at 5 years post-IPF diagnosis in patients who received AAT in comparison to those who did not.

These results further underline that:

- Neither the efficacy nor the safety of AAT as a treatment of GERD in patients with IPF can be supposed at this point.
- Further evaluation of anti-reflux therapy in patients with IPF in prospective studies is necessary.

For further information, follow this link to “New insights into ILD diagnosis and management”

3. Umeda T, et al. ATS San Diego 2018; B103: PA4256

WRAP-IPF: Weighing risks and benefits of laparoscopic anti-reflux surgery in patients with IPF
GERD: Gastroesophageal reflux disease
AAT: Antacid treatment
SINGLE-CELL SEQUENCING AS A TOOL IN IPF RESEARCH

Background: The arrival of next-generation sequencing (NGS) technology has opened many new doors in genetic research. Single-cell sequencing allows for genomic and transcriptomic studies on a cellular level. Several examples of cutting-edge research that apply this method to IPF pathobiology research were presented at the ATS 2018, two of which are summarized below.

Valenzi et al.¹
- Single-cell sequencing was used to confirm the origin cells of IPF biomarkers, such as MMP7, CCL18, and MUC1 in lung tissue samples from IPF patients.
- They found that those biomarkers, associated with progressive IPF, are expressed in AT2 cells, macrophages, and fibroblasts.

Reyfman et al.²
- Combined single-cell sequencing and RNA-sequencing was used to identify and directly compare lung cell populations from healthy donors and IPF patients.
- 13 distinct cell populations were identified.
- Cell populations were enriched for genes previously associated with pulmonary fibrosis.

For further information on NGS applications in IPF, follow this link to the “New insights into ILD diagnosis and management” chapter of this report.

¹ Valenzi E, et al. ATS San Diego 2018; B107: PA4356
² Reyfman P, et al. ATS San Diego 2018; A71: PA 2286
Background: Recent advances in IPF research have highlighted the role that mitochondrial dysfunction plays in the development of lung fibrosis. Factors such as mitochondrial bio-energetics, uncoupling protein-2 and thyroid hormone function (DIO2) have dynamic roles in the preservation of lung function.

Rangarajan et al.¹

- A strong association between idiopathic fibrosis and aging was recently demonstrated
- Mitochondrial dysfunction may lead to senescence
- A high level of membrane mitochondrial uncoupling protein (UCP-2)¹ was detected in the fibroblasts of patients with progressive fibrosis. UCPs regulate mitochondrial membrane potential and play a potent role in thermogenesis and bio-energetics
- Human subjects with rapidly progressing IPF showed high expression of UCP-2, which promotes myofibroblast senescence
- These findings support the important role of mitochondrial function in lung health

Yu et al.²

- Levels of iodothyronine deiodinase 2 (DIO2), an enzyme that activates thyroid hormone (TH), were higher in lungs from patients with IPF and correlated with disease severity
- In DIO2-knockout mice (more prone to develop bleomycin-induced lung fibrosis), TH aerosol delivery reduced pulmonary fibrosis and increased survival
- TH delivery improved mitochondrial biogenesis & attenuated mitochondria-regulated apoptosis in alveolar epithelium
- Thyroid hormone has anti-fibrotic properties that may help to protect alveolar epithelial cells, representing a potential therapy for pulmonary fibrosis

To learn about research in this area that was presented at the ATS 2018, follow the link to the “Pathobiology of IFP” chapter of this report

INTERSTITIAL LUNG ABNORMALITIES (ILAS): MEANING AND MANAGEMENT

Background: ILAs are subclinical bilateral interstitial densities detected on CT (computed tomography). Fibrotic ILAs most likely represent a form of idiopathic interstitial pneumonia, and progression of this pattern was observed in 37% of affected patients\(^2\). ILAs are often incidentally detected on lung cancer screening CT (LCS-CT)\(^1\)

Diagnosis of ILAs on LCS-CTs\(^1\)
- In a retrospective cohort analysis, 781 LCS-CTs were screened by radiologists with ILD expertise, revealing 59 ILAs
- Review of medical records of ILA-positive patients showed that only 64% of ILAs were reported originally

Consequences for patient management\(^1\)
- 15% of patients with ILA had CT findings suggestive of undiagnosed IPF
- Of patients with reported ILA, 45.5% were referred to a pulmonologist during their original presentation; only 18.9% of those with non-reported ILA received a referral
- In total, only 20% of patients with ILA detected on CT by radiologists with ILD expertise received a pulmonologist referral

Education programs to improve radiologist reporting of ILAs and pulmonology referrals of ILA patients are needed\(^1\)

1. Oldman J, et al. ATS San Diego; A23: PA1098
New data on antifibrotic treatment and results from new clinical trials
New data on nintedanib and pirfenidone
**REDUCTION IN PREDICTED VERSUS OBSERVED MORTALITY IN IPF PATIENTS ON NINTEDANIB¹**

**Rationale**
Retrospective comparison of observed mortality in IPF patients treated with nintedanib or placebo (n=1228) in the TOMORROW® and INPULSIS® trials with predicted mortality based on GAP stage at baseline

**Results**
- Fewer deaths occurred in both the nintedanib and placebo groups than predicted, based on GAP stage at baseline (see figure)
- This may be because patients who enrolled in these trials had less severe disease than patients who participated in the studies used to develop the GAP index

**Conclusion**
Based on the difference between observed and predicted deaths, treatment with nintedanib was associated with a reduction in the risk of mortality over 1 year compared with placebo

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1. Ryerson CJ, et al. ATS San Diego 2018; A103; PA2534
EFFECT OF PIRFENIDONE ON SEASONAL VARIATION IN HOSPITALIZATION AND IMPACT OF EARLY PHYSIOLOGICAL RESPONSE

Effect of season on hospitalization in patients with IPF

**Rationale:** Post hoc pooled analysis of phase II ASCEND and CAPACITY trials (n=1247), assessing safety and efficacy of pirfenidone on seasonal variation in hospitalizations in patients with IPF

**Results:**
- Higher rate of respiratory hospitalizations or deaths from any cause were observed during fall and winter than during spring and summer in the placebo group
- Anti-fibrotic treatment with pirfenidone seems to blunt seasonal peaks in respiratory hospitalizations (see figure)

**Conclusion:** Pirfenidone attenuates seasonal variation of non-respiratory hospitalizations in patients with IPF

Prognostic impact of the early physiological response to pirfenidone

**Rationale:** Retrospective review from two Japanese centers of 96 consecutive patients with IPF, to investigate prognostic factors including early evaluation of treatment efficacy to pirfenidone

**Results:** Multivariate Cox proportional hazards regression analysis showed that low %FVC at baseline, use of supplemental oxygen and worsened disease status at early evaluation of treatment efficacy to pirfenidone were significantly associated with poor prognosis outcome

**Conclusion:** Early evaluation of therapeutic efficacy of pirfenidone may be important for survival outcome in IPF

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1. Ley B, et al. ATS San Diego 2018; C23: PA4526

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**Figure:** Respiratory hospitalizations by treatment and season for patients with IPF
INSIGHTS ON NINTEDANIB / PIRFENIDONE COMBINATION THERAPY

INJOURNEY™

- Single-arm, open-label study (n=89) to assess safety and tolerability of 24 weeks nintedanib and pirfenidone in combination in patients with IPF
- 69 patients completed treatment; no significant difference in treatment-completion rate was seen between subgroups
- Safety profiles of examined subgroups were similar to the overall population

Adverse events analysis of INJOURNEY™

- Further characterization of the gastrointestinal adverse events, confirmed that combination-therapy is associated with a manageable safety and tolerability profile, in line with the side-effects described for the individual drugs

Drug-drug interaction study (NCT0266877)

- The open-label, multi-center, two-group trial (n=37) found no relevant pharmacokinetic drug-drug interactions between nintedanib and pirfenidone when co-administered in patients with IPF

1. Flaherty K, et al. ATS San Diego 2018; B103: PA4252
2. Vancheri C, et al. ATS San Diego 2018; A42: PA1648
3. Richeldi L, et al. ATS San Diego 2018; D103: PA7470
### Switching from Pirfenidone to Nintedanib: Two Retrospective Studies

**Hogben et al.**

**Rationale**
Single-center analysis of IPF patients who had switched from pirfenidone to nintedanib (n=53), exploring indications for switching and subsequent effect on healthcare utilization (HCU)

**Results**
- 37 patients continued treatment with nintedanib; 9 discontinued it due to side effects, after switching from pirfenidone
- Evidence of reduction in HCU, defined as telephone or email communication initiated by patients seeking clinical advice on drug side effect management
- The most common indications for switching therapy were side effects and disease progression

**Conclusion**
Switching anti-fibrotic therapy was feasible and tolerable in the examined patient population

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**Ikeda et al.**

**Rationale**
30 patients with IPF, who switched to nintedanib after previously taking pirfenidone, were reviewed to evaluate safety, tolerability and efficacy of the treatment switch

**Results**
- High rates of early termination of nintedanib were observed in patients who switched from pirfenidone
- Anorexia and weight loss during previous pirfenidone therapy may be associated with higher early termination of nintedanib

**Conclusion**
Due to weight loss during prior pirfenidone treatment, early termination of nintedanib may be more likely in patients who previously received pirfenidone in comparison to pirfenidone-naive patients

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2. Ikeda S, et al. ATS San Diego 2018; B103: PA4257
### Side Effects of Antifibrotic Treatment: New Insights

| **Weight loss** | • A retrospective single-center study (n=52) of patients with IPF who were treated with antifibrotic therapy examined the effect of weight loss and possible correlations with clinical variables  
• Individuals with significant weight loss due to antifibrotic therapy show a trend towards decreased loss of lung function as measured by FVC, which may be due to improved chest wall mechanics in previously overweight individuals. |
| **Impact of gender and BMI** | • The effect of baseline gender and weight as predictors of tolerability of anti-fibrotic treatment was examined in a retrospective single-center study (n=152)  
• Female gender ($p=0.05$) and lower baseline BMI ($p=0.006$) predicted poor tolerance to antifibrotic therapy at one year in IPF patients² |
| **Elderly patients** | • Efficacy and safety of antifibrotic therapy in patients aged 75 years and older was tested in a retrospective single-center study (n=73)  
• Results suggest that elderly patients had lower tolerability to anti-fibrotic agents, however patients who continued on antifibrotic therapy showed longer periods of progression-free survival³ |

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2. Weir NA, et al. ATS San Diego 2018; B103: PA4259  
Data on new anti-fibrotic drugs in IPF
PHASE II CLINICAL TRIAL OF AUTOTAXIN INHIBITOR GLPG1690 IN PATIENTS WITH IPF

Rationale
Randomized, placebo-controlled, double blind phase IIa clinical trial to assess primary outcomes safety and tolerability, pharmacokinetics, and pharmacodynamics of autotaxin inhibitor GLPG1690 (n=15) vs placebo (n=5) over 12 weeks in patients with IPF

Results
• Treatment-emergent adverse events were reported in similar proportions of patients in the placebo and treatment groups
• PK/PD properties were consistent with those reported in healthy individuals
• Although the study was not designed or powered to investigate efficacy, FVC and functional respiratory imaging results provided promising preliminary efficacy signals

Conclusion
Safety and PK/PD profiles of GLPG1690 are encouraging and support possible further clinical assessment of this drug

PHASE II CLINICAL TRIAL TESTS EFFICACY OF RECOMBINANT HUMAN PENTRAxin-2 IN PATIENTS WITH IPF TREATMENT

Rationale
Randomized, double-blind, placebo-controlled, multicenter trial to test the effect of 28 weeks of recombinant human pentraxin-2 (n=77) on change from baseline in mean FVC % predicted (primary endpoint) vs placebo (n=39) in patients with IPF

Results
- Significant effect of recombinant human pentraxin-2 vs placebo on the primary endpoint, least squares mean change in FVC % predicted, was observed (see figure)
- Patients in the treatment arm experienced stabilization in the observed mean change in the 6-minute walk test over time, whereas patients in the placebo arm experienced a decline
- No notable difference in adverse event rates between treatment groups

Conclusion
Human pentraxin-2 demonstrated efficacy in slowing lung function decline in patients with IPF in this phase II clinical trial

Figure: Effect of recombinant human pentraxin 2 vs placebo

RESULTS FROM ADDITIONAL PHASE II CLINICAL TRIALS OF NEW ANTI-FIBROTIC DRUGS

Effect of anti-fibrotic drug PBI-4050 on blood markers linked to IPF

- This phase II study (n=39) found that treatment with PBI-4050 leads to significant increase in expression of blood markers linked to IPF (IL-9, IL-7 and MIP-1β)
- Combination therapy of PBI-4050 and nintedanib leads to reduced CCL-18 levels (p=0.03)

Effect of PBI-4050 on IPF blood marker expression levels

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>IL-9</th>
<th>IL-7</th>
<th>MIP-1β</th>
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<tbody>
<tr>
<td>Fold change from baseline to week 12 (%)</td>
<td>1.35 (+35%)</td>
<td>1.14 (+14%)</td>
<td>1.11 (+11%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.04</td>
<td>0.04</td>
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mTor inhibitor sirolimus reduces rates of circulating fibrocytes in patients with IPF

- A phase II double-blind, placebo-controlled trial (n=30) with mTor inhibitor sirolimus found that the safety profile was acceptable
- Short-term treatment with sirolimus resulted in reduction of circulating fibrocyte concentrations in IPF

Anti-αvβ6 antibody (BG00011) decreases TGF-β signaling in IPF patients

- A phase IIa randomized, double-blind, placebo-controlled dose-escalation trial (n=41) determined that BG00011 treatment is safe and leads to a decrease in active TGF-β signalling in IPF patients

The encouraging results from phase II trials may warrant further investigation of these new drugs in the future

PHASE II CLINICAL TRIALS WITH NEGATIVE RESULTS

RIFF¹

- Phase II study on the efficacy of humanized monoclonal antibody binding IL-13, lebrikizumab, showed no benefit on lung function or mortality of 250 mg subcutaneous lebrikizumab given every month over 52 weeks in patients with IPF
- Results suggest that targeting the IL-13 pathway alone may not be sufficient for achieving a therapeutic benefit in patients with IPF

WRAP-IPF²

- The phase II trial Weighing Risks and benefits of laparoscopic Anti-reflux surgery in Patients with IPF did not meet its primary endpoint (change in FVC over 48 weeks)
- However, treatment was associated with fewer acute exacerbations and deaths as well as fewer patients with 10% FVC decline

ESTAIR³

- Phase II trial to test monoclonal antibody binding to IL-13 and IL-4, SAR156597
- No difference between treatment and placebo group in lung function, death or all-cause mortality
- Safety profile of SAR156597 was also unfavorable

1. Swigris JJ, et al. ATS San Diego 2018; D12: OA6167
RESULTS FROM PHASE I CLINICAL TRIALS OF POSSIBLE NEW MOLECULES FOR IPF TREATMENT

Novel MAPKAP kinase II inhibitor MMI-0100 demonstrates favorable safety and pharmacokinetic profile¹

• The safety, tolerability and pharmacokinetic (PK) profile of MMI-0100 was examined in three double-blind, randomized and placebo-controlled phase I trials (n=106)
• MMI-0100 had a safety profile similar to placebo and little to no measurable plasma concentrations of the compound were detected, confirming rapid cellular uptake of the molecule

Angiotensin AT2-receptor antagonist C21 is safe in humans and shows pharmacodynamic effects²

• Safety, tolerability and pharmacokinetics of C21 were tested in two randomized, double-blind phase I trials (n=18)
• C21 was well tolerated at a daily dose up to 100 mg and in overweight subjects, C21 administration resulted in changes in the pattern of lipoproteins, strongly suggesting a pharmacodynamic effect on lipid metabolism

Promising safety and pharmacokinetics/dynamics results from phase I trials may encourage investigation of these new drugs in further clinical studies

¹ Luber A, et al. ATS San Diego 2018; D103: PA7488
² Steckelings UM, et al. ATS San Diego 2018; A42: PA1629
INSIGHTS FROM PRE-CLINICAL STUDIES OF NEW PROMISING MOLECULES FOR ANTI-FIBROTIC TREATMENT

Histone deacetylase (HDAC)-inhibitor panobinostat induces apoptosis in IPF fibroblasts

Rationale
The effects of pirfenidone and the pan-HDAC-inhibitor panobinostat on survival, fibrotic activity and proliferation of primary IPF fibroblasts were tested in vitro.

Results
• Treatment of IPF fibroblasts with pirfenidone or panobinostat resulted in significant downregulation of various extracellular matrix-associated genes.
• Both drugs decreased protein level of phosphorylated (p)-STAT3, a transcription factor mediating pro-fibrotic responses.
• Panobinostat, but not pirfenidone treatment induced ER-stress and apoptosis in IPF-fibroblasts.

Conclusion
Pirfenidone reduces profibrotic signalling through weak epigenetic alterations in IPF-fibroblasts, thereby permitting their survival; in contrast, panobinostat reduces profibrotic expression while inducing cell death in IPF-fibroblasts.

siRNA directed against HSP47 leads to resolution of lung fibrosis in rat model

Rationale
A lipid nanoparticle encapsulating siRNA directed against HSP47 (ND-L02-s0201) was tested for efficacy in treatment of lung fibrosis in a bleomycin-induced (BLM) rat model.

Results
• This study demonstrated dose-dependent and statistically significant reduction in lung weight, collagen deposition and fibrosis scores following ND-L02-s0201 treatment of rats with pulmonary fibrosis.
• Statistically significant improvement of lung function was determined by running endurance capacity.
• Bleomycin-induced lung fibrosis led to a >5-fold increase in myofibroblasts and ND-L02-s0201 treatment reduced the myofibroblasts to sham levels.

Conclusion
The above results suggest that ND-L02-s0201 shows therapeutic effect in resolving pulmonary fibrosis in a bleomycin-induced rat model.

1. Korfei M, et al. ATS San Diego; C71: PA5751
2. Liu L, et al. ATS San Diego; A73: PA2352
**EXPERT COMMENTS**

Tolerability of nintedanib and pirfenidone seems to depend on clinical variables like gender, age and BMI. Switching from one to the other antifibrotic drug seems to be effective and safe.

A plethora of new molecules for IPF are under investigations in Phase II and Phase I clinical trials: for pamrevlumab, PRM 151 and GPLG 1890 confirmatory phase III trials are going to be started.

A number of studies presented at ATS 2018 continue to document the important role of antifibrotics in improving the outcomes of IPF patients and point to the potential role of these treatments in non-IPF progressive fibrotic diseases.

The influence of gastroesophageal reflux on IPF disease course remains debated. The phase II trial WRAP to determine the impact of laparoscopic anti-reflux surgery on change in FVC over 48 weeks did not meet its primary endpoint.
New insights into ILD diagnosis and management
NEW CLINICAL GUIDELINES FOR IPF DIAGNOSIS

How to make a quick, safe and reliable diagnosis of IPF, is an area of ongoing research. An update on the clinical guidelines for IPF diagnosis was presented at the ATS 2018.

Main updates included:

1. A weak recommendation was given for bronchoalveolar lavage (BAL). It has been included in the diagnostic algorithm, as a useful tool to exclude ILDs other than IPF.
2. No recommendation has been made for transbronchial cryobiopsy, due to the paucity of evidence. However, cryobiopsy may be performed in experienced centers upon indication made by multidisciplinary discussion (MDD).
3. The use of MDD was suggested for diagnostic decision-making.
4. No recommendation was made for measuring serum markers for the purpose of distinguishing IPF from other ILDs.

The version of the updates presented at the ATS 2018 is preliminary. The definitive version of the IPF diagnosis guideline 2018 is expected to be published later this year.

1. Raghu G. ATS San Diego 2018; C93: Diagnosis of Idiopathic Pulmonary Fibrosis
GENETIC TESTING IN PATIENTS WITH IDIOPATHIC INTERSTITIAL PNEUMONIA (IIP)

- In recent years, genomic investigations have identified several genetic variants associated with susceptibility to ILD, which may also have prognostic value concerning disease outcomes.
- In light of these developments, the question whether genetic screening should be routinely performed in the diagnosis and management of IIP was the topic of an expert discussion session at this year’s ATS.
- This slide summarizes the main points that the speakers put forward concerning this issue.

**PRO**
Routine genetic testing in IIP faces several hurdles:
- Molecular medicine/genetic testing is under-represented in diagnostic guidelines.
- Genetic medicine is a relatively young field and many clinicians are not familiar with its application and potential benefits.
- Lack of infrastructure to bring genetic testing from the laboratory to the bedside.

Despite these challenges, genetic evaluation holds the hope for a more personalized approach of diagnosis and treatment of IIP patients in the future.

**CONTRA**
- Genetic testing cannot be justified in the diagnosis and management of IIP at this point.
- However, genetic screening should be used in all phase III IIP/IPF clinical trials to help assess drug efficacy and toxicity in individual patients.

Overall, discussion suggests that genetic testing is a promising tool to diagnose and treat ILD, but not yet ready for routine use in clinical practice.

2. Armanios M. ATS San Diego 2018; B2: Genetic Screening Should Not be Routinely Done for Patients with Interstitial Pneumonia of Unknown Etiology
3. Schwartz D. ATS San Diego 2018; B2: Genetic Screening Should be Routinely Done for Patients with Interstitial Pneumonia of Unknown Etiology.
**LUNG FIBROSIS MEASURED BY QUANTITATIVE HIGH-RESOLUTION COMPUTED TOMOGRAPHY (QHRCT) IN IPF PATIENTS TREATED WITH PAMREVLUMAB\(^1\)**

<table>
<thead>
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<th>Rationale</th>
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<tr>
<td>• PRAISE is a multi-national, double-blind, placebo-controlled phase II trial (n=103) that tests the efficacy of pamrevlumab, a monoclonal antibody binding connective tissue growth factor (CTGF), in patients with IPF</td>
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<tr>
<td>• Change in pulmonary fibrosis was assessed using qHRCT at baseline, and at weeks 24 and 48</td>
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<tr>
<th>Results</th>
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<td>• Significant change from baseline to week 48 of 75.7 mL in the treatment group compared to 159.1 mL in the placebo group (relative difference, -50.3% ((p=0.038)))</td>
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<tr>
<td>• A correlation between FVC % predicted and qHRCT outcomes was confirmed at 24 and at 48 weeks</td>
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<td>• Some patients on pamrevlumab experienced reversal/stabilization of fibrosis, seen at 24 and 48 weeks</td>
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<table>
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<th>Conclusion</th>
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<tr>
<td>• IPF patients treated with pamrevlumab showed less lung fibrosis progression in comparison to placebo</td>
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1. Gorina E, et al. ATS San Diego 2018; A73: A7688

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CARDIOVASCULAR RISK IN PATIENTS WITH IPF

Rationale
Retrospective analysis of 178 IPF patients at time of diagnosis within a tertiary care ILD unit in the UK applied the QRISK-2 scoring system to predict cardiovascular risk

Results
- The mean QRISK-2 for the cohort was 25.4% (SD ±11.0) and the relative risk for the population was 1.4
- In total, 65.7% of the entire cohort had a high (>20%) QRISK-2 score. A score of ≥10% indicates need for further intervention to reduce risk whereas ≥20% is defined as high risk

Conclusion
The results suggest that screening for CV risk at IPF diagnosis should be mandatory to allow appropriate cardiovascular intervention

Figure: QRISK-2

RA: Rheumatoid arthritis; FHx IHD: Family history of ischemic heart disease (angina or heart attack); CKD 4 or 5: Chronic kidney disease stage 4 or 5; AF: Atrial fibrillation; HTN Rx: Anti-hypertensive treatment

1. Denneny EK, et al. ATS San Diego 2018; D103: PA7471
Rationale
A retrospective chart review of 246 patients with IPF from 2004-2016 at a single center to evaluate the effect of antacid therapy (PPI or H2-blocker) on transplant-free survival (TFS)

Results
• Kaplan-Meier TFS estimates at one year post-diagnosis for IPF patients on and off antacids at time of diagnosis were 78% (95% CI 69-87) vs 91% (CI 87-96), respectively
• Oxygen significantly increases risk of death or transplant at 5 years, but not 1 year post-diagnosis
• Pulmonary hypertension increases risk of death or transplant at 5 years post-diagnosis, but not at 1 year post-diagnosis
• Antacid treatment significantly increases risk of death or transplant at one year and at 5 years post-diagnosis

Cox proportional hazards ratio
Transplantation or death:
Time-varying antacid therapy vs no therapy

<table>
<thead>
<tr>
<th>Time frame</th>
<th>Coefficient</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>One year</td>
<td>Antacid therapy (vs none)</td>
<td>4.54 (1.93, 10.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Five years</td>
<td>Antacid therapy (vs none)</td>
<td>2.94 (1.93, 4.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>One year</td>
<td>Pulmonary hypertension</td>
<td>1.78 (0.79, 4.04)</td>
<td>0.165</td>
</tr>
<tr>
<td>Five years</td>
<td>Pulmonary hypertension</td>
<td>1.82 (1.16, 2.88)</td>
<td>0.01</td>
</tr>
<tr>
<td>One year</td>
<td>Oxygen use</td>
<td>1.21 (0.55, 2.68)</td>
<td>0.63</td>
</tr>
<tr>
<td>Five years</td>
<td>Oxygen use</td>
<td>1.61 (1.05, 2.48)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Conclusion
Safety and efficacy of antacid therapy in IPF patients requires further evaluation in prospective studies

1. Umeda T, et al. ATS San Diego 2018; B103: PA4256
HEALTH-RELATED QUALITY OF LIFE (HRQoL) IN PATIENTS WITH IPF: DATA FROM THREE STUDIES

**INPULSIS®¹**
- A retrospective analysis of the INPULSIS® trials (n=864) evaluated the impact of decline in lung function measured by FVC on HRQoL in patients with IPF
- Results suggest patients with greater declines in FVC % predicted at week 52 of the INPULSIS® trials had greater worsening in all measures of HRQoL

**PROOF registry²**
- Longitudinal development of HRQoL was analyzed in a real-world population of IPF patients treated with pirfenidone in the PROOF registry (n=233)
- HRQoL was examined at baseline and 1 year later
- No clinically meaningful changes in longitudinal cough severity or HRQoL were observed after 1 year in patients treated with pirfenidone in this group

**PRAISE³**
- In PRAISE, a phase II placebo-controlled trial of pamrevlumab in patients with IPF (n=100), HRQoL change from baseline at week 48 is a secondary efficacy endpoint
- Mean total score showed improvement from baseline at week 48 in the treatment group, while mean placebo scores worsened
- This implies that pamrevlumab may also lead to improvement of HRQoL in IPF patients

---

1. Kreuter M, et al. ATS San Diego 2018; A41: PA1604  
2. Wuyts W, et al. ATS San Diego 2018; B103: PA4271  
3. Gorina E, et al. ATS San Diego 2018; B103: PA4254
## Lung Transplantation in Patients with IPF

### Telomere-related gene mutations\(^1\)
- A retrospective cohort study of 262 patients with pulmonary fibrosis who underwent lung transplantation and whole-exome sequencing showed that those with deleterious mutations in telomere-related genes TERT, RTEL1, or PARN have worse post-transplant survival and higher rates of chronic lung allograft dysfunction compared to patients without mutations.

### Effect of acute exacerbations of IPF (AE-IPF)\(^2\)
- A retrospective, single-center study found that IPF patients who received a lung transplant during an AE-IPF (n=28) required significantly greater hospital resources and had worse short- and long-term survival than patients who were transplanted during stable disease (n=52).

### Anti-fibrotic treatment as a bridge to lung transplant\(^3\)
- A single-center retrospective cohort analysis of 37 IPF patients placed on the lung transplant list examined peri-operative and post-transplant outcomes, depending on whether patients received anti-fibrotic drugs prior to transplant or not.
- No difference in outcomes was found between control (n=23) and intervention (n=14) group, suggesting that anti-fibrotic medication is likely safe for IPF patients awaiting lung transplant.

---

1. Swaminathan A, et al. ATS San Diego 2018; D93; OA7369
2. Dotan Y, et al. ATS San Diego 2018; D93; OA7370
3. Li D, et al. ATS San Diego 2018; A42; PA1630
**EXPERT COMMENTS**

Imaging phenotyping as well as changes in fibrosis scores over time seem to correlate well with disease outcome and survival in IPF. They are progressively used in clinical trials as important secondary endpoints to assess clinical response and to stratify patients.

Increasing evidence suggests that comorbidity burden can negatively influence ILD disease course and patients’ quality of life. Stratification for cardiovascular risk at baseline should be mandatory in every patient newly diagnosed with ILD.

Genetic studies in pulmonary fibrosis have provided a new perspective on the pathogenesis, diagnosis and treatment of IPF; although not ready for prime time, we are hopeful that genetics can improve the care of IPF patients and eager to incorporate genetic testing in clinical practice.

Multiple studies focused on health-related quality of life in IPF patients. This remains an important unmet need: to accomplish our goal of healing, we need to be able to document that our patients feel better.
IPF pathobiology

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Novel immunological aspects of lung fibrosis

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IMMUNITY IN LUNG FIBROSIS

Protective role of ICOS in IPF\textsuperscript{1,2}
- Inducible T-cell co-stimulatory (ICOS) molecule is expressed on peripheral blood mononuclear cells; low levels of ICOS predicts decreased survival of IPF patients\textsuperscript{1}
- ICOS expression on peripherally circulating CD4+ T-cells is a predictor of lung function decline\textsuperscript{2}
- In IPF patients with worse disease course, ICOS is decreased. In contrast, an increase is observed in end-stage fibrotic lungs\textsuperscript{2}
- Studies show that IL-5 treatment protected ICOS knockout mice from injury induced death\textsuperscript{1,2}

Interleukin-17A (IL-17A) drives pulmonary fibrosis\textsuperscript{3}
- Interleukin-17A, a pro-inflammatory cytokine is involved in chronic inflammation & autoimmune diseases, and is elevated in fibrotic lung diseases\textsuperscript{3}
- Rebound IL-17 neutrophilic inflammation is caused by blockade of IL-4/IL-13\textsuperscript{4}
- α-V integrin is also a crucial component of fibrosis as it promotes IL-17A/TGF-β driven fibrosis & suppresses IL-4/13 dependent inflammation\textsuperscript{4}

Conclusion
- IL-17A signaling pathway is a potential therapeutic target for treatment of fibro-proliferative lung diseases\textsuperscript{3,4}

Conclusion
- Therapy promoting ICOS signaling via IL-5 might benefit IPF patients\textsuperscript{1,2}

2. Sperling Al, et al. ATS San Diego 2018; C8: T-cell co-stimulatory molecules in Idiopathic Pulmonary Fibrosis: Biomarkers or Players?
4. Wynn T. ATS San Diego 2018; B9: IL-17A drives infectious and non-infectious pulmonary fibrosis

ICOS: Inducible T-cell co-stimulatory molecule
(Role of the IL-17/TGF-β axis in pulmonary inflammation and fibrosis)
NEW PATHWAYS IN LUNG FIBROSIS

Programmed death-1 ligand (PD-L1) in pulmonary fibrosis (PF)

• PD-L1/PD-1 pathway is an immune checkpoint known to suppress the immune system. The upregulation of PD-1 in ILD patients was tested
• Higher levels of PD-1+ Th-17 cells were found in ILD patients. Increased Th-17-related pathway gene expression is linked to reduced IPF life expectancy
• Blocking PD-1 pathway reduced collagen production & pulmonary fibrosis

Targeting TAM receptors ameliorates fibrotic mechanisms in IPF

• The study investigated whether targeting RTK pathways inhibits fibroblast activation and pulmonary fibrosis in mice models
• In IPF, increased expression & activity of Gas6/TAM receptors is observed
• Gas6/TAM was increased in both rapidly and slowly progressive IPF lung samples and fibroblasts

Conclusion
Fibrotic lung diseases show overlapping immunologic pathways. Targeting the PD-1/PD-L1 pathways may offer novel treatments for patients with PF

Conclusion
In IPF, Gas6/TAM receptor activity activates pulmonary fibroblasts. Targeting the RTK pathway might be an effective antifibrotic strategy

1. Drake WP. ATS San Diego 2018; B9: Significance of the Th17 pathway signalling in IPF clinical outcome

PD-L1: Programmed death-1 ligand
PD-1: Programmed death protein 1 (CD279)
TAM: Tyro3 (TYRO3 protein tyrosine kinase 3)
RTK: Receptor tyrosine kinase
Gas6: Growth arrest specific ligand 6
**PD-1/ PD-L1: A NOVEL IPF DIAGNOSTIC MARKER**

**Aim**
Programmed death-1 ligand (PD-L1) suppresses the immune system. It’s role as a potential IPF biomarker was tested using 12 IPF lung tissue samples (formalin fixed, paraffin embedded, FFPE).^1^

**Method**
Surgical biopsy samples with low PD-L1 expression and down-regulated CD274 gene were taken. For PD-L1 detection, immunohistochemical assay was done. Expression levels were tested via Tumour Proportion Score (TPS).

**Conclusion**
Results show PD-L1 is over-expressed in IPF biopsy tissue samples.^1^

<table>
<thead>
<tr>
<th>Patient's tissue</th>
<th>Macrophages</th>
<th>PDL-1 positive %</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Large number</td>
<td>&gt;50%</td>
<td>positive</td>
</tr>
<tr>
<td>02</td>
<td>Moderate number</td>
<td>&gt;1%-50% (20%)</td>
<td>positive</td>
</tr>
<tr>
<td>03</td>
<td>Small number</td>
<td>&lt;1%</td>
<td>negative</td>
</tr>
<tr>
<td>04</td>
<td>Small number</td>
<td>&gt;1%-50% (40%)</td>
<td>positive</td>
</tr>
<tr>
<td>05</td>
<td>Large number</td>
<td>&gt;50%</td>
<td>positive</td>
</tr>
<tr>
<td>06</td>
<td>Large number</td>
<td>&gt;50%</td>
<td>positive</td>
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<tr>
<td>10</td>
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<td>&lt;50% (40%)</td>
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<tr>
<td>11</td>
<td>Moderate number</td>
<td>&gt;1% (5%)</td>
<td>positive</td>
</tr>
<tr>
<td>12</td>
<td>Moderate number</td>
<td>&gt;1% (10%)</td>
<td>positive</td>
</tr>
</tbody>
</table>

PD-L1 positive if TPS ≥50% of viable alveolar macrophages showed membrane staining

---

Novel genetic aspects

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MITOCHONDRIA: MICE STUDIES REVEAL NOVEL TARGETS FOR IPF

Protective role of Cyb5R3 in IPF

- Role of Cyb5R3, an external mitochondrial NADH-dependent reductase in IPF pathobiology was studied
- Young, old and IPF donor lungs were lysed to test Cyb5R3 and concentration of NAD+ and NADH. Cyb5R3 flox and knockout mice were bred
- Aged & IPF lungs showed lower levels of Cyb5r3 and NAD+/NADH
- Cyb5R3 knockout mice showed increased collagen deposition and increased inflammatory response

Conclusion

Strategies restoring the ratio of pyridine nucleotides or modulating Cyb5R3 expression may reduce pulmonary fibrosis

Mitochondrial-DNA (mt-DNA) & oxidative stress

- Mitochondrial 8-oxoguanine DNA glycosylase (mtOGG1), is a mt-DNA base-excision repair enzyme
- mtOGG1 in relation to oxidant-induced mt-DNA damage, fibrosis and apoptosis was studied in wildtype (C57BI/6J) and PINK-KO1 mice
- mtOGG1-EE mice were protected from bleomycin-induced lung fibrosis and higher mt-DNA damage
- OGG-1-deficient mice have higher lung fibrosis due to high mt-DNA damage

Conclusion

mtOGG1 maintenance of AEC mt-DNA is a crucial checkpoint for preventing mitophagy defects, apoptosis and fibrosis

1. Bueno M. ATS San Diego 2018; C85: Cyb5R3 an external mitochondrial NADH-depant reductase confers protection against lung fibrosis
2. Kim S. ATS San Diego 2018; C85: Mitochondrial 8-Oxoguanine DNA Glycosylase (mtOGG1) Mitigates Asbestos-Induced Aec Mitophagy Defects, Mitochondrial DNA Damage, Apoptosis And Lung Fibrosis

NADH: Nicotinamide adenine dinucleotide
Mitophagy: Selective degradation of mitochondria by autophagy
EE: Environmentally enriched
FOXO ACTIVATION IN TREATING PH & IPF

Rationale

- Forkhead box group O (FoxO) is a transcription factor characterized by a conserved fork-head box DNA-binding domain\(^1\).
- Role of FoxO in IPF lungs was analyzed in both human IPF lungs & mice models\(^1\).

Results

- Ex-vivo cultured myo-fibroblasts from human IPF lungs and bleomycin-challenged mice showed decreased expression of FoxO3\(^2\).
- In human lung fibroblasts, FoxO3 loss of function induced differentiation and hyper-proliferation phenotypes. In mice, this led to bleomycin-induced fibrosis and increased mortality\(^2\).

Conclusion

FoxO3 is a protective factor against fibrosis. Increasing FoxO3 levels may have therapeutic effects.

---

1. Pullamsetti SS, ATS San Diego 2018; D7: FoxO: Critical integrator of growth factor and inflammatory signalling hubs-FoxO activation as a strategy to treat PH and IPF.
2. Al-Tamari HM et al. EMBO Molecular Medicine 2017. doi: 10.15252/emmm.201606261

---

PH: Pulmonary hypertension
IPF: Idiopathic pulmonary fibrosis
Pathobiology of fibrosis: new targets
**PD-L1 IS UPREGULATED IN FIBROBLASTS DERIVED FROM IPF AND MURINE LUNGS**

**Rationale**
Programmed cell death receptor (PD-L1, aka CD274) is an immune checkpoint used by cancer cells to escape immune surveillance.

Its role in fibroblast function was studied in IPF and non-IPF lung fibroblasts in mice.

**Method**
Matrigel invasion assay was used to isolate lung fibroblasts. Techniques, such as qRT-PCR, flow cytometry analysis & single cell western blot, were used to measure levels of PD-L1 mRNA.

**Result**
- PD-L1 mRNAs were up-regulated in invasive fibroblasts. Also, cell surface expression of PD-L1 was higher on IPF lung fibroblasts than healthy controls.
- Knockdown of PD-L1 in lung fibroblasts inhibited cell growth, cell migration and invasion.

**Conclusion**
PD-L1 was seen to be up-regulated in invasive lung fibroblasts and could serve as a potential therapeutic target for treating pulmonary fibrosis.

ENHANCED INVADOSOME FORMATION IN MURINE MODEL OF FIBROSIS

Invadosomes are dynamic structures of the plasma membrane in cancer cells

Aim
To determine whether invadosome formation is increased in fibroblasts cultured from mice lungs. Lungs with bleomycin-induced fibrosis or fibroblasts exposed ex-vivo to lysophosphatidic acid (LPA) or hypoxia were tested

Method
Control & bleomycin-exposed mice were used for isolation of lung fibroblasts

Result
• Increased invadosome formation was seen in lung fibroblasts isolated from bleomycin-exposed murine lungs
• LPA stimulation & incubation in hypoxia increased invadosome formation in control mice

Conclusion
Lung fibroblasts from bleomycin-exposed murine lungs show increased invadosome formation capacity

1. Lebel M, et al. ATS San Diego 2018; C72: PA5774
EXPERT COMMENTS

New aspects in the pathobiology of IPF are represented by the activation of lymphocytes through the IL17 pathway and overexpression of PD1 on macrophages, fibroblasts and lymphocytes, which in turn trigger TGF-β fibrotic pathway.

Mitochondrial DNA instability as a consequence of oxidative stress seems to drive profibrotic pathways and affect apoptosis of different cell populations involved in fibrogenesis.

From the evolutionary origin of the mitochondria, to mitochondrial specific disease mechanisms and insight into mitochondria directed therapeutics for lung fibrosis, the 2018 ATS meeting was a superb Mito-Meeting!
Non-IPF ILDs

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**LYMPHANGIOLEIOMYOMATOsis (LAM)**

Lymphangioleiomyomatosis is a rare, progressive & systemic disease resulting in cystic lung destruction, mostly affecting women during child-bearing years.

**NHLBI LAM registry**¹
- A prospective study of women with LAM (n=217) looked at rate of decline in FEV₁ and variables in lung function decline.
- Menopausal status at enrollment impacted FEV₁ decline (118 mL/y in pre-menopausal vs. 74 mL/y post-menopausal).
- Post-menopausal status, higher baseline FEV₁ or DLCO had an independent association with death/transplant risk.

**Conclusion**
Rate of decline in FEV₁ and survival of LAM patients depends upon baseline menopausal status and structural/physiological markers of disease.

**VEGF-C as LAM biomarker**²
- Sporadic occurrence of LAM is observed in patients with tuberous sclerosis complex (TSC).
- Data from the MILES trial (n=89) and a separate cohort of healthy controls and patients with TSC (TSC only), TSC-LAM and S-LAM was used to explore serum VEGF-C as a biomarker.

**Conclusion**
Elevated serum VEGF-C was found in S-LAM, but not in TSC-LAM patients; VEGF-C may prove useful for diagnostics and as a predictive biomarker.

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¹. Gupta N, et al. ATS San Diego 2018; D14: OA6180
². Wu H, et al. ATS San Diego 2018; A23: PA1100
**LAM GUIDELINES: DIAGNOSIS AND MANAGEMENT**

Newest recommendations regarding diagnosis of LAM (lymphangioleiomyomatosis) and management of pneumothorax in patients with LAM (published November 2017) were presented at the ATS 2018

- Females with cystic changes on HRCT chest characteristic of LAM but no other confirmatory LAM features should consider transbronchial lung biopsy for diagnosis
- Pleurodesis to be offered after an initial pneumothorax and not postponed until first recurrence
- Advise against using pleurodesis as a reason to exclude patients from lung transplantation

AML: Angiomyolipoma; CT: Computed tomography
HRCT: High resolution computed tomography
MRI: Magnetic resonance imaging
PFTs: Pulmonary function tests; TSC: Tuberous sclerosis complex
VEGF-D: Vascular endothelial growth factor-D

**Clinical suspicion of LAM**

- HRCT chest with features characteristic of LAM
- Yes
- Detailed clinical evaluation confirms the presence of TSC
- No
- Obtain: 1. Serum VEGF-D
  2. Non-contrast CT or MRI abdomen/pelvis
  3. Chylous fluid/node/mass aspiration (if applicable)
- Are any of the following present?
  1. Serum VEGF-D greater than or equal to 800 pg/mL
  2. Renal AMLs or lymphangioleiomyomas
  3. Positive cytology
- No
- Is histopathological confirmation desired/required?
  1. Transbronchial lung biopsy with characteristic features of LAM
  2. Surgical lung biopsy
- No

**Consider alternative diagnosis**

**Confirmed diagnosis of TSC-LAM**

**Confirmed diagnosis of LAM**

**Continue close monitoring with serial PFTs every 3-4 months**

**Confirmed diagnosis of LAM**

**Confirmed diagnosis of LAM**

**Figure: Diagnostic algorithm for LAM as presented in the clinical guidelines**

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Am J Respir Crit Care Med; 196: 1337-1348

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**MMP ACTIVITY IN ILD: CLINICAL OPTICAL MOLECULAR IMAGING**

**Rationale**
- Matrix metalloproteinases (MMPs) are over-expressed in ILD lungs
- This is the first in-situ optical molecular imaging investigation of MMP activity in distal human lungs of patients
- 8 patients with confirmed ILD were included: 4 with IPF, 2 connective tissue disease and 2 chronic HP; a total of 26 discrete lung segments were investigated
- MMP activity in alveolar space was captured via fibre endoscopy (FE) with a MMP-specific fluorescent smartprobe (FIBOne for MMP-2, -9 & -13)

**Results**
- A significant increase (p<0.01) in fluorescence was observed in segments with saline pre-dose after FIBOne delivery

**Conclusion**
- Imaging drug engagement may benefit early assessment of response to novel therapies in ILD

MMPs: Matrix metalloproteinases

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RADIOLOGIC PHENOTYPE AS PREDICTOR OF CLINICAL COURSE IN PATIENTS WITH HYPERSENSITIVITY PNEUMONITIS (HP) AND IPF

Study design

• A retrospective single-center study examined the association between transplant-free survival and post-baseline lung function trajectory with baseline radiological phenotype in 118 patients with HP and 152 patients with IPF
• Subjects were grouped by clinical diagnosis and three radiologic phenotypes: a) honeycomb present; b) non-honeycomb fibrosis; c) non-fibrotic

Results

• Within fibrotic and non-fibrotic groups, HP subjects fared non-significantly better than IPF
• Within HP and IPF, non-fibrotic subjects have the longest transplant-free survival, and those with honeycombing the shortest
• In adjusted FVC% trajectory analyses for 12-months post-baseline, non-fibrotic HP subjects experienced a gain in lung function whilst other groups declined

Conclusion

• Radiological phenotype identifies HP and IPF patients with distinct survival times, while clinical diagnosis did not maintain statistical significance for predicting transplant-free survival after accounting for associations by radiologic phenotype

NINTEDANIB ATTENUATES HISTOPATHOLOGY OF INTERSTITIAL PNEUMONIA IN A TRANSGENIC MOUSE MODEL OF ARTHRITIS

Study design
- A transgenic mouse model, showing a high susceptibility for both arthritis and rheumatoid lung fibrosis, was used to test efficacy of nintedanib
- Mice were immunized with low-dose of bovine collagen type II (bCII) and joint inflammation was monitored by clinical score
- 35 weeks after stimulation with bCII adjuvant, nintedanib, or vehicle was orally administered for 8 weeks

Results
- Observed histopathology of interstitial pneumonia was less pronounced in the nintedanib group compared with controls, although levels of serum SP-D were only marginally lower in the nintedanib group
- Nintedanib did not affect liver disease biomarker expression

Conclusion
- Nintedanib seems to attenuate chronic interstitial pneumonia in a mouse model of arthritis


SP-D: Surfactant protein D
NEW INSIGHTS ON SYSTEMIC SCLEROSIS (SSC) RELATED TO INTERSTITIAL LUNG DISEASE (ILD)

Molecular evidence for anti-fibrotic potential of nintedanib in ILD associated with SSC¹

In lung fibroblasts isolated from SSC patients and healthy controls:

• Nintedanib significantly reduced PDGF-induced delayed calcium efflux in SSC and in control lung fibroblasts
• Nintedanib inhibited PDGF-induced lung fibroblast proliferation and cell migration and reduced PDGF- and TGFβ-induced collagen
• Nintedanib down-regulated high basal levels of collagen, increased MMP-13 and reduced PDGF-induced MMP-3, TIMP-1 and TIMP-2 in SSC lung fibroblasts

Conclusion
Nintedanib demonstrates significant anti-fibrotic effects in SSC lung fibroblasts

Predicting mortality in SSC-related ILD in two independent cohorts²

A retrospective analysis of the Scleroderma Lung Study (SLS) I and II (n=300) found:

• There was no significant difference in time to death in SSC patients treated with cyclophosphamide (CYC) for one year in comparison to placebo
• The course of FVC was a better predictor of mortality than baseline FVC

Conclusion
Early changes in surrogate measures of SSC-ILD progression may have important effects on long-term outcomes

PDGF: Platelet-derived growth factor; TGFβ: Transforming growth factor beta; MMP: Matrix metalloproteinase; TIMP: Tissue inhibitor of metalloproteinase

¹. Akter T, et al. ATS San Diego 2018; C26: PA4638
². Tashkin PD, et al. ATS San Diego 2018; D14: PA6178
EXPERT COMMENTS

Rapid progress in IPF research has increased interest and accelerated studies in other ILD's.

Evidence from experimental models suggests efficacy of nintedanib for treating interstitial lung disease associated with connective tissue diseases, especially for rheumatoid arthritis and systemic sclerosis.

New guidelines are available for the diagnosis and management of lymphangiomyomatosis, providing a clear and useful tool to clinicians dealing with this rare ILD. Inclusion of biomarkers in the diagnostic flow chart makes these guidelines one of the most innovative in the field of ILD.
Appendix and acknowledgements

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Angina or
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Q
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L
S
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I
I
Anti
C
T
T
M
Q
L
U
M
F
V
M

ABBREVIATIONS

GAP
FoxO
FFPE
F
Hx
IHD
FoxO
FPF
FVC
GAP

AntiAcid Therapy
Airway Basal Cells
Acute Exacerbation
Alveolar Epithelial Cell
Acute Exacerbation of IPF
Atrial Fibrillation
Angio/yolipoma
Alveolar Type II
ATS
BAL
bCII
BMI
BTLA
CCL
CI
CKD
CT
CTGF
CV
CybOR3
DIOP
Dlco
EE
FE
FEV1
FFPE
F
Hx
IHD

Ac
Ac
AE
AEC
AE-IPF
AF
AML
AT2
ATS
BAL
bCII
BMI
BTLA
CCL
CI
CKD
CT
CTGF
CV
CybOR3
DIOP
Dlco
EE
FE
FEV1
FFPE
F
Hx
IHD

Gender, Age, and Physiology index
GERD
GRADE

GastroEsophageal Reflux Disease
Grading of Guidelines, Recommendations, Assessment, Development, and Evaluation
HealthCare Utilization
Histone DeAcetylation
High Density Lipoprotein
Hypersensitivity Pneumonitis
Hazard Ratio
High Resolution Computed Tomography
Health-Related Quality of Life
Anti-hypertensive treatment
Inducible T-cell CO-Stimulatory molecule
Immunoglobulin G1
Initiated
Idiopathic Interstitial Pneumonia
Interleukin
Interstitial Lung Abnormalities
Interstitial Lung Disease
Idiopathic Pulmonary Fibrosis
Lymphangiioleiohyomatosis
Lung Cancer Screening Computed Tomography
Low Density Lipoprotein
Lysophosphatic Acid
LipoPoySacharide
Multidisciplinary Discussion
MAP Kinase-activated protein kinase 2
Matrix Metalloproteinase
Magnetic Resonance Imaging
Mitochondrial-DNA
Mitochondrial 8-Oxo Guanine DNA Glycosylase
Mechanist Target Of Rapamycin
MUC1
NADH
NHLBI
PD-1
PD-L1
PF
PFTs
PH
PK
Qd
qHRCT
QLF
QoL
RA
SD
SQR
S-LAM
SNP
TEAE
TGFI
TH
TPS
TSC
UCP-2
UCSD
UIC
UK
US
VAS
VEGF

Mucin 1
Nicotinamide Adenine Dinucleotide
National Heart, Lung and Blood Institute
Programmed Death-1
Programmed Death Ligand 1
Pulmonary Fibrosis
Pulmonary Function Tests
Pulmonary Hypertension
Pharmacokinetic
Once Daily
Quantitative High Resolution Computed Tomography
Quantitative Lung Fibrosis
Quality of Life
Rheumatoid Arthritis
Standard Deviation
St George’s Respiratory Questionnaire
Sporadic occurrence of Lymphangiioleiohyomatosis
Single Nucleotide Polymorphism
Treatment-Emergent Adverse Event
Transforming Growth Factor
Thyroid Hormone
Tumour Proportion Score
Tuberculosis Complex
UnCoupling Protein
UCSD Shortness Of Breath Questionnaire
Usual Interstitial Pneumonia
United Kingdom
United States of America
Visual Analog Scale
Vascular Endothelial Growth Factor

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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.
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