The American Thoracic Society's International Conference (ATS) – one of the largest gatherings of pulmonary, critical care, and sleep medicine professionals in the world – was held May 13th–18th in San Francisco, California, USA.

In numerous interstitial lung disease (ILD) and idiopathic pulmonary fibrosis (IPF) sessions, international pulmonary specialists discussed exciting topics.

- **ATS Keynote:** IPF
- **Clinical Year in Review:** ILD
- **Real world experience with antifibrotics in IPF**
- **New data on nintedanib**
- **New data on pirfenidone**
ATS Keynote: What is effective IPF management?

During the ATS 2016 keynote session on IPF, Talmadge E. King, MD (from the UCSF School of Medicine, San Francisco, USA) highlighted three major issues that recurred at various sessions during the conference:

1. A confident and timely diagnosis of IPF is key
2. Approved anti-fibrotic treatment (nintedanib, pirfenidone) should be started as early as possible
3. Patients have to be managed aggressively, with special focus on comorbidities

Goals of effective IPF management (adapted from Talmadge E. King)

- Relieve symptoms
- Improve exercise tolerance and health status
- Prevent and treat complications and exacerbations
- Prevent disease progression
- Reduce mortality

In addition, King highlighted the findings of a couple of papers published in 2016:

- Results from the PANORAMA study (safety and tolerability of N-acetylcysteine (NAC) combined with pirfenidone) suggest that addition of NAC does neither change the tolerability of pirfenidone, nor does it improve outcomes in patients with IPF.¹
- Antiacid therapy (AAT) also did not improve outcomes in patients with IPF and might even be associated with an increased risk of infection in patients with IPF and FVC>70% predicted.²

Diagnostic journey of patients with ILD (INTENSITY survey)³

Most common first symptoms of ILD (600 US residents responded to the survey)

- 77% Shortness of breath
- 53% Cough
- 38% Fatigue

Patients diagnosed with IPF (47% of respondents)

- Median time to diagnosis: 7 months
  For 28% of patients, the diagnostic process took over 2 years
- Median number of physician visit: 3
  14% of patients saw more than 6 physicians
- 56% of patients were initially misdiagnosed
  Most frequent misdiagnoses: asthma, pneumonia, bronchitis and allergies.
ATS Clinical Year in Review: ILD

David Lederer, MD (from the Columbia University Medical Center, New York, USA), speaker for the Clinical Year in Review series, named the following key clinical research publications since the last ATS in 2015 as most important and influential for the field of interstitial lung disease (ILD):

**Update of the 2011 clinical practice guidelines for the treatment of IPF**

Lederer highlighted that the updated guidelines, apart from giving the two FDA and EMA approved anti-fibrotic treatments nintedanib and pirfenidone a conditional recommendation for use, still kept a strong recommendation for oxygen therapy, pulmonary rehabilitation and lung transplantation.

→ Watch the Professors Behr and Vancheri discuss the 2015 update on the treatment guidelines

**In-hospital mortality after surgical lung biopsy (SLB) for interstitial lung disease in the United States (2000 to 2011)**

The authors (Hutchinson et al) found that in-hospital mortality was significantly higher (16.0%) after non-elective SLBs compared to elective procedures (1.7%), and identified risk factors for increased mortality included male sex, increasing age, increasing comorbidity, open surgery and provisional diagnosis of IPF or CTD-ILD.

**Longitudinal change in collagen degradation biomarkers in idiopathic pulmonary fibrosis: an analysis from the prospective, multicenter PROFILE study**

The researchers (Jenkins et al.) investigated the longitudinal change in concentration of several extracellular matrix (ECM) protein fragments in the serum of patients with IPF or idiopathic non-specific interstitial pneumonia (participants of the ongoing PROFILE study) and found that

- Elevated concentration of several protein fragments in the serum was associated with disease progression
- The rate of increase in concentration predicted survival

**Classification of usual interstitial pneumonia in patients with interstitial lung disease: assessment of a machine learning approach using high-dimensional transcriptional data**

RNA expression levels of patients with ILD (samples obtained by surgical lung biopsy) were analyzed using next-generation RNA sequencing (RNAseq). Based on this, the group developed a classifier for UIP, which showed a specificity of 92% (95%; CI 81-100) and sensitivity of 82% (95%; CI 64-95), demonstrating that genomic signatures can be used to predict pathological UIP pattern.
Real world experience with anti-fibrotic treatments in IPF

A study from the University of Michigan by Margret L Salisbury and co-workers elucidated treatment recommendations and usage patterns for US patients diagnosed with IPF after FDA approval of nintedanib and pirfenidone. 71.6% (78 patients) of the 109 patients were recommended to start anti-fibrotic treatment, but only 65.7% of those patients (52 patients) actually started the treatment, with 54% of those still receiving treatment when the data was analyzed in April 2016. Patients with poorer pulmonary function and biopsy-confirmed IPF diagnosis were more likely to receive treatment recommendations.

Anti-fibrotic drugs well tolerated in patients with greater burden of disease

Jonathan Galli and other investigators from the Temple University School of Medicine, Philadelphia, compared 107 US patients with IPF on anti-fibrotic treatment in that center to the patient populations enrolled in the respective Phase III clinical studies (CAPACITY and ASCEND for pirfenidone\textsuperscript{10,11} and INPULSIS\textsuperscript{®} for nintedanib\textsuperscript{12}): Although real world patients had lower FVC and DL\textsubscript{CO} at baseline (compared with the patients on clinical trials) and the majority of patients required home oxygen, occurrence of adverse events and drug discontinuation rates were similar, indicating that the drugs are reasonably well tolerated in patients with greater burden of disease.

Most common adverse events and drug discontinuation rates from AEs for pirfenidone

![Bar chart showing the most common adverse events and drug discontinuation rates from AEs for pirfenidone.]

Most common adverse events and drug discontinuation rates from AEs for nintedanib

![Bar chart showing the most common adverse events and drug discontinuation rates from AEs for nintedanib.]

\*CAPACITY and ASCEND trials (n=623)

\*INPULSIS\textsuperscript{®} trials (n=638)
Real-world experience with nintedanib

German compassionate use program with nintedanib

<table>
<thead>
<tr>
<th>Baseline characteristics (n=62)</th>
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</thead>
<tbody>
<tr>
<td>• Age: 71±8 years</td>
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<tr>
<td>• FVC: 64±17% predicted</td>
</tr>
<tr>
<td>• DLCO: 40±10% predicted</td>
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</tbody>
</table>

Mean duration of treatment
31±15 weeks.

Mild to moderate adverse events
Occurred in 68% of patients
• 63% diarrhea
• 53% weight loss

Dose reductions
in 32% of patients

Temporary discontinuation
• On average 106 days after treatment initiation
• Median duration: 17 days (range 1-91)
• Definite discontinuation: in 10% of patients

Post-marketing experience in the US
Analysis of adverse events in patients with IPF (n= 6758) 1 year after nintedanib launch in the US confirmed that most frequently reported adverse are non-serious and of gastrointestinal nature, and are consistent with the INPULSIS® Phase III studies.

Real-world experience with pirfenidone: Safety in the US population

<table>
<thead>
<tr>
<th>Baseline characteristics (n=1620)</th>
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<tbody>
<tr>
<td>• Age: 71±7.7years</td>
</tr>
<tr>
<td>• Male sex: 74.7%</td>
</tr>
<tr>
<td>• Definite UIP on HRCT: 66.5%</td>
</tr>
<tr>
<td>• Possible UIP on HRCT: 33.2%</td>
</tr>
</tbody>
</table>

Mean duration of prescribed exposure
22.8±9.6 weeks.

Adverse events (AEs)
Occurred in 64.9% of patients
• 22.6% nausea
• 19.6% fatigue

Discontinuation
Discontinuation due to AEs / Serious AEs: 13%

In a multicenter, German compassionate use program including non-naive patients (77% of patients switched from pirfenidone), safety and efficacy of treatment with nintedanib were comparable to clinical trials.

Nintedanib was generally well tolerated and the majority of patients (66%) had stable disease (defined by decline in FVC < 5% from baseline and no worsening of symptoms or radiologic findings) at six months following initiation of nintedanib.

The safety profile of pirfenidone in US patients enrolled in an open access program (n=1620) was comparable to clinical trials and no safety signals were identified. 75.4% of patients completed the program.

One third of the enrolled patients in the program had possible UIP on HRCT. This is unlike the pirfenidone Phase III trials, where mainly patients with definite UIP on HRCT were enrolled.
New data on Nintedanib in IPF

**Nintedanib in IPF: Pooled analyses of the INPULSIS® trials**

**Effect of nintedanib on disease progression**

In an ad hoc analysis of the pooled data from the INPULSIS® trials (n= 1061), nintedanib significantly reduced the risk of disease progression, defined as an absolute FVC decline $\geq$ 10% predicted or death over 52 weeks, versus placebo (HR 0.60 [95% CI: 0.49, 0.74]; p<0.0001). The beneficial effect of nintedanib on reducing disease progression was consistent across subgroups defined by baseline FVC % predicted.

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=423)</th>
<th>Nintedanib (n=638)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression</td>
<td>41%</td>
<td>27%</td>
</tr>
<tr>
<td>HR</td>
<td>0.60 [95% CI: 0.49, 0.74]; p&lt;0.0001</td>
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</tbody>
</table>

**Kaplan-Meier estimate of absolute decline in FVC ≥10% predicted or death (%)**

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Nintedanib 150 mg bid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nintedanib 150 mg bid</td>
<td>638 611 593 581 576 571 543 540 537 510 505 503 492 415</td>
<td>423 411 400 377 377 345 337 333 293 288 283 277 232</td>
</tr>
<tr>
<td>Placebo</td>
<td>423 411 400 377 377 345 337 333 293 288 283 277 232</td>
<td>492 415</td>
</tr>
</tbody>
</table>
Effect of nintedanib on decline in FVC over time\textsuperscript{17}

Another ad hoc analysis of the pooled data from the INPULSIS\textsuperscript{®} trials (n= 1061), showed, that nintedanib significantly reduced adjusted mean change from baseline in FVC compared with placebo, which is consistent with a slowing of disease progression. This effect was observed as early as week 12 and was maintained up to week 52.

Cumulative distribution of patients by change in FVC % predicted\textsuperscript{18}

In the INPULSIS\textsuperscript{®} trials in patients with IPF, a higher proportion of patients treated with nintedanib than placebo had no decline or an improvement in FVC % predicted over 52 weeks, while a smaller proportion had absolute declines in FVC $\geq$5% predicted and $\geq$10% predicted. These data support the effect of nintedanib on reducing disease progression in patients with IPF.
Effect of baseline GAP index stage on decline in lung function with nintedanib

A post-hoc subgroup analysis on pooled data from the INPULSIS® trials showed that nintedanib slowed decline in lung function independent of GAP stage at baseline. In contrast, decline in lung function in patients who were treated with placebo was similar for those with GAP I compared to GAP II/III at baseline.

- A greater proportion of patients at GAP stage II/III at baseline had an acute exacerbation compared with patients at GAP stage I.
- There was no significant treatment-by-subgroup interaction for time to first acute IPF exacerbation over 52 weeks (p=0.1408).
- The difference in adjusted mean change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at week 52 was numerically higher in patients with GAP stage II/III compared to patients with GAP stage I.

### Baseline characteristics (n=62)

<table>
<thead>
<tr>
<th></th>
<th>GAP I (n=500)</th>
<th>GAP II/III (n=560)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63 years</td>
<td>70 years</td>
</tr>
<tr>
<td>Male sex</td>
<td>68%</td>
<td>70%</td>
</tr>
<tr>
<td>Mean FVC % predicted</td>
<td>86%</td>
<td>74%</td>
</tr>
<tr>
<td>DLCO</td>
<td>54%</td>
<td>41%</td>
</tr>
</tbody>
</table>

### No. of patients

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>GAP stage I – nintedanib</th>
<th>GAP stage II/III – nintedanib</th>
<th>GAP stage I – placebo</th>
<th>GAP stage II/III – placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAP stage I</td>
<td>297 292 291</td>
<td>290</td>
<td>282</td>
<td>280</td>
</tr>
<tr>
<td>GAP stage II/III</td>
<td>329 324 322</td>
<td>314</td>
<td>305</td>
<td>289</td>
</tr>
<tr>
<td>GAP stage I</td>
<td>196 192 193</td>
<td>192</td>
<td>189</td>
<td>184</td>
</tr>
<tr>
<td>GAP stage II/III</td>
<td>220 215 213</td>
<td>210</td>
<td>206</td>
<td>198</td>
</tr>
</tbody>
</table>

The preparation of this PDF was sponsored by Boehringer Ingelheim International GmbH. ATS was neither author nor reviewer of the content.
Efficacy of nintedanib on acute exacerbations reported as serious adverse events

Post-hoc analysis of patients with acute exacerbations (n=63) found that nintedanib significantly reduced the risk of acute exacerbations reported as serious adverse events (SAEs). Acute exacerbations classified as SAEs were associated with a much higher risk of death compared to acute exacerbations reported as non-serious adverse events (61% versus 7%, respectively).

Proportion of first investigator-reported acute exacerbations reported as SAEs

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nintedanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAEs</td>
<td>6.1% (n=26)</td>
<td>3.6% (n=23)</td>
</tr>
<tr>
<td>HR</td>
<td>0.57 [95% CI: 0.32, 0.99]; p=0.0476</td>
<td></td>
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</tbody>
</table>

Relationship between nintedanib exposure and absolute change in FVC

A longitudinal disease progression model was developed to investigate the relationship between nintedanib exposure and absolute change in FVC (data from 1403 patients enrolled in the TOMORROW and INPULSIS® studies).

The model supports the selected starting dose of nintedanib 150 mg bid for the treatment of IPF across the investigated population, as this results in efficacious exposure levels in the majority of patients.

The exposure-response relationship does not seem to differ between any of the investigated subpopulations.

Additional findings
- Trend towards higher drug efficacy: diarrhea and higher baseline FVC % predicted
- Trend towards a slower FVC decline: female sex
- Current smokers: higher baseline FVC % predicted and a slower rate of FVC decline were found
- No significant effect on FVC decline or drug efficacy: age, height, ethnicity, study and presence of honeycombing
New data on pirfenidone in IPF

Pirfenidone in IPF: Pooled analyses of the ASCEND and CAPACITY trials

Antiacid therapy (AAT) and disease progression under pirfenidone treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AAT</th>
<th>non-AAT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression</td>
<td>23.4%</td>
<td>29.4%</td>
<td>0.09</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2.9%</td>
<td>4.0%</td>
<td>0.47</td>
</tr>
<tr>
<td>IPF-related mortality</td>
<td>1.1%</td>
<td>2.0%</td>
<td>0.37</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>16.1%</td>
<td>17.1%</td>
<td>0.73</td>
</tr>
<tr>
<td>Observed mean FVC decline</td>
<td>-2.7%</td>
<td>-3.1%</td>
<td>0.44</td>
</tr>
<tr>
<td>Severe GI AEs</td>
<td>4.4%</td>
<td>1.1%</td>
<td>0.011</td>
</tr>
<tr>
<td>Severe pulmonary infections</td>
<td>3.3%</td>
<td>1.1%</td>
<td>0.062</td>
</tr>
</tbody>
</table>

Patients randomized to pirfenidone treatment (n=623) in the Phase III clinical trials ASCENDII and CAPACITY were investigated with regards to concomitant antacid treatment (AAT; 44% of patients)

- No significant differences in disease progression (absolute decrease in FVC ≥10% predicted, decrease of ≥50 m in 6MWD, or death) and other outcomes
- Severe gastrointestinal AEs and severe pulmonary infections were more frequent in AAT users.

Effect of pirfenidone on non-elective hospitalizations

Pooled data (n=1247) from ASCEND and CAPACITY trials were analyzed with regards to the risk of non-elective hospitalizations during treatment with pirfenidone or placebo over 12 months. It was found that pirfenidone may reduce the risk of non-elective respiratory-related hospitalizations over 12 months.

Non-elective hospitalizations - patients with ≥ 1 event

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n=624)</th>
<th>Pirfenidone (n=623)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>p=0.662</td>
<td>p=0.004</td>
</tr>
<tr>
<td>Respiratory-related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients (%)</td>
<td>n=112</td>
<td>n=106</td>
</tr>
<tr>
<td></td>
<td>n=74</td>
<td>n=44</td>
</tr>
</tbody>
</table>
Cardiovascular events in pirfenidone Phase III trials

A retrospective analysis described the occurrence of cardiovascular and bleeding adverse events (AEs) in patients with IPF enrolled in three Phase III trials of pirfenidone. In this blinded review of treatment-emergent cardiovascular and bleeding adverse events (AEs), patients on pirfenidone and on placebo exhibited similar incident rates.

Effect of continued treatment with pirfenidone following a ≥10% relative decline in FVC % predicted

Of the pooled patient population experiencing an initial ≥10% relative decline in %FVC, 80 and 140 patients received pirfenidone and placebo, respectively. In the subsequent 6 months, 17 (21.3%) patients in the pirfenidone and 50 (35.7%) patients in the placebo groups, experienced a ≥10% relative decline in %FVC or death.
Pirfenidone studies: Effect of pirfenidone on acute IPF exacerbations and cough

Efficacy of pirfenidone for acute IPF exacerbations

In this retrospective analysis, 26 patients experiencing an acute exacerbation were treated with corticosteroid (CS) pulse therapy (3 days) followed by maintenance dose of CS and recombinant human soluble thrombomodulin (rhTM) (6 days). In addition, part of the group was started on pirfenidone (combination treatment). The authors concluded that the combination treatment may improve survival.

Effect of pirfenidone on cough

Analysis of first 30 patients of the observational Cough-IPF study (NCT02009293) showed that pirfenidone reduced objective 24-hour cough counts by 35% (95% CI 16-49; p=0.002) over 12 weeks and that this effect was already measurable at 4 weeks (19%, CI 12-26; p=0.03). In addition, a positive effect on subjective measurements of cough, such as LCQ scores, was also observed.

Patient characteristics and demographics of patients treated with pirfenidone

Several publications have characterized the IPF patient population. At this year’s ATS, 2 new posters reported on the characteristics of patients treated with pirfenidone- one of US patients treated with pirfenidone after launch and one on the pooled ASCEND and CAPACITY patient population. Not surprisingly, cardiovascular risk factors and comorbidities are common in patients with IPF.

US patients treated with pirfenidone after launch

Age and gender demographics of patients who recently initiated pirfenidone in the US were similar to patients treated with pirfenidone in the open-label European PASSPORT registry. Interestingly, only 7% of patients had been subjected to surgical lung biopsy. Cardiovascular conditions and GERD were quite common (35% and 28%, respectively) and over half of the patients (57%) used supplemental oxygen.

Patient characteristics in pooled pirfenidone Phase III trials

Findings from the pooled analysis of the ASCEND and CAPACITY patient population were also consistent with results from PASSPORT and other registries. Cardiovascular risk factors and conditions were common and concomitant medications were used often during the trials. More than half of the patients had hypertension (52%), and were former or current smokers (66%).
References


Glossary

6MWD = 6-minute walk distance
AAT = Antiacid therapy
AE = Adverse event
ATS = American Thoracic Society
CI = Confidence interval
CS = Corticosteroid
CTD-ILD = Connective tissue disease associated ILD
Dlco = Diffuse capacity of the lung for carbon monoxide
ECM = Extracellular matrix
EMA = European Medicines Agency
FDA = Food and Drug Administration
FVC = Forced vital capacity
GAP = Gender-Age-Physiology index
GERD = Gastroesophageal reflux disease
HR = Hazard ratio
HRCT = High resolution computed tomography

HRQoL = Health-related quality of life
ILD = Interstitial lung disease
IPF = Idiopathic pulmonary fibrosis
LCQ = Leicester Cough Questionnaire
MACE = Major adverse cardiac events
MD = Doctor of Medicine
NAC = N-acetylcysteine
rhTM = Recombinant human soluble thrombomodulin
RNA = Ribonucleic acid
SAE = Serious adverse event
SLB = Surgical lung biopsy
SP-D = Surfactant protein D
UCSF = University of California, San Francisco
UIP = Usual Interstitial Pneumonia
US = United States
USA = United States of America

Explore the educational resources in the IPF learning center and find out more about nintedanib’s safety and efficacy on global.OFEV.com!