113th ATS Congress

American Thoracic Society

19 - 24 MAY 2017 • WASHINGTON • USA

PEER-REVIEWED CONFERENCE REPORT

Auxiliary benefits in Cystic Fibrosis

Ivacaftor decreases ADAM-17 activity and circulating levels of the sIL- 6r/IL-6 complex in neutrophils, resulting in reduction of inflammation in cystic fibrosis patients.

read more on PAGE 11

Late-breaking news

A possibly game-changing study showed effective prolonging of time until hospital readmission or death within 12 months, in patients with persistent hypercapnia following an acute exacerbation of COPD.

read more on PAGE 7

Retrospective cohort analysis

An analysis in the USA of adult outpatients with community-acquird pneumonia suggested that almost a quarter fail on antibiotics. Moreover, multiple predictors were identified.

read more on PAGE 16

MEDICOM MEDICAL PUBLISHERS

Editor Prof. dr. Richard Dekhuijzen, Radboud Universitair Medisch Centrum, Nijmegen

Contents

COLOPHON

Editor Prof. dr. Richard Dekhuijzen
Radboud Universitair Medisch Centrum, Nijmegen

Editorial Manager Lisa Colson
Editorial Co-ordinators Bas Braakman, MSc.
Dr. Rose-Minke Schure
Executive Publisher Rene Draper, MSc.
Medical Writer Dr. Michiel Tent
Production Manager Desiree Heijl
Graphic Design MOOZ grafisch ontwerp

MEDICOM
MEDICAL PUBLISHERS

Postal address
Medicom Medical Publishers
PO Box 90
Zipcode 3740 AB
City Baarn
Country The Netherlands

Head Office
Medicom Medical Publishers
Faas Eliaslaan 5
3742 AR Baarn
The Netherlands

Telephone +31 85 4012 560
Fax +31 85 4012 569
E-mail publishers@medicom.nl

ISSN 2458-8765 17:8

Letter from the Editor

Prof. Richard Dekhuijzen

Dear Reader,

This year's International Congress of the American Thoracic Society (ATS) was again the place to be to get the most recent update in important areas of pulmonary diseases.

There are increasing data on the effects and safety of biologicals in very severe asthma. Modulators of IL-5 activity show important clinical effects. Also of interest are the new data on the effects of bronchial thermoplasty.
The main changes in the GOLD 2017 recommendations for COPD include a new way to categorise patients by splitting level or airflow limitation and levels of complaints and exacerbations. Also, the upcoming data on LABA/LAMA combinations and when they are preferred to LABA/ICS combinations were presented. The addition of home non-invasive ventilation to home oxygen therapy significantly prolonged time to readmission or death for patients with persistent hypercapnia following a life-threatening exacerbation.

Encouraging results of inhaled ciprofloxacin in non-cystic fibrosis bronchiectasis and chronic Pseudomonas aeruginosa infection were presented. Also, an auxiliary benefit of the CFTR regulator ivacaftor in CF was revealed. A study in patients (homozygous for the F508del gene) who have very severe CF, indicates that they too seem to benefit from treatment with lumacaftor/ivacaftor.
Besides the topics indicated above, interesting findings regarding lung cancer and pulmonary hypertension were presented. While you may not have been able to experience these aspects of the ATS yourself, this report outlines the most significant advancements discussed and practical advice disseminated. So, we hope that you will enjoy reading this Conference Report!

Kind Regards,
Prof. Richard Dekhuijzen

Biography

Prof P.N. Richard Dekhuijzen (Amsterdam, the Netherlands, 1956) is Professor of Pulmonology at the Radboud university medical center in Nijmegen, the Netherlands. His specific area of research interest is in asthma, COPD and inhalation technology.
He studied Medicine at the Free University Amsterdam and completed his training in Pulmonology at the Onze Lieve Vrouwe Gasthuis in Amsterdam and in the Academic Hospital Nijmegen. In 1989 he finished his PhD thesis on training of the respiratory muscles in COPD, followed by a PhD thesis on steroid-induced myopathy of the diaphragm in 1994 at the Catholic University Leuven, Belgium.
He is author/co-author of over 320 peer-reviewed papers and many text book chapters on Respiratory Medicine. Until 2016, he was chair of the Department of Pulmonary Diseases and chair of the Heart-Lung Centre Nijmegen, and he was head of the department of Cardiology in 2008-2010. Until 2016 he was chair of the Medical Staff of the Radboudumc. Currently, he is chair of the Medical Ethical Committee of the Radboudumc.

Asthma

Asthma is both easy and hard to treat. It is easy to treat because the vast majority of patients with asthma require little medication for a lot of benefit. It becomes hard to treat when asthma control is not obtained with the first choice of a controller; usually treatment then needs to be stepped up [1]. Choices are limited, but now extend into the use of biologics. Consequently, severe asthma and biologics took centre stage at the ATS 2017 meeting. In the past few years, monoclonal antibodies that target key cells and mediators driving inflammatory responses in the asthmatic lung, have been developed and tested as treatment of more severe types of asthma. Significant clinical effects are most likely in carefully selected patient populations that take asthma phenotypes into account.

Benralizumab reduces oral corticosteroid use in severe asthma

The anti–interleukin-5 receptor alpha monoclonal antibody benralizumab significantly reduced add-on oral corticosteroid (OCS) dosages by a median of 75% compared with placebo (25%) in the ZONDA trial [2]. The outcomes were simultaneously published in the NEJM [3].

The ZONDA trial was specifically designed to evaluate OCS dosage-sparing effects of benralizumab in patients with severe asthma. Patients with uncontrolled asthma despite high-dosage inhaled corticosteroids plus long-acting β2-agonists (ICS/LABA) may need add-on oral OCS treatment to manage symptoms. However, "frequent or long-term use of systemic corticosteroids can lead to potentially life-threatening complications, including osteoporosis, diabetes, cardiovascular disease and adrenal suppression," said lead author Dr. P. Nair (Hamilton, Canada). Benralizumab induces direct, rapid, and nearly complete depletion of eosinophils. In phase 3 trials benralizumab significantly reduced annual exacerbation rates for patients with severe, eosinophilic asthma.

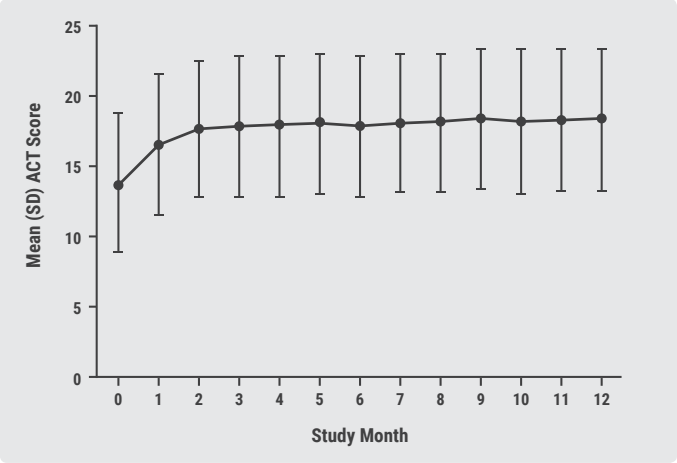
Participants of the ZONDA trial were 271 patients aged 18–75 years with severe, uncontrolled asthma (eosinophil counts ≥150 cells/μL) receiving high-dosage ICS/LABA and OCS (7.5–40 mg/d). In an initial 2- to 8-week run-in/optimisation period their OCS was titrated to the minimum effective dosage without losing asthma control. Eligible patients were then randomised for 28 weeks to benralizumab 30 mg SC every 4 weeks (Q4W) or every 8 weeks (Q8W) or placebo every 4 weeks. The treatment period comprised a 4-week induction phase (optimised OCS dosage maintained), a 20-week reduction phase (OCS dosage reduced), and a final 4-week maintenance phase. Primary efficacy endpoint was percentage reduction from baseline in final OCS dosage, while maintaining asthma control, at week 28.

Of 220 patients 207 (94.1%) completed treatment. Benralizumab significantly reduced final OCS dosages by a median of 75% with the Q4W and Q8W regimens ($p<0.001$) compared with placebo (25%). The odds of a reduction in OCS dosage (Q4W and Q8W, respectively) were 4.09 and 4.12 times greater ($p<0.001$) than with placebo. Benralizumab also significantly reduced annual asthma exacerbation rates by 55% ($p=0.003$) and 70% ($p<0.001$) compared with placebo, despite reduction in OCS dosages in the active treatment groups. FEV1 did not significantly differ with placebo at the end of the study, but it did not decline. About 20% of patients did not respond to benralizumab. "It is possible that these patients' asthma was not critically dependent on the eosinophils, or they may not have had significant airway eosinophil activity," Dr. Nair commented. AEs were numerically lower in the benralizumab Q4W and Q8W groups vs. placebo: 68.1% and 75.3% vs. 82.7%. No major AEs were related to benralizumab use.

Quality of life

In pooled analyses of two phase 3 trials, benralizumab-treated patients demonstrated nominally statistically significant improvement in activity impairment for patients with severe, uncontrolled asthma with baseline blood eosinophil counts ≥300/μL when compared with placebo [4]. Participants received benralizumab 30 mg either every 4 weeks (Q4W, n=515) or every 8 weeks (Q8W, first 3 doses Q4W, n=501) or placebo Q4W (n=514) for 48 weeks. Patients treated with the Q8W dosing regimen had statistically significant reductions in all three aspects of activity impairment (asthma-related activity limitations, the need to pace themselves during activities, and activity avoidance) and in patient-perceived feelings of stress and tiredness compared with placebo. These results are consistent with previously published findings that

Figure 1 ACT Scores from baseline to month 12



ACT= asthma control test; SD= standard deviation

benralizumab treatment both reduces exacerbations and asthma symptoms, and improves asthma-specific health-related quality of life (HRQoL).

Early asthma symptom control improves with omalizumab

After initiating omalizumab, adult and adolescent patients reported early allergic asthma symptom control improvement, which continued through 12 months of treatment in the PROSPERO study [5].

The main objective of this study was to gain insight in the way omalizumab affects patient-reported asthma symptom control and HRQoL, and in the treatment effectiveness as perceived by investigators and patients. PROSPERO was a US-based, multicentre, 48-week prospective single-arm open-label registry of patients of ≥12 years old with allergic asthma initiating treatment with omalizumab. Participants completed the following patient-reported outcome assessments: Asthma Control Test (ACT, baseline and monthly), Asthma Quality of Life Questionnaire (AQLQ+12, baseline and every 6 months), Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ, baseline and study end), and the Global Evaluation of Treatment Effectiveness (GETE, study end).

A total of 806 patients were enrolled (63.5% female, 70.3% white, mean age 47.3 years). ACT score, minimally important difference = 3) increased by 4.4 points from a mean 13.9 at baseline; the improvement began at month 1, continued through month 3, and reached a plateau thereafter.

Overall AQLQ+12 scores, minimally important difference = 0.5) increased from 4.0 at baseline to 5.3 after 12 months. Individual AQLQ-12 domain scores improved in a similar way. For activities, mean values at baseline, month 6, and month 12 were 4.3, 5.3 and 5.5, respectively; for emotions 3.6, 5.1, and 5.2; for symptoms 3.9, 5.2, and 5.3; and for environment 3.9, 5.0, and 5.1. Overall MiniRQLQ score decreased from 2.7 points at baseline to 1.7 at 12 months. Individual MiniRQLQ mean domain scores changed similarly: activity limitations decreased from 2.7 to 1.6, practice problems from 3.0 to 2.0, nose symptoms from 2.7 to 1.8, eye symptoms from 2.3 to 1.4, and other symptoms from 3.0 to 1.9.

At study end, most patients and investigators rated treatment effectiveness as either 'Good' or 'Excellent'. Based on GETE scores, effectiveness was 'Good' according to 50.2% of investigators and 47.0% of patients, and 'Excellent' according to 26.2% and 29.2%, respectively.

Protective effect

A large post-hoc analysis of data from two clinical studies (the EXTRA and INNOVATE) extended prior findings in children and suggested that omalizumab may provide a protective effect on lung function in adolescents and adults who experience asthma exacerbations [6].

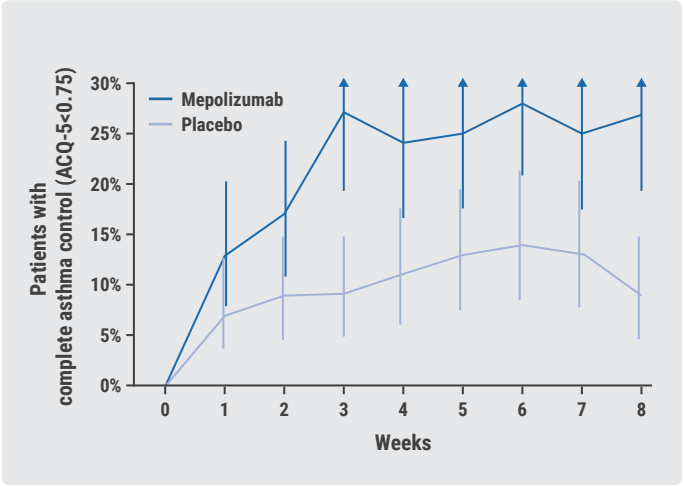
A total of 1090 adolescents and adults were included in this analysis. Baseline patient characteristics in the pooled population were generally similar, with a population that was mostly female, white and were between 12-75 years old, with an average age of 44 years. Baseline mean FEV1 percent predicted (ppFEV1) was lower in the omalizumab exacerbators (61.5) and placebo exacerbators (61.5) than omalizumab non-exacerbators (65.2) and placebo non-exacerbators (64.8). Omalizumab exacerbators showed greater improvement in ppFEV1 at week 12 and maintained this improvement in ppFEV1 compared with placebo exacerbators through week 28, with lung function values similar to omalizumab non-exacerbators. Omalizumab non-exacerbators demonstrated statistically significant improvement in ppFEV1 at week 12 compared with placebo non-exacerbators, which was maintained through week 28.

Controlling severe eosinophilic asthma with mepolizumab

Among patients with uncontrolled severe eosinophilic asthma, mepolizumab significantly increased the odds of achieving complete asthma control at 32 weeks in the MENSA study, despite a high placebo response [7].

In this post-hoc analysis of results from the MENSA study, asthma control was assessed by the Asthma Control Questionnaire-5 (ACQ-5). MENSA enrolled 576 patients with severe asthma, ≥12 years of age receiving high-dose inhaled corticosteroids (ICS) plus additional controller(s), with a history of ≥2 exacerbations in the previous year and an

Figure 2 Uncontrolled patients at baseline that achieve Asthma Control



eosinophilic phenotype. This type of patient represents 3-5% of American asthma patients. Patients were evaluated who received mepolizumab 100 mg SC or placebo every 4 weeks. Complete Control, partial control and uncontrolled asthma were defined by ACQ-5 scores of <0.75, 0.75 - <1.5, and ≥1.5 respectively. At baseline, 67% of patients in both groups reported their asthma to be uncontrolled. After 32 weeks of treatment, 57% and 45% of patients in the mepolizumab and placebo groups, respectively, had an improvement of asthma control that was clinically important, which was defined as an improvement of ≥0.5 in ACQ-5 score. Of patients with uncontrolled asthma, 27% versus 9% reported complete asthma control (OR 4.17); 52% versus 31% of patients reported complete or partial control.

The authors note that the majority of severe eosinophilic asthma patients in the MENSA study were uncontrolled at baseline, despite treatment with high dose ICS and a second controller. Among these patients mepolizumab significantly increased the odds of achieving complete asthma control at 32 weeks compared to placebo. Additionally, of the uncontrolled patients at baseline more than half on mepolizumab were controlled or partially controlled (52%) at the end of the study compared to 31% in the placebo group. The high placebo effect may be accounted for by the good standard of care the placebo group received.

Real world clinical setting

In a real world clinical setting, about 60% of patients with high blood eosinophils achieved a measurable improvement in asthma outcomes over 3 or more months of treatment with mepolizumab. This was the result of a single-centre chart review of 30 patients with blood eosinophil counts >300/ml, and treated with mepolizumab for 3 months or more [8]. Their mean pre-treatment and pre-bronchodilator ppFEV1 was 76%. The average treatment time with mepolizumab was 5.4 months. Eight (27%) patients had complex eosinophilic asthma, and another 8 were on other immunosuppressants, including azathioprine. At follow up, 11 (37%) patients improved ppFEV1 by >5%, 7 (23%) reduced OCS dose by >50%, and 9 (30%) had no asthma exacerbations. Twelve patients (40.0%) were non-responders, 10 (33.3%) moderate responders, and 8 (26.7%) successful responders. Six patients (20%) had stopped treatment, 3 due to worsening of asthma, 3 due to AEs (2 with local reaction, 1 with transient ischemic attack).

Tiotropium add-on effective in children with severe asthma

Tiotropium added to maintenance therapy improved lung function and lowered exacerbation risk in children and adolescents with severe symptomatic asthma, irrespective of IgE levels and blood eosinophil counts. This was the conclusion of a pooled analysis of two 12-week, phase 3, randomised, double-blind, placebo-controlled, parallel-group trials in patients aged 6-17 years with severe symptomatic asthma [9]. These trials were called VivaTinA-asthma and PensieTinA-asthma. The goal was to see if tiotropium Respimat® add-on to ICS and other controllers is effective in these patients, irrespective of potential allergic asthma status. Patients received once-daily tiotropium, 2.5 µg or 5 µg, or matching placebo, as add-on to ICS (>400 µg budesonide/equivalent daily) plus another controller medication, or ICS (200-400 µg or 200-800 µg) plus two other controller medications. Primary endpoint was a change from baseline after 12 weeks in peak forced expiratory volume in 1 second (FEV1) within 3 hours post-dose.

A total of 793 patients were randomised. The addition of tiotropium improved peak FEV1 at week 12 by 64 mL for the 2.5 µg dose (p=0.027) and by 117 mL for the 5 µg dose (p<0.001) compared with placebo. FEV1 trough improved by 64 mL for the 2.5 µg dose (p=0.062) and by 71 mL for the 5 µg dose (p=0.040). Analysis of time to first asthma exacerbation showed hazard ratios (HRs) <1 for tiotropium versus placebo, demonstrating that both tiotropium doses were effective versus placebo, irrespective of baseline IgE levels and blood eosinophil counts.

Similar results were obtained in a pooled analysis of two 48-week, phase 3, randomised, double-blind, placebo-controlled, parallel-group trials in patients (6-17 years) with moderate, symptomatic persistent asthma [10]. Patients received once-daily tiotropium or placebo, as add-on to inhaled corticosteroids (RubaTinA-asthma study)

or budesonide (CanoTinA-asthma study). Adjusted mean differences in peak FEV1 were 159 mL for the 2.5 µg dose, and 168 mL for the 5 µg dose versus placebo (p<0.0001 for both). Adjusted mean differences in trough FEV1 were 105 and 118 mL, respectively. First author of this analysis, Dr. M. Vandewalker from Columbia in Missouri, noted that the severity of asthma did not serve as a marker for better response to the tiotropium add-on, nor that the phenotype of the disease had any impact on treatment with tiotropium. He called the side effect profile of tiotropium "excellent", with AE rates similar to placebo.

Bronchial thermoplasty relatively safe and effective

Bronchial thermoplasty is relatively safe and effective in high-risk severe asthma patients [11]. A prospective, randomised trial in patients with high risk severe asthma is necessary to confirm the retrospective data from 4 pulmonary services of consecutive bronchial thermoplasty cases. They were performed in individuals not meeting AIR2 study enrolment criteria.

A total of 179 procedures were performed by the 4 centres between June 2010 and August 2016. The 147 patients who did meet AIR2 enrolment criteria were aged 54.3 years on average with a range of 18-86 years, and had a mean BMI of 33.6 kg/m2. Exclusion criteria of AIR2 included FEV1 <60% in 75 patients (51%), age >65 years in 31 patients (21%), systemic corticosteroid use >10 mg daily in 42 patients (29%), frequent exacerbations in 79 patients (54%), life threatening asthma in 38 patients (26%) and any immunosuppressive medications in 4 patients (3%). Safety data were available for 3 centres (n=126). Post procedure hospital observation occurred in 13.7% of patients. Peri-procedural complications occurred in 6 subjects (5%). Treatment period outcomes included 36 hospitalisations in 24 patients (21%) and 44 corticosteroid boosts independent of hospitalisations in 36 patients (28.8%) during this 12 weeks period, compared to hospitalisations in 16 subjects (8.4%) during the treatment period in AIR2. Moderate or severe AEs occurred at a rate of 0.56 events/bronchoscopy, which is similar in the AIR2 trial. Pre- and post-treatment efficacy outcomes were available for 3 centres (n=88) and included the following:

Table 1 Differences between cannabis users and non-users

	Previous Year	Post-treatment period†	p-value
Oral corticosteroid dose	9.6 ± 15.6 (n=83)	5.8 ± 13.3 (n=64)	0.04
Using oral corticosteroids	40/83 (48.2%)	21/64 (32.8)	0.06
Omalizumab use	22/82 (26.8%)	12/59 (20%)	NS
Exacerbation rate (event rate/year) ‡	4.2 ± 4.4 (n=74)	2.5±3 (n=59)	0.0052
Hospitalisation rate ‡	1.53 ± 2 (n=71)	0.75 ± 2 (n=59)	0.0003
Total event rate/year‡^	5.4 ± 5.4 (n=78)	3.26 ± 4.1 (n=60)	0.001
Pre BD FEV1 % predicted	57.6 ± 17.7% (83)	59.17 ± 18.6 (n=63)	0.66

*Mean ± SD. † Different N=88 because of missing data, ‡ post treatment period exacerbations and hospitalisations were measured independent of the 6 weeks post procedure and annualised. ^Total event rate include exacerbations and hospitalisations.

References

1. Von Mutius E and Drazen JM. Choosing asthma step-up care. N. Engl. J. Med. 2010;362(11):1042–3.
2. Nair P, et al. Benralizumab Significantly Reduced Oral Corticosteroid Dosages and Asthma Exacerbation Rates for Patients with Severe, Uncontrolled Asthma: Results of the ZONDA Phase III Trial. ATS 2017, A4678.
3. Nair P, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med. 2017 May 22. doi: 10.1056/NEJMoa1703501. [Epub ahead of print]
4. O'Quinn S, et al. Improvement in Patient-Reported Activity Impairment, Stress, and Tiredness in Patients with Severe, Uncontrolled Asthma with Eosinophilic Inflammation: Pooled Results from Two Phase III Trials of Benralizumab. ATS 2017, A3188.
5. Carr TF, et al. Improvements in Asthma Symptom Control, Quality of Life, and Perception of Treatment Effectiveness After Omalizumab Initiation in Adolescents and Adults: Results from a 48-Week, Observational Study. ATS 2017, P998.
6. Busse WW, et al. Asthma Exacerbations and Lung Function Decline in a Pooled Analysis of Adolescents and Adults From Randomised Controlled Trials of Omalizumab. ATS 2017, A4676.
7. Llanos-Ackert J, et al. Asthma Control in Patients with Severe Eosinophilic Asthma Treated with Mepolizumab. ATS 2017, A3192.
8. Zhang P, et al. Real World Effectiveness and Safety of Anti-IL-5/Mepolizumab in an Academic Severe Asthma Clinic. ATS 2017, A3187.

COPD

The addition of home non-invasive ventilation to home oxygen therapy significantly prolonged time to readmission or death for patients with persistent hypercapnia following a life-threatening exacerbation, as was communicated in a late-breaking and possibly 'game-changing' study. Furthermore, the main changes in the GOLD 2017 recommendations for COPD were well explained; for example, why LABA/LAMA combinations are now preferred to LABA/ICS combinations. A few of the countless studies of LABA/LAMA combinations and other therapies are presented here.

New GOLD recommendations for COPD put into perspective

In the last ATS session, the updated GOLD (Global Initiative for the Diagnosis, Management and Prevention of Chronic Obstructive Lung Disease) recommendations on COPD were elucidated [1]. A revised COPD definition, (non-)pharmacological treatment, and comorbidities were discussed among the topics.

The new recommendations replace the 2011 version. The definition of COPD has been broadened to include the impact of chronic respiratory symptoms and the role of airway abnormalities in the development of COPD. The full definition (changes in cursive) now reads: "chronic obstructive pulmonary disease (COPD), a common, preventable, and treatable disease, is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases." Chronic respiratory symptoms may exist without spirometric changes; many patients (usually smokers) may have structural evidence of COPD without airflow limitation.

COPD assessment has been refined to separate the spirometric assessment from symptom evaluation. "Spirometry is not enough anymore to categorise patients", as Dr. C.F. Vogelmeier (Marburg, Germany) explained. ABCD groups are now proposed to be derived from patient symptoms and their history of exacerbations, in the following manner:

Group A	Low symptom severity, low exacerbation risk
Group B	High symptom severity, low exacerbation risk
Group C	Low symptom severity, high exacerbation risk
Group D	High symptom severity, high exacerbation risk

Prevention and treatment recommendations

Smoking cessation remains the most important prevention and 'treatment' strategy for COPD. Offer nicotine replacement, cessation counselling, and pharmacotherapy (varenicline, bupropion or nortriptyline). Due to insufficient evidence, the use of e-cigarettes is not supported. Influenza and pneumococcal vaccinations are recommended.

There is a stronger recommendation of short-acting beta-agonists and short-acting muscarinic antagonists (SABA/SAMA) combined, probably being superior to SABD monotherapy. The pharmacologic treatment algorithm has changed in several ways. LABA/LAMA combinations are preferred to LABA/ICS combinations as a mainstay of treatment, because LABA/LAMAs result in greater bronchodilation. These are the recommendations for each of the groups:

Group A	Start with single bronchodilator (short- or long-acting), escalate to alternative class of bronchodilator if necessary.
Group B	Start with LABA or LAMA, escalate to LABA/LAMA if symptoms persist.
Group C	Start with LAMA, escalate to LABA/LAMA (preferred) or LABA/ICS if exacerbations continue.
Group D	Start with LABA/LAMA (preferred) or LAMA monotherapy, escalate to LABA/LAMA/ICS (preferred) or try LABA/ICS before escalating to LAMA/LABA/ICS if symptoms persist or exacerbations continue; the PDE4 inhibitor roflumilast and/or a macrolide may be considered if further exacerbations occur with LABA/LAMA/ICS.

Non-pharmacological therapies have also been comprehensively reviewed, including pulmonary rehabilitation, exercise training, oxygen therapy, vaccinations, interventional bronchoscopy, surgery, and palliative care.

The importance of co-morbid conditions in managing COPD, such as cardiovascular disease, osteoporosis, gastroesophageal reflux, obstructive sleep apnea, and mood disorders, is also addressed. "Look for comorbidities," advised Prof. L.M. Fabbri (Modena, Italy). "Usually they are there, and usually they have not been diagnosed."

Home non-invasive ventilation reduces readmissions

Among patients with persistent hypercapnia following an acute exacerbation of COPD, adding home non-invasive ventilation (NIV) to home oxygen therapy prolonged the time to readmission or death within 12 months. This is the main result of the 'game-changing' randomised HOT-HMV trial,

presented at the ATS meeting and simultaneously published in the JAMA [2].

The use of NIV in COPD has been controversial for decades; the only current treatment for these patients is oxygen therapy. In the randomised clinical HOT-HMV trial, 116 patients with persistent hypercapnia ($Paco_2$ >53 mmHg) were randomised to home oxygen alone (median oxygen flow rate, 1.0 L/min) or to home oxygen plus home NIV (median oxygen flow rate, 1.0 L/min). Sixty-four patients (28 in home oxygen alone and 36 in home oxygen plus home NIV) completed the 12-month study period. Adherence was reasonably good: 4.7 hours per night at 6 weeks and 7.6 hours per night at 12 months. There were 18 cross-overs from the control group to the experimental group, but 17 of these occurred after the primary endpoint had been measured. The median time to readmission or death was 4.3 months, with an interquartile range = 1.3-13.8 months in the home oxygen plus home NIV group, vs. 1.4 months (interquartile range = 0.5-3.9 months) in the home oxygen alone group. The adjusted HR was 0.49 (95% confidence interval (CI), 0.31-0.77; p=0.002). The 12-month risk of readmission or death was 63.4% vs. 80.4% respectively, with an absolute risk reduction of 17.0% (95% CI, 0.1%-34.0%). At 12 months, 16 (28%) vs. 19 (32%) patients had died in the respective groups. The authors conclude that addition of home NIV to home oxygen should be considered if patients with severe COPD have persistent hypercapnia after a life-threatening exacerbation.

Furoate/vilanterol reduces COPD relapses in patient subgroups

Therapy with fluticasone furoate/vilanterol (FF/VI) reduced the annual rate of moderate/severe exacerbations across a range of patient subgroups in the SLS COPD study [3]. This is an open-label randomised controlled trial that aims to guide COPD treatment choices by generating effectiveness and safety data in UK primary care, in a large, real-world population of patients with COPD in routine primary care. All general practitioners in Salford participated, plus over 130 pharmacists. Unlike in clinical efficacy trials, the percentage of excluded participants was low. It is the first study of its kind to explore the effectiveness and safety of a pre-licenced drug versus existing maintenance therapy (usual care, UC). The annual rate of moderate/severe exacerbations in the primary effectiveness analysis population was significantly reduced with FF/VI therapy by 8.41% (p=0.025) [4]. These results, published in 2016, were supplemented with effectiveness outcomes according to patient subgroups.

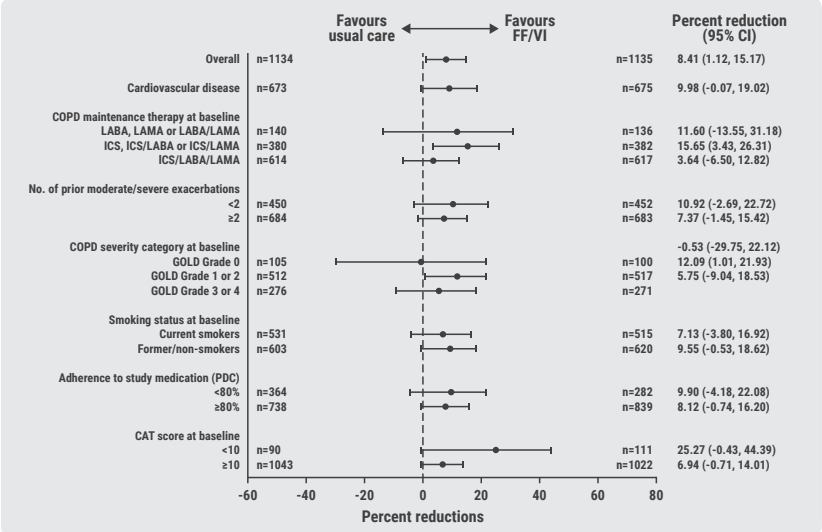
Participants were treated with ICS, LABA or LAMA either alone or in combination, and were aged ≥40 years, had a general practitioners' diagnosis of COPD and ≥1 COPD exacerbation in the last 3 years. They were randomised to either initiate once-daily inhaled FF/VI (100/25 µg) or to continue on their UC. Randomisation was stratified by baseline COPD maintenance therapy and exacerbation history in the previous year.

A total of 2,269 (80.98%) patients formed the primary effectiveness analysis population. Reductions in the annual rate of moderate/severe exacerbations in this population were consistently observed in patient subgroups. The pre-defined subgroups were: baseline COPD maintenance therapy, COPD severity (GOLD) at baseline, exacerbation history, smoking status, adherence to study medication (proportion of days covered was used as a measure of treatment adherence) and CATTM score at baseline. Similar findings were observed in the intention-to-treat population and in patients receiving fluticasone propionate/salmeterol at baseline (10.12% reduction in the number of exacerbations). The effectiveness of FF/VI on reduction in exacerbations in predefined subgroups was consistent with the findings of the overall study population.

Safety findings in the Salford Study

Analyses of safety findings in SLS COPD were also presented. In SLS COPD, there was a higher incidence of SAEs and fatal SAEs compared to efficacy trials [5]. This is likely due to enrolment of patients with multiple and sometimes severe or undiagnosed comorbidities. Differences in causality rates associated with FF/VI versus UC may relate to: the open-label nature of the study, FF/VI was being unlicensed at study

Figure 3 Percent reductions in the number of exacerbations in the FF/VI group versus UC



commencement (and when licensed, was a new medicine and unfamiliar to investigators), the SAE detection method (electronic health record), patients in the UC arm continuing on their pre-study medication at the point of randomisation. The open-label design and conduct of SLS COPD, enrolling patients with many comorbidities and using EHRs for real-time safety monitoring, sets a precedent for the evaluation of future treatments.

With regard to pneumonia SAE incidence, FF/VI treatment was non-inferior to UC [6]. The risk of pneumonia with FF/VI seems similar to other ICS containing treatments in the broad population of primary care patients in routine clinical practice.

Indacaterol/glycopyrrolate in moderate-to-severe COPD

With an increased importance attached in the GOLD recommendations to LAMA/LABA (in groups B, C and D), one of the combinations that was extensively reviewed at the ATS meeting was indacaterol/glycopyrrolate. Three pooled analyses were presented of the FLIGHT1 and FLIGHT2 studies. FLIGHT1 and FLIGHT2 were replicate, 12-week, multicentre, double-blind, parallel-group studies in patients with moderate-to-severe COPD which demonstrated the efficacy and safety of indacaterol/glycopyrrolate compared with its monocomponents and with placebo [7].

One of the pooled analyses indicate that twice-daily indacaterol/glycopyrrolate can be an effective treatment option in reducing the use of rescue medication at night and nocturnal symptoms [8]. After 12 weeks, indacaterol/glycopyrrolate showed significant reduction in the mean nocturnal number of rescue medication puff use, when compared with placebo: least squares mean treatment difference was -0.50 ($p<0.001$). The percentage of nights with no awakenings significantly increased with indacaterol/glycopyrrolate, the least squares mean treatment difference was 7.7 ($p<0.001$).

A second pooled analysis presented the efficacy of indacaterol/glycopyrrolate on time-weighted mean FEV1 [9]. Versus placebo, it demonstrated significant improvement in standardised area under the curve from 0-4, 0-6, 4-8 and 8-12 hours on day 1 and at week 12 (all p-values <0.001). On day 1, the treatment difference versus placebo ranged from 0.159 to 0.179 L, and at week 12 from 0.223 to 0.281 L.

A third pooled analysis showed that a significantly higher proportion of patients achieved superior bronchodilation (≥200 mL improvement in FEV1 from baseline) with twice-daily indacaterol/glycopyrrolate versus placebo [10]. At 5 minutes post-morning dose on day 1, this proportion was 18% vs. 2.1%. Similar results were observed for trough FEV1 at day 2 (47.4% vs. 7.6%) and day 86 (51.6% vs. 12.1%) (all p-values <0.001)

Lung function data from the randomised long-term safety study FLIGHT3 showed a consistently superior improvement in lung function of twice-daily indacaterol/glycopyrrolate 27.5/15.6 mcg versus once-daily indacaterol 75 mcg over 52 weeks [11]. In pre-dose trough FEV1, treatment difference was 80 mL ($p<0.001$). Improvement in 1-hour post-dose FEV1 was also consistently superior throughout 52 weeks, with a treatment difference of 108 mL ($p<0.001$).

Other long-acting bronchodilator therapies

- Fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) via a single ELLIPTA® inhaler was associated with greater improvements in symptom scores, dyspnoea, and rescue medication use, compared with budesonide/formoterol (BUD/FOR) via the Turbuhaler® [12]. These patient reported preferences were part of the phase 3 trial FULFIL trial. The intent-to-treat population included 1810 participants, aged ≥40 years with advanced, symptomatic COPD at risk of exacerbations. Over 24 weeks, FF/UMEC/VI produced significantly greater reductions from baseline in mean E-RS: COPD (Evaluating Respiratory Symptoms in COPD) score ($p<0.001$). The OR of response versus non-response was significantly in favour of FF/UMEC/VI (odds ratio (OR) 1.59–1.76). Similar results were observed for the E-RS: COPD subscales of breathlessness/cough, and sputum/chest symptoms. FF/UMEC/VI demonstrated statistically significant improvements in Transitional Dyspnoea Index at week 4: 1.78 versus 1.29, and at week 24: 2.29 versus 1.72. Over weeks 1–24, FF/UMEC/VI demonstrated a statistically significant reduction in rescue medication use ($p<0.001$ for all above mentioned comparisons). A total of 52% of participants preferred the ELLIPTA inhaler, 15% the Turbuhaler.
- Glycopyrrolate/formoterol fumarate (GFF), a novel, long-acting LAMA/LABA fixed-dose combination delivered by metered dose inhaler decreased the risk of patients experiencing a first clinically important deterioration (CID) or sustained CID compared with placebo and monocomponent MDIs [13]. This was the main conclusion of a pooled analysis of the phase 3 studies PINNACLE-1 and -2. This finding suggests broader benefits of GFF metered dose inhaler on airway stability and prevention of disease deterioration for patients with COPD. It is important to understand whether treatments can prevent disease deterioration in patients with COPD. CID is an exploratory composite endpoint.
- There was a low incidence of potential age-related effects in the 1-year TONADO studies, which included a considerable proportion of elderly patients with pre-existing disease and co-morbidity [14]. The TONADO studies were two replicate

phase 3 trials that assessed tiotropium/olodaterol (T/O) 2.5/5 and 5/5 mcg, compared to the monocomponents T 2.5 and 5 mcg, and O 5 mcg (all via Respimat® inhaler) in patients with moderate to very severe COPD. Overall, the proportion of patients with AEs appeared to increase with increasing age. However, there was no differential increase or decrease in AE incidence with age comparing T/O versus T or O alone, and T/O was safe and well tolerated at all ages.

Investigational drug-device combination SUN-101

There are no approved nebulized, LAMAs currently available for use in COPD. SUN-101 is an investigational drug–device combination of an inhaled LAMA (glycopyrrolate) administered by an innovative eFlow® closed-system nebulizer. GOLDEN 3 and GOLDEN 4 both phase 3, randomised, double-blind, placebo-controlled studies, SUN-101/eFlow demonstrated statistically significant, clinically important improvements in pulmonary function and was generally well-tolerated in a real-world COPD population. Improvements in lung function were also observed in SUN-101 patients with and without background LABAs [15]. These data support nebulized SUN-101 as a potential maintenance therapy in patients with moderate-to-very-severe COPD.

In GOLDEN 3 and 4, 653 and 640 patients, aged ≥40 years with a ≥10 pack-year smoking history and moderate-to-very-severe COPD, were randomised to receive placebo, or SUN-101 (25 or 50 mcg BID). The primary endpoint was change from baseline at week 12 in trough FEV1. ICS use was 29%. Both doses of SUN-101 led to statistically significant, clinically important improvements in the placebo-adjusted change from baseline in trough FEV1 and forced vital capacity (FVC) (Table 2). There were also statistically significant improvements in St George's Respiratory Questionnaire (SGRQ) compared with placebo, but no effect on rescue medication use. The combined overall incidence of treatment-emergent adverse events (TEAEs) was lower with SUN-101 25 and 50 mcg than with placebo (43.4% and 50.7% versus 52.3%). The most frequent TEAEs were COPD, cough and dyspnoea. Discontinuations due to TEAEs were numerically highest in the placebo group.

The safety results of the 12-week pivotal studies were consistent with the safety findings from the GOLDEN 5 study. In a real-world population, SUN-101 was generally well-tolerated, with an acceptable long-term safety profile [16]. The improvement in trough FEV1 persisted over 48 weeks. Improved lung function was seen in patients with and without background LABAs.

Table 2 Placebo-adjusted changes from baseline in trough FEV1 and trough FVC at week 12

Parameter		GOLDEN 3		GOLDEN 4	
		SUN-101 25 mcg BID N=217	SUN-101 50 mcg BID N=218	SUN-101 25 mcg BID N=214	SUN-101 50 mcg BID N=214
Trough FEV1 at week 12	LS Mean Difference ± SE	0.096 ± 0.019	0.104 ± 0.019	0.081 ± 0.020	0.074 ± 0.020
	95% CI	0.059, 0.133	0.066, 0.141	0.042, 0.120	0.035, 0.113
	Adjusted p-value	<0.0001	<0.0001*	0.0001	0.0002*
Trough FVC at week 12	LS Mean Difference ± SE	0.137 ± 0.031	0.133 ± 0.031	0.119 ± 0.031	0.093 ± 0.031
	95% CI	0.076, 0.197	0.072, 0.194	0.058, 0.180	0.033, 0.154
	Adjusted p-value	<0.0001	0.0002	0.0008	0.0101

*Unadjusted p-value; the primary comparison was 50 mcg vs. placebo for trough FEV1. All other reported p-values were adjusted for multiplicity using a gate-keeping procedure.
CI, confidence interval; EOS, end of study; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; LS, least squares; NS, not significant; SGRQ, St George's Respiratory Questionnaire.

References

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org
2. Murphy PB, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomised Clinical Trial. JAMA. 2017;317(21):2177-86.
3. Bakerly N, et al. Clinical Effectiveness of Fluticasone Furoate/Vilanterol (FF/VI): The Impact on Exacerbations in COPD Patient Subgroups of the Salford Lung Study (SLS COPD). ATS 2017, P1098.
4. Vestbo J, et al. Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice. N Engl J Med. 2016;375(13):1253-60.
5. Collier SD, et al. Interpretation of Safety Findings in Clinical Effectiveness Trials: Insights from the Salford Lung Study (SLS COPD). ATS 2017, P373.
6. Collier SD, et al. Serious Adverse Events of Pneumonia in Patient Subgroups of the Salford Lung Study Chronic Obstructive Pulmonary Disease (SLS COPD) Population. ATS 2017, P1151.
7. Mahler DA, et al. FLIGHT1 and FLIGHT2: Efficacy and Safety of QVA149 (Indacaterol/Glycopyrrolate) versus Its Monocomponents and Placebo in Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2015;192(9):1068-79.
8. Donohue JF, et al. Indacaterol/Glycopyrrolate Significantly Reduces Nocturnal Rescue Medication Use and Awakenings in Patients With Moderate-to-Severe COPD: Results from a Pooled Analysis of FLIGHT1 and FLIGHT2 Studies. ATS 2017, A5461.
9. Donohue JF, et al. Significant and Sustained Bronchodilation with Indacaterol/Glycopyrrolate Versus Placebo: Pooled Analysis of FLIGHT1 and FLIGHT2 Studies. ATS 2017, A5462.
10. Kerwin EM, et al. Indacaterol/Glycopyrrolate Is More Effective than Placebo in Improving FEV1 by ≥200 mL from Baseline in Patients with Moderate-to-Severe COPD: FLIGHT1/FLIGHT2 Pooled Analysis. A5463.
11. Mahler DA, et al. Improvement in Lung Function with Twice-Daily Indacaterol/Glycopyrrolate Versus Once-Daily Indacaterol in Patients with Moderate-to-Severe COPD: Results from the FLIGHT3 Study. ATS 2017, A5468.
12. Tabberer M, et al. Single Inhaler Triple Therapy (ICS/LAMA/LABA) in Patients with Advanced COPD: Patient Reported Symptom and Inhaler Preference Results from the FULFIL Trial. ATS 2017, P1100.
13. Rabe KF, et al. LAMA/LABA Glycopyrrolate/Formoterol Fixed-Dose Combination, Delivered Using a Novel MDI Co-Suspension™ Delivery Technology Reduces Risk of Clinically Important Deteriorations in COPD Versus Placebo and Monocomponent MDIs. ATS 2017, A3594.
14. Ferguson GT, et al. Long-Term Safety of Tiotropium/Olodaterol Respimat® in Elderly Patients with Moderate to Very Severe COPD in the TONADO® Studies. ATS 2017, A3587.
15. Kerwin EM, et al. Efficacy and Safety of SUN-101/eFlow® (Nebulized Glycopyrrolate) in Moderate-To-Very-Severe COPD: Results from the Glycopyrrolate for Obstructive Lung Disease Via Electronic Nebulizer (GOLDEN) 3 and 4 Studies. ATS 2017, A5464.
16. Ferguson GT, et al. Long-Term Safety of SUN-101/eFlow® in Moderate-to-Very-Severe COPD: Results from the Glycopyrrolate for Obstructive Lung Disease Via Electronic Nebulizer (GOLDEN) 5 Study. AS 2017, A3588.

Cystic Fibrosis and other Bronchiectatic Diseases

Encouraging results of inhaled ciprofloxacin in non-cystic fibrosis bronchiectasis (NCFB) and chronic Pseudomonas aeruginosa (PA) infection were presented. Also, an auxiliary benefit of ivacaftor in CF was revealed. And a study in patients (homozygous for the F508del gene) who have very severe cystic fibrosis (CF), indicates that they too seem to benefit from treatment with lumacaftor/ivacaftor.

Ivacaftor decreases inflammation in cystic fibrosis by reducing ADAM-17 activity

Irish researchers reported an auxiliary benefit of ivacaftor therapy in CF. They found that it reduces activity of the plasma membrane metalloproteinase ADAM-17, resulting in reduced inflammation [1]. The plasma membrane metalloproteinase ADAM-17, found on monocytes and neutrophils, cleaves membrane interleukin-6 receptor (mIL-6r) to its soluble form (sIL-6r). Complexes of sIL-6r bound to IL-6 in circulation can increase the inflammatory burden by activating endothelial cells.

Neutrophils isolated from CF patients demonstrated increased ADAM-17 activity (n=4), and decreased mIL-6r (n=3). In the plasma of CF patients, elevated levels of IL-6 (n=6), sIL-6r (n=6), and a complex of sIL-6r /IL-6 (n=6) were found. Neutrophils isolated from patients receiving ivacaftor therapy had reduced ADAM-17 activity (n=3) and increased mIL-6r (n=5). Furthermore, ivacaftor therapy decreased plasma levels of IL-6 (n=6) and sIL-6r (n=6).

These results demonstrate for the first time that reduced plasma membrane cholesterol in CF neutrophil membranes increases ADAM-17 activity and circulating levels of the sIL-6r/IL-6 complex, further augmenting inflammation.

Ivacaftor/lumacaftor in severe cystic fibrosis

In CF patients homozygous for the F508del gene with very severe disease, treatment with lumacaftor/ivacaftor led to a significant improvement in Six Minute Walk Test Distance (6MWT) [2]. This result was evident by 4 weeks (89.6m) and continued to improve at 12 weeks (110.6 m) (p=0.03).

This treatment had already been shown to improve lung function and reduce exacerbations in patients with FEV1 >40% predicted. However, the impact of lumacaftor/ivacaftor on patients with severe airflow obstruction is not well documented, since they were excluded from these trials. The researchers recruited 9 adult patients, mean age 30.4 years, all with FEV1 <40% predicted when stable on optimal therapy. At baseline subjects had very severe lung disease with mean FEV1 33.7% (6.7) and a 6MWT distance of 435 m. There was no significant improvement seen in FEV1, though the nitrogen multiple breath washout demonstrated a change in lung clearance index by 3.3, and a significant decline in functional residual capacity by 1.2 L after 12 weeks of treatment.

First in-human trial shows promising results ENaC inhibitor

AZD5634 is an inhibitor of epithelial sodium channels (EnaC) in development for the treatment of CF. In the first in-human trial, AZD5634 was well tolerated following inhaled administration in doses up to 1692 µg. Low systemic exposure and renal clearance suggests low risk of systemic AEs such as hyperkalaemia in future multiple dose studies [3].

ENaC play an important role in airway surface liquid homeostasis. In CF, ENaC hyperactivity contributes to depletion in epithelial airway surface liquid, resulting in reduced mucociliary clearance, recurrent infections and chronic lung disease. In Part A of a randomised, single blinded, placebo-controlled, single ascending dose sequential group study, healthy adult subjects were administered nebulised AZD5634 at one of 7 dose levels between 10 and 1692 mcg, at a ratio of 6:2 vs. placebo in each cohort. In Part B, 6 subjects received an intravenous dose of AZD5634 followed by an inhaled dose with an intervening wash-out period.

- AZD5634 was well tolerated at all doses and no serious AEs (SEAs) were reported.
- No trends toward increased blood potassium levels were observed at any dose level.
- Measureable plasma levels of AZD5634 were observed in 5 of the inhaled doses (81, 216, 648, 1296 & 1692 mcg) and increased with dose.
- AZD5634 appears to have a low steady state volume of distribution (<70 L) and moderate clearance (36 L/h).

- Bioavailability via the inhaled route was <10% over the measureable time course.
- Urinary levels of AZD5634 represented <5% of the IV dose over 48 hours with low renal clearance of parent material.

Inhaled ciprofloxacin in non-cystic fibrosis bronchiectasis and chronic PA infection

In a 48-week trial, ARD-3150 was associated with a significant reduction in exacerbations in patients with NCFB and chronic PA infection [4]. ARD-3150 significantly reduced sputum PA density without attenuation of antibiotic activity during each treatment cycle. Treatment was safe and well tolerated.

ARD-3150 is an inhaled formulation of ciprofloxacin containing liposome encapsulated ciprofloxacin 150 mg / 3 mL and free ciprofloxacin 60 mg / 3 mL. A pooled analysis was presented of 2 identical multi-national, randomised, double blind, placebo-controlled trials, ORBIT-3 and ORBIT-4. The 582 participants had NCFBE, chronic infection with PA and ≥2 PEs treated with antibiotics in the preceding year. Nebulized ARD-3150 or placebo was administered once daily for 6 cycles of 28 days on treatment, separated by 28 days off treatment.

ARD-3150 was associated with a statistically and clinically significant increase of over 3 months in median time to first exacerbation that required treatment with antibiotics. Furthermore, ARD-3150 was associated with a significant reduction in the annual exacerbation rate, regardless of antibiotic treatment, relative to placebo. Median time to first exacerbation did not differ significantly. ARD-3150 reduced sputum PA density significantly, while PA mean inhibitory concentrations remained stable during each treatment period. A PK substudy performed during the open label extension to ORBIT-3 showed sputum levels of ciprofloxacin several orders of magnitude above the minimum inhibitory concentration during the dosing periods, while serum levels were one order of magnitude lower than those achieved during high dose systemic ciprofloxacin therapy.

There were no significant differences in changes in FEV1, FVC or carbon monoxide diffusing capacity (DLCO) between the experimental and placebo groups. The rates of TEAEs and serious TEAEs were also similar.

Ciprofloxacin DPI in NCFB patients: RESPIRE 2 study

During the randomised phase 3 study RESPIRE 2 the incidence of exacerbation was lower than anticipated (0.6), but there was a trend towards increased time to first exacerbation and decreased frequency of exacerbation for both ciprofloxacin dry powder for inhalation (DPI) treatment regimens [5]. The 521 randomised NCBF patients had had ≥2 exacerbations in the 12 months prior to the study and positive predefined bacterial culture in sputum (including Pseudomonas aeruginosa). They were randomised 2:1 to ciprofloxacin DPI 32.5 mg or matching placebo b.i.d. Two regimens were studied: 14 days on/off or 28 days on/off, for 48 weeks. Ciprofloxacin DPI prolonged time to first exacerbation vs. pooled placebo in both regimens, but did not reach statistical significance: HR=0.87, p=0.40; and HR=0.71, p=0.05, respectively. All point estimates for primary endpoints in RESPIRE 2 favoured ciprofloxacin DPI treatment over placebo, suggesting a benefit for NCFB patients with evidence of respiratory pathogens and frequent exacerbations. Ciprofloxacin DPI was well tolerated in both treatment groups.

References

1. White MM, et al. Ivacaftor Therapy Reduces ADAM-17 Activity in Peripheral Blood Neutrophils, Thereby Decreasing the Inflammatory Burden in Cystic Fibrosis. ATS 2017, P984.
2. Wark PA, et al. Ivacaftor/Lumacaftor Improves Six Minute Walk Test Distance and Improves Lung Clearance Index and Functional Residual Capacity in Cystic Fibrosis Patients Homozygous for DF508 with Very Severe Lung Disease. ATS 2017, A4729.
3. Gardiner P, et al. ENaC Inhibitor AZD5634 First in Human Trial Reveals Promising Clinical Profile for the Treatment of Cystic Fibrosis. ATS 2017, A7306.
4. Haworth C, et al. Inhaled Liposomal Ciprofloxacin in Patients with Bronchiectasis and Chronic Pseudomonas Aeruginosa Infection: Results from Two Parallel Phase III Trials (ORBIT-3 and -4). ATS 2017, A7604.
5. Aksamit TR, et al. RESPIRE 2: Ciprofloxacin DPI 32.5 mg b.i.d. Administered 14 Days On/Off or 28 Days On/Off vs. Placebo for 48 Weeks in Patients with Non-Cystic Fibrosis Bronchiectasis (NCFB). ATS 2017, A7642.

Interstitial Lung Diseases and Idiopathic Pulmonary Fibrosis

An important novel finding for patients with fibrotic interstitial lung disease (ILD) that the authors expect will influence guidelines: ambulatory oxygen was associated with significantly improved health status. Retrospective data for pirfenidone in idiopathic pulmonary fibrosis (IPF) are also discussed, along with PBI-4050 with or without nintedanib or pirfenidone.

Ambulatory oxygen improves health status in fibrotic interstitial lung disease

Ambulatory oxygen was associated with significantly improved health status in patients with fibrotic ILD in a randomised, cross-over controlled clinical trial [1]. This so-called AmbOx-study evaluated health status, breathlessness, and mobility during two weeks on ambulatory supplemental oxygen, used during routine daily activities, compared to two weeks off. Inclusion criteria were: oxygen saturation (SaO_2) ≥94% at rest, dropping to ≤88% on 6MWT, and stable symptoms during a 2 week run-in period. Health status was assessed by the 15 item King's Brief Interstitial Lung Disease Questionnaire (KBILD) including breathlessness and activities, chest symptoms, and psychological.

There were 84 participants, 43 of whom had possible/definite IPF, while 53 were ever smokers. They were randomised to ambulatory oxygen or no oxygen, crossing to the alternative arm after two weeks. FVC was 73.3, DLCO 38.7. Seven patients did not complete the study. SEAs were equally distributed across arms and not related to ambulatory oxygen usage. Ambulatory oxygen was associated with a 3.7 point higher total KBILD score (p<0.0001). The breathlessness and activity domain improved, with a difference of 8.7 points (p<0.0001), which was more than the minimal clinical important difference of 7; the chest symptoms domain also improved, with a difference of 7.6 points (p=0.009). Only the difference in psychological symptoms (2.4 point; p=0.12) was not significant.

Encouraging results of PBI-4050 in idiopathic pulmonary fibrosis

PBI-4050 with or without nintedanib or pirfenidone had a strong safety profile in patients with IPF. PBI-4050 alone and with nintedanib demonstrated promising efficacy, but not combined with pirfenidone [2].

PBI-4050 is a novel orally active compound which displays anti-inflammatory and anti-fibrotic activities in fibrosis models in different organs: lung, kidney, heart, liver, and pancreas. An open-label phase 2 study was to evaluate the safety, tolerability, pharmacokinetics, and efficacy of PBI-4050 alone or in combination with nintedanib or pirfenidone in subjects with IPF. A total of 41 patients were enrolled. For a period of 12 weeks, they were randomised to 800 mg PBI-4050 alone (n=9), 800 mg PBI-4050 + nintedanib (n=16) or 800 mg PBI-4050 + pirfenidone (n=16). The mean change from baseline to week 12 in FVC was not significantly different for PBI-4050 & nintedanib (+7.0 mL) and PBI-4050 alone (-13.0 mL). However, it was reduced (-104.7 mL) for PBI-4050 + pirfenidone (p=0.0272 vs. PBI-4050 & nintedanib and p=0.1319 vs. PBI-4050 alone). There were no deaths, no patients experienced a decline of 10% of their FVC, and no TEAEs required study drug discontinuation. Diarrhoea was the most frequent TEAE in all groups, but less significantly so in the PBI-4050 alone group. Pharmacokinetics revealed a possible drug-drug interaction between PBI-4050 and pirfenidone.

Retrospective data for pirfenidone in idiopathic pulmonary fibrosis

New retrospective data analyses for pirfenidone in IPF were presented at the ATS 2017 conference. Pooled subgroup

Table 3 Baseline characteristics and change from baseline in lung function (N=nintedanib; P=pirfenidone)

	PBI-4050 alone (N=9)	PBI-4050 +N (N=16)	PBI-4050 +P (N=15)
Age (years, SD)	71.6 (5.9)	69.4 (8.3)	66.1 (5.5)
Male Gender (%)	66.7	75.0	80.0
FVC Baseline (L, SD)	2.88 (0.72)	2.76 (0.51)	2.85 (0.72)
FVC Change from Baseline (mL, 95% CI)	-13 (-102,+77)	+7 (-54, +68)	-105 (-176, -33)
% Predicted FVC Baseline (SD)	83.1 (16.4)	71.5 (16.3)	70.8 (14.3)
% Predicted FVC Change from Baseline (95% CI)	-1.11 (-3.8, 2.2)	-0.01 (-1.9, 2.0)	-2.69 (-4.8, -0.6)
% Predicted DLCO Baseline (SD)	47.2 (11.0)	50.8 (14.3)	49.1 (15.8)
% Predicted DLCO Change from Baseline (95% CI)	-4.0 (-8.8, 0.8)	-1.5 (-3.2, 0.2)	-2.7 (-5.7, 0.5)

analyses from the ASCEND and CAPACITY trial showed treatment with pirfenidone resulted in clinically meaningful benefits for all-cause mortality and FVC decline in patients with baseline FVC <50% and/or DLCO <35% [3]. A total of 170 patients (90 pirfenidone, 80 placebo) had low DLCO (n=157) or FVC (n=13) at baseline. In this subgroup, treatment with pirfenidone was associated with a 72% reduction in the risk of all-cause mortality over 12 months vs. placebo (4 vs. 12 deaths; HR, 0.28; p=0.018). There was a 56% relative reduction in the proportion of patients with a 10% absolute decline in FVC or death at 12 months vs. placebo (18.9% vs. 42.5%; p=0.0038). The annual rates of FVC decline were 150 and 278 mL in the pirfenidone and placebo arms, respectively (p=0.003). These data suggest that patients with more severe lung function impairment can also benefit from pirfenidone therapy.

Another pooled analyses from ASCEND and CAPACITY compared the effect of pirfenidone on progression-free survival (PFS) using a pre-specified PFS definition vs. a novel definition of PFS using respiratory-related hospitalisations instead of 6 minutes walking distance (6MWD) [4]. The pre-specified definition of PFS was time to the first occurrence of ≥10% absolute decline from baseline in FVC, ≥50 m decrease in the 6MWD or death. The novel definition of PFS was time to the first occurrence of a respiratory-related hospitalisation (determined by AE report), ≥10% absolute decline from baseline in FVC or death. The novel definition, despite having a lower event rate over 12 months, was at least as discriminating as the pre-specified definition of PFS for estimating the treatment effect of pirfenidone (HR in favour of pirfenidone using the pre-specified and the new definition: 0.62% vs 0.4%, respectively (p<0.0001 in both cases). Although 6MWD remains an important endpoint in IPF, the authors concluded, respiratory-related hospitalisations may provide an interesting new patient-centred endpoint that goes beyond functional parameters.

In a third pooled analysis of ASCEND and CAPACITY, pirfenidone reduced the progression of breathlessness compared with placebo in IPF patients with moderate lung function impairment [5]. Patients receiving pirfenidone showed less change from baseline in University of California, San Diego Shortness of Breath Questionnaire (UCSD-SOBQ) score and a lower proportion of patients had more pronounced increases in UCSD-SOBQ scores at 12 months.

Combined use of pirfenidone and nintedanib

In an interim analysis after 12 weeks, combined use of pirfenidone and nintedanib in 41 IPF patients did not suggest a different AE profile to that expected for either treatment alone [6]. The patients in this study were already tolerating a stable dose of pirfenidone prior to the initiation of nintedanib, which may explain the higher incidence of TEAEs related to nintedanib compared with pirfenidone. Longer follow-up is necessary to evaluate the safety and tolerability, and potential efficacy, of this combination.

References

1. Visca D, et al. AmbOx: A Randomised Controlled, Crossover Trial Evaluating the Effects of Ambulatory Oxygen on Health Status in Patients with Fibrotic Interstitial Lung Disease. ATS 2017, A7603.
2. Parker J, et al. PBI-4050 Is Safe and Well Tolerated and Shows Evidence of Benefit in Idiopathic Pulmonary Fibrosis. ATS 2017, A7606.
3. Nathan SD, et al. Effect of Pirfenidone on All-Cause Mortality (ACM) and Forced Vital Capacity (FVC) in Idiopathic Pulmonary Fibrosis (IPF) Patients With Low FVC and/or Low DLCO: Analysis of Pooled Data From ASCEND and CAPACITY. ATS 2017, A5390.
4. Lederer DJ, et al. Effect of Pirfenidone on a Novel Definition of Progression-Free Survival (PFS) in Patients with Idiopathic Pulmonary Fibrosis (IPF): Pooled Analysis from Phase III Trials. ATS 2017, A5393.
5. Glassberg MK, et al. Effect of Pirfenidone on Breathlessness as Measured by the UCSD-SOBQ Score in Patients with Idiopathic Pulmonary Fibrosis (IPF) with Moderate Lung Function Impairment. ATS 2017, A5406.
6. Flaherty KR, et al. Safety of the Combined Use of Pirfenidone and Nintedanib in Patients with Idiopathic Pulmonary Fibrosis (IPF): Results from an Interim Analysis After 12 Weeks. ATS 2017, A5398.

Pulmonary Hypertension

Treatment options for inoperable pulmonary hypertension caused by chronic obstruction of the pulmonary arteries are limited. Macitentan seems to be an effective option, as it improves cardiopulmonary haemodynamics and 6MWT. In pulmonary arterial hypertension (PAH), riociguat may significantly improve quality of life.

Macitentan for inoperable chronic thrombo-embolic pulmonary hypertension

In patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), the dual endothelin receptor antagonist macitentan led to significant improvements in cardiopulmonary haemodynamics and exercise capacity [1]. This conclusion is based on results from the MERIT study, which was presented as a late-breaking abstract.

MERIT was a randomised, double-blind, placebo-controlled study evaluating macitentan for the treatment of patients with primary inoperable CTEPH (WHO functional class II–IV), including patients receiving PAH treatment at baseline. The 80 eligible patients were randomised 1:1 to placebo or macitentan 10 mg once daily for 24 weeks. At baseline, 61% of patients were receiving treatment with a PAH therapy. Compared with placebo, pulmonary vascular resistance (PVR) after 16 weeks, which was the primary endpoint, significantly improved in the macitentan-treated group, declining from 929 to 723 (-27%). In the placebo group PVR declined from 984 to 899 (-12.8%). The treatment effect ratio for macitentan was 0.84 (p=0.04). The 6MWD after 24 weeks also improved significantly by 35 m, compared to 1 m in the placebo group (p=0,03). The effects on PVR and 6MWD were similar in patients with and without PAH treatment at baseline.

Macitentan treatment also improved mean right atrial pressure, cardiac index at week 16, and N-terminal pro B-type natriuretic peptide at week 24 compared with placebo (pre-specified endpoints). Macitentan was well tolerated. The most common AE in the active treatment group versus placebo were peripheral oedema (22.5% and 10.0%, respectively) and decreased haemoglobin/anaemia (17.5% and 2.5%). Haemoptysis was reported in 1 patient in each group; neither was a SEA. Five patients, all in the placebo group, prematurely discontinued treatment. Two patients in the placebo group died.

Macitentan in patients with Pulmonary Arterial Hypertension

Survival data of the SERAPHIN study and its open-label extension support long-term treatment with macitentan in patients with PAH [2]. Macitentan was well tolerated, with a low incidence of treatment discontinuation. In total, 242 patients were randomised to macitentan 10 mg; 182 patients continued to receive macitentan 10 mg in the extension, and 101 patients were ongoing. Median exposure was 4.4 years. Survival estimates at 1, 2, 3, 4 and 5 years were 95.0%, 89.1%, 84.0%, 78.2% and 71.2%, respectively. The proportion of patients with at least one AE or serious AE was 95.9% and 60.3%. Annualised rates of alanine and/or aspartate aminotransferase abnormalities >3 times the upper limit of normal, haemoglobin decrease ≤10 g/dL, and oedema (patients with ≥1 oedema AE) were 1.7%, 3.8%, and 8.6% per year, respectively. The proportion of patients who discontinued macitentan treatment due to an AE was 14.9% (Annualised rate 4.3%).

Riociguat may significantly improve HRQoL in pulmonary arterial hypertension

Riociguat monotherapy may significantly improve HRQoL among newly diagnosed patients with PAH [3]. Few PAH trials so far have evaluated treatment-related change in patient-reported outcomes such as HRQoL. The prospective open-label MOTION study is designed to explore patient-reported outcomes in PAH patients treated with riociguat. Patients received riociguat over a 10-week titration phase, from a starting dosage of 0.5 mg 3 times daily (TID) increased every 2 weeks in 0.5 mg increments, until individual optimal dosage was reached. Patients remained on therapy during a 14-week maintenance phase. The primary endpoint is the reported change from baseline in the Living with Pulmonary Hypertension (LPH) questionnaire after 24 weeks of treatment. LPH scores range from 0 to 105; higher scores indicate worse HRQoL. Of 75 enrolled patients 65 completed the trial; week 24 LPH data were available for 58 patients. PAH was categorised as idiopathic (65%, n=49), connective tissue disease–associated (28%, n=21), and portal hypertension (3%, n=2). LPH score improved from baseline to last visit by −5.4 (±27.8) in the intent-to-treat (n=75) analysis (p=0.048) and from baseline to Week 24 by −10.8 (±21.9) in the completers (n=58) analysis (p=0.0002).

New safety data for riociguat

An interim analysis of the ongoing EXPERT study resulted in new safety data for riociguat. At study entry, there were similar proportions of patients who were pre-treated or newly treated with riociguat. Newly treated patients experienced more AEs than pre-treated patients. The AEs and SAEs reported to date in EXPERT are consistent with the known safety profile of riociguat, and no new safety signals were identified.

Baseline data were available for 713 patients (79% of the planned cohort). Of these, 169 had PAH, 511 had CTEPH, and 33 had other forms of PH [4]. At study entry, 54% of patients with PAH and CTEPH were pre-treated with riociguat for ≥3 months. The median duration of follow-up was 133 days. A total of 914 AEs occurred in 277 (39%) patients, drug-related AEs occurred in 104 (15%) patients, and SAEs occurred in 161 (23%) patients, while 36 (5%) patients died. The most common drug-related AEs were dizziness (4%), dyspepsia (2%), and hypotension (2%); the most common SAEs were right ventricular failure (3%), dyspnoea (3%), and syncope (3%); and the most common AE with fatal outcome was right heart failure (2%).

References

1. Ghofrani H, et al. Efficacy and Safety of Macitentan for Inoperable Chronic Thromboembolic Pulmonary Hypertension: Results from the Randomised Controlled MERIT Study. ATS 2017, A7601.
2. Souza R, et al. Long-Term Survival and Safety with Macitentan in Patients with Pulmonary Arterial Hypertension: Results from the SERAPHIN Study and Its Open-Label Extension. AS 2017, A2294.
3. Sood N, et al. Results of the Prospective, Multicenter, Single-Arm, Open-Label, Phase 4 MOTION Study of Riociguat in Pulmonary Arterial Hypertension. ATS 2017, A2287.
4. Klose H, et al. Riociguat for the Treatment of Pulmonary Hypertension: Safety Data from the EXPERT Registry. ATS 2017, A2292.

Miscellaneous

In this chapter some of the most important studies of other respiratory diseases are presented, ranging from a promising treatment for chronic cough – a significant unmet clinical need – to suicide among lung cancer patients. Most of these studies were presented during the ATS meeting late-breaking abstracts.

Almost a quarter of adult outpatients with community-acquired pneumonia fail on antibiotics

Approximately one in four adult outpatients prescribed antibiotic monotherapy for community-acquired pneumonia (CAP) fail treatment. A retrospective cohort analysis of outpatient CAP in the US identified multiple predictors of failure and clinically meaningful differences between antibiotic classes.

A total of 251,947 adult outpatients met inclusion criteria. They had to be ≥18 years old and received antibiotic treatment following an outpatient visit for CAP. Patients were required to have a monotherapy antibiotic prescription claim for one macrolide, fluoroquinolone, beta-lactam or tetracycline. Mean age was 52.2 years. The majority of patients were prescribed azithromycin (40.3%) followed by levofloxacin (37.7%). Total antibiotic failure rate was 22.1%. Multivariate predictors of antibiotic failure included: diagnosis of pneumococcal pneumonia ($p<0.02$), older age ($p<0.0001$), and female gender ($p<0.0001$). Various comorbidities were associated with higher rates of antibiotic failure including:

- hemiplegia/paraplegia (OR=1.33);
- rheumatologic disease (OR=1.28);
- chronic pulmonary disease (OR=1.25);
- cancer (OR=1.14);
- diabetes (OR=1.07);
- asthma (OR=1.05).

Beta-lactams were associated with the highest antibiotic failure rate (25.7%), followed by macrolides (22.9%), tetracyclines (22.5%), and fluoroquinolones (20.8%). The authors conclude that prescribers should be aware of those CAP patients who are at risk for poor outcomes and consider these factors to guide a comprehensive treatment plan, including more appropriate antibiotic treatment. "Our findings suggest that the community-acquired pneumonia treatment guidelines should be updated with more robust data on risk factors for clinical failure," said first author Dr. J. McKinnell from Los Angeles. "Our data provide numerous insights into characteristics of patients who are at higher risk of complications and clinical failure. Perhaps the most striking example is the association between age and hospitalization: patients over the age of 65 were nearly twice as likely to be hospitalised compared to younger patients when our analysis was risk adjusted and nearly three times

more likely in unadjusted analysis. Elderly patients are more vulnerable and should be treated more carefully, potentially with more aggressive antibiotic therapy."

Inhaled nitric oxide in patients with acute submassive pulmonary embolism

Inhaled nitric oxide is unlikely to be an effective treatment for acute pulmonary embolism. Delivered by nasal cannula at 50 ppm for 24 hours, it caused no AEs, but did not improve right ventricular function or reduce cardiac necrosis associated with submassive pulmonary embolism [2]. The increased plasma nitrate concentrations indicated adequate drug delivery.

Eligible patients for this phase 2 randomised, double blind, placebo-controlled trial had acute pulmonary embolism, were normotensive, and had right ventricular dysfunction. A total of 76 subjects were randomised to either 50 ppm $NO+O_2$ at 4 L per minute (treatment) or O_2 only at 4 L per minute (placebo). The composite primary outcome required normal right ventricular diameter (<43 mm) and function on echo (TAPSE >16 mm, FAC >33% and RIMP (Tei index) <0.55) and high-sensitive troponin I <14 pg/mL. No patient developed sustained hypotension or increased methaemoglobin or died during treatment. From the total, nine patients (24%) reached the primary outcome with $NO+O_2$ and 6 of 38 (16%) with placebo (p=0.55). With $NO+O_2$, plasma nitrate concentrations (µM) increased from a median of 11.7 at enrolment to 26.9 (p<0.001) at 24 hours; with placebo, plasma nitrate was unchanged from 14.9 at enrolment to 15.7 at 24 hours.

Clinical benefits of mepolizumab in eosinophilic granulomatosis with polyangiitis

Treatment with mepolizumab significantly increased the likelihood and duration of remission, while reducing glucocorticoid use in patients with eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss) [3]. The safety profile of mepolizumab was consistent with previous studies in severe asthma and EGPA. These results demonstrate consistent and meaningful clinical benefits of mepolizumab in patients with EGPA.

In other hypereosinophilic syndromes and in eosinophilic asthma, mepolizumab had already been shown to reduce blood eosinophil counts with concomitant clinical improvement. In patients with EGPA and a history of relapsing or refractory disease on stable therapy with prednisolone/prednisone ≥7.5–≤50mg/day with or without additional immunosuppressive therapy for ≥4 weeks, a phase 3, randomised, placebo-controlled, double-blind, parallel-group, multi-centre study was conducted. Patients were randomised to mepolizumab 300 mg or placebo subcutaneously, in addition to standard of care, every 4 weeks for 52 weeks. After Week 4, glucocorticoid dose could be tapered. Co-primary endpoints were:

- Accrued duration of remission: Birmingham Vasculitis Activity Score =0, and prednisolone/prednisone dose ≤4 mg per day over 52 weeks.
- The proportion of patients in remission at both weeks 36 and 48.

The intent-to-treat population included 136 randomised patients. Duration of remission accrued over 52 weeks was significantly prolonged with mepolizumab vs. placebo (OR: 5.91; p<0.001). A significantly higher proportion of patients was in remission at weeks 36 and 48 (32% vs. 3%, respectively; OR: 16.74; p<0.001). Significant reductions in average daily glucocorticoid dose during weeks 49–52 were seen with mepolizumab vs. placebo (OR: 0.20; p<0.001). Median prednisolone/prednisone dose during weeks 49–52 was 5.0 (range: 0.0–113.4) mg/day in the mepolizumab group and 10.0 (0.0–46.3) mg/day in the placebo group. Time to first EGPA relapse was significantly longer with mepolizumab vs. placebo (HR: 0.32; p<0.001). Rates of AEs and SAEs were similar for mepolizumab and placebo.

High risk of suicide in lung cancer patients

Compared to the most common types of non-skin cancers, a diagnosis of lung cancer seems to result in the greatest risk of suicide. Over a period of 40 years, cancer diagnoses were associated with 6,661 suicides [4].

Lung cancer associated suicide rates were explored in a large national database compared to the general population as well as to the three most prevalent non-skin cancers: breast, prostate, and colorectal cancer (CRC). Furthermore, suicidal trends over time and timing from cancer diagnosis to suicide were estimated for each cancer type. Among lung cancer patients, suicide SMR (standardised mortality ratio) of different demographic, social and tumour related factors were identified.

A total of 3,640,229 patients diagnosed with cancer between 1973 and 2013 were identified. Among these, 6661 committed suicide. The cancer associated suicide rate is nearly twice that of US-general population: 27.5/100,000 person-years (SMR=1.6) compared to 13/100,000 person-years. Suicide risk was highest among lung cancer patients (SMR = 4.2), particularly older patients, widowed, males, and patients with unfavourable tumour characteristics. The risk was very notably elevated in Asians: SMR 13.7. Lung cancer was followed by CRC (SMR=1.4), breast cancer (SMR=1.4) and prostate cancer (SMR=1.2). Median time to suicide was 7 months from diagnosis in lung cancer, 56 months in

prostate ca, 52 months in breast cancer and 37 months in CRC (p<0.001). There was a trend towards the decrease in suicide SMR over time, which was also most notable for lung cancer. "I think it's fair to say that most clinicians do not think about suicide risk in cancer patients", said M. Rahouma, research fellow in New York. "This study, I hope, will change that by making us more aware of those at greatest risk of suicide, so that this catastrophe in the care of our patients doesn't happen."

P2X3 receptor antagonist reduces cough frequency

Targeting the purinergic receptor P2X3 with MK-7264 significantly reduced the frequency of cough in patients with refractory chronic cough after 12 weeks of treatment compared with placebo [5]. MK-7264 was well tolerated, with changes in taste being the most frequently experienced AE.

MK-7264 (formerly AF-219) had previously demonstrated efficacy at a high dose in a study of patients with refractory chronic cough [6]. A larger, clinical phase 2b trial further explored safety, efficacy, and the therapeutic dose range of MK-7264 for the treatment of chronic cough. It was a 12-week, randomised, double-blind, placebo-controlled, parallel group study conducted at 46 sites in the United States and United Kingdom. A total of 253 patients with chronic cough were randomised to placebo or MK-7264 at doses of 7.5, 20, or 50 mg BID.

MK-7264 50 mg demonstrated a significant reduction in Awake Cough Frequency (coughs/hour) compared with placebo (p=0.0027); the difference from placebo for the two lower doses were not significant. These results were consistent with patient-reported Cough Severity (Table 4). The most common AE was dysgeusia; taste-related AEs (dysgeusia, hypogeusia, or ageusia) were observed in 6%, 10%, 49%, and 81% of patients on placebo, 7.5 mg, 20 mg, and 50 mg of MK-7264, respectively; of these, only 1 patient on placebo and 6 patients in the 50 mg group discontinued due to a taste-related AE.

Mid-life respiratory burden of marijuana use

Marijuana smoking either alone or concurrently with cigarettes increases the risk of exacerbations.

In a study of 5,291 people aged 40 years and older, randomly recruited from the population in Canada, marijuana smoking was defined as having smoked at least 50 joints in a lifetime. The cohort was stratified into 5 groups: smoking marijuana only, smoking tobacco only; concurrently smoking marijuana and cigarettes and not smoking either. The prevalence of marijuana smoking in middle aged and elderly population was 20% overall: 27% in men and 14% in women. The subgroups consisted of 2,299 (43.5%) not smoking either; 181 (3.4%) of marijuana smokers; 885 (16.7%) of marijuana and cigarette smokers, and 1,926 (36.4%) who smoked cigarettes only. Compared with people who did not smoke marijuana or tobacco, increased odds for exacerbation–like events of at least 1 in the past year occurred in smokers of marijuana only (adjusted OR 1.49) and in dual smokers of marijuana and cigarettes (adjusted OR 1.39). Those who smoked cigarette only also had an increased odds for exacerbation-like events: adjusted OR 1.51. Compared with never smokers, cigarette smokers were significantly more likely to experience chronic cough, chronic phlegm, wheeze, dyspnoea, and severe dyspnoea, whereas marijuana smokers were only significantly more likely to experience wheezing.

References

1. McKinnell J, et al. Clinical Predictors of Antibiotic Failure in Adult Outpatients with Community-Acquired Pneumonia. ATS 2017, A2644.
2. Kline JA, et al. Randomised Placebo-Controlled Trial of Inhaled Nitric Oxide to Improve Right Ventricular Function in Patients with Acute Submassive Pulmonary Embolism. A7605.
3. Wechsler ME, et al. Mepolizumab for the Treatment of Patients with Eosinophilic Granulomatosis with Polyangiitis: A Phase III Randomised, Placebo-Controlled Trial. ATS 2017, A7602.
4. Rahouma M, et al. Lung cancer patients have the highest malignancy-associated suicide rate in USA: a population based analysis. ATS 2017, A8321.
5. Smith, JA, et al. MK-7264, a P2X3 Receptor Antagonist, Reduces Cough Frequency in Patients with Refractory Chronic Cough: Results from a Randomised, Controlled, Phase 2b Clinical Trial. ATS 2017, A7608.
6. Abdulqawi R, et al. Lancet. P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. Lancet 2015;385:1198-205.

Table 4 Change from baseline in Awake Cough Frequency and Cough Severity (VAS) after 12 Weeks of Treatment

	Placebo n=61	MK-7264 7.5 mg n=59	MK-7264 20 mg n=59	MK-7264 50mg n=57
LS Mean (SE) Change from Baseline in Awake Cough Frequency	-0.40 (0.11)	-0.64 (0.11)	-0.65 (0.11)	-0.86 (0.11)
Estimated % Change over Placebo (95% CI)	--	-22.0% (-41,8%, 4,6%)	-22.2% (-42.0%, 4.3%)	-37.0% (-53.3%, -14.9%)
p-value (vs. placebo)	--	0.097	0.093	0.003
LS Mean (SE) Change from Baseline in Cough Severity (0-100 mm VAS)	-15.2 (3.00)	-12.9 (3.04)	-23.4 (3.03)	-31.1 (3.09)
LS Mean Difference vs. Placebo (95% CI)	--	-4.0 (-12.3, 4.4)	-8.2 (-16.6, 0.1)	-15.9 (-24.3, -7.5)
p-value vs. placebo	--	0.351	0.052	0.0003

Mixed model repeated measures analysis (change from baseline used as the dependent variable, and includes the treatment group, visit, country, the interaction between treatment and visit at fixed factors, and baseline as a covariate)