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PEER-REVIEWED CONFERENCE REPORT

Does Vilobelimab Reduce Mortality in Severe COVID-19?

Vilobelimab may reduce mortality in patients with severe COVID-19 pneumonia, the phase 3 PANAMO trial showed. Western-European patients in particular appeared to benefit from the intervention.

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STARR2: Reduced COPD Exacerbations

A point-of-care, eosinophil-guided prescription of prednisolone was non-inferior to standard-of-care prescription of prednisolone in the treatment of COPD exacerbations, the multicentre, randomised STARR2 trial showed.

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Tezepelumab in Asthma: Mucus Plugging Down, Lung Function Up

Tezepelumab is the first biologic agent to demonstrate reduced mucus plugging in patients with moderate-to-severe asthma. Reductions in mucus scores correlated with improvements in lung function.

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Letter from the Editor

Dear colleagues,

Luckily, the ERS of 2022 was held live in Barcelona, Spain, with lots of 'physical' attendees. And many other interested colleagues could follow many sessions on line. Again, numerous speakers were able to present the most recent updates in important areas of pulmonary diseases. Some of these studies and findings are highlighted below.

An awake prone position did not result in improved clinical outcomes compared with usual care in patients with acute hypoxemic respiratory failure from COVID-19. Although the intervention appeared to be safe, maintaining a prone position for many hours is challenging for patients. The full paper has been published in JAMA.

Complement activation (C5a) has been shown to play an important role in severe COVID-19 and vilobelimab is a first-in-class anti-C5a monoclonal antibody. C5a levels are high in patients with severe COVID-19 and are related to disease severity. Vilobelimab may reduce mortality in patients with severe COVID-19 pneumonia, the phase 3 PANAMO trial showed.

A post-COVID syndrome (PCS) scoring tool was developed, including the entire clinical spectrum of PCS in 12 binary questions. The tool was validated and could potentially be used for the diagnosis and stratification of patients with PCS. Also, the scoring tool could serve as a possible endpoint for clinical studies.

The addition of icenticaftor on top of triple inhalation therapy for 24 weeks resulted in a clear dose-response on 5 endpoints in patients with COPD and chronic bronchitis. The 300 mg, twice-daily dose of the drug showed an encouraging benefit-risk profile and will be investigated in further trials.

A point-of-care, eosinophil-guided prescription of prednisolone was non-inferior to standard-of-care prescription of prednisolone in the treatment of COPD exacerbations, the multicentre, randomised STARR2 trial showed.

Tezepelumab reduced mucus plugging in patients with moderate-to-severe asthma. Moreover, reductions in mucus scores correlated with improvements in lung function. Tezepelumab is the first biologic agent to demonstrate these results in a randomised-controlled trial.

This report outlines the most significant advancements discussed at the ERS conference. So, we hope that you will enjoy reading this Conference Report!

Stay healthy and kind regards,
Prof. em. Richard Dekhuijzen

Biography

Prof. P.N. Richard Dekhuijzen is Professor of Pulmonology at the Radboud University Medical Center in Nijmegen, the Netherlands. His specific area of clinical and research interest includes asthma, COPD, and inhalation technology. He studied medicine at VU 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 330 peer-reviewed papers and many textbook chapters on respiratory medicine. From 2008-2010, he was Head of the Cardiology Department at Radboudumc. Until 2016, he chaired the Department of Pulmonary Diseases, the Heart-Lung Centre Nijmegen, and the Medical Staff at Radboudumc. He is the scientific chair of the Aerosol Drug Management Improvement Team (ADMIT) and chair of the Dutch Inhalation Technology Working Group. Currently, he is chair of the Medical Ethical Committee of the Radboudumc.

Conflict of Interest Statement:
In the last 3 years, Richard Dekhuijzen and/or his department received research grants, unrestricted educational grants, and/or fees for lectures and advisory board meetings from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Mundipharma, Novartis, Sandoz, Teva, and Zambon.

COVID-19: What Is New?

Does vilobelimab reduce mortality in severe COVID-19?

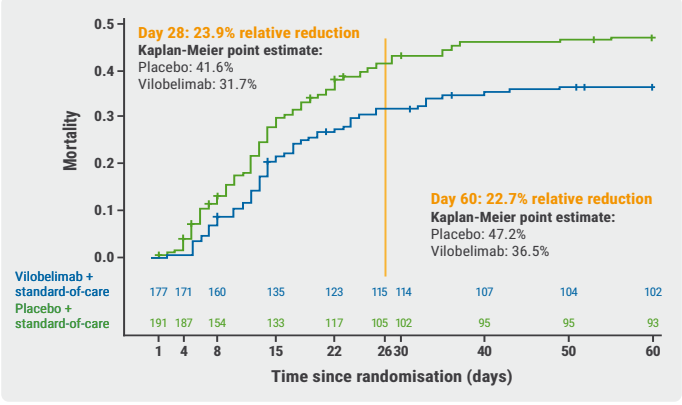
Vilobelimab may reduce mortality in patients with severe COVID-19 pneumonia, the phase 3 PANAMO trial showed. Western-European patients in particular appeared to benefit from the intervention. Since vilobelimab displayed an acceptable safety profile in this population, the developers aim to discuss the results with the regulatory authorities.

Complement activation (C5a) has been shown to play an important role in severe COVID-19 [1] and vilobelimab is a first-in-class anti-C5a monoclonal antibody that leaves the membrane attack complex (MAC) intact. Since it has been shown that C5a levels are high in patients with severe COVID-19 and related to disease severity [2], Prof. Alexander Vlaar (Amsterdam UMC, the Netherlands) and co-investigators deemed it reasonable to assess C5a inhibition in patients with severe COVID-19.

After the successful results of the PANAMO phase 2 study [3], the PANAMO phase 3 study (NCT04333420) was initiated [4]. This study randomised 368 critically-ill, intubated patients with COVID-19 1:1 to vilobelimab plus standard-of-care or to placebo plus standard-of-care. All-cause mortality after 28 days was the primary outcome.

The results displayed a trend towards a reduced risk of all-cause mortality in the vilobelimab arm compared with the placebo arm (31.7% vs 41.6%; see Figure).

Figure: 28-day mortality rate of vilobelimab- versus placebo-treated COVID-19 patients [4]



However, this relative risk reduction of 23.9% was not statistically significant following site-stratified Cox regression (P=0.094), which was the approach recommended by the FDA. In Western-European participants receiving vilobelimab, the observed relative risk reduction for all-cause mortality was 43.0% compared with placebo. In other words, 1 additional life was saved for every 6 participants if they received vilobelimab. Furthermore, participants with more severe disease appeared to benefit more from treatment with vilobelimab than those with less severe disease.

In terms of safety, an acceptable safety profile of vilobelimab was reported. The rate of infections and infestations was 62.9% in the intervention arm and 59.3% in the placebo arm.

"A clinically meaningful, but non-significant, benefit was observed for treatment with vilobelimab in this critically-ill population," said Prof. Vlaar. "The developer aims to present the results to the regulatory authorities."

1. Java A, et al. JCI Insight. 2020;5(15):e140711.
2. Carvelli J, et al. Nature. 2020;588:146-150.
3. Vlaar APJ, et al. Lancet Rheumatol. 2020;2(12):e764-e773.
4. Vlaar APJ, et al. Phase 3 RCT of C5a-Specific Vilobelimab in Severe COVID-19 Pneumonia. ALERT 3, RCT2881, ERS International Congress 2022, Barcelona, Spain, 4–6 September.

Awake proning not positive in COVID-19

An awake prone position did not result in improved clinical outcomes compared with usual care in patients with acute hypoxemic respiratory failure from COVID-19. Although the intervention appeared to be safe, maintaining a prone position for many hours is challenging for patients, argued the authors.

"We've known for many years that in invasively mechanically ventilated patients, prone positioning may improve oxygenation and reduce ventilator-induced lung injury, due to the more homogenous alveolar strain and more uniform alveolar sizes [1]," explained Prof. Jason Weatherald (University of Alberta, Canada). "This helps to improve clinical outcomes." The effects of prone positioning in COVID-19 are largely unknown. Prof. Weatherald and co-investigators aimed to assess whether awake prone positioning prevents intubation and improves survival in patients with COVID-19. For this purpose, the

COVI-PRONE trial (NCT04350723) randomised 400 patients with acute hypoxemic respiratory failure due to COVID-19 1:1 to an awake prone position (8–10 hours/day) or usual care (not instructed to prone) [2]. Endotracheal intubation at 30 days was the primary outcome of the study. The results were published in *JAMA* [3].

The primary outcome was not met: 34% of the participants in the intervention arm and 41% of the participants in the usual care arm were intubated at 30 days (HR 0.81; 95% CI 0.59–1.12). Likewise, the investigators observed no difference in mortality rates at 60 days between the 2 groups (22% vs 24%). The intervention was safe, with 0% of the participants experiencing a serious adverse event in the intervention arm.

"This trial did not demonstrate a clear effect of awake prone positioning on intubation or other clinical outcomes," concluded Prof. Weatherald.

1. Kallet RH. Respir Care. 2015;60(11):1660–1687.
2. Alhazzani W, et al. Awake Prone Positioning in Acute Hypoxemic Respiratory Failure from COVID-19: A Randomized Clinical Trial. ALERT 1, RCT716, ERS International Congress 2022, Barcelona, Spain, 4–6 September.
3. Alhazzani W, et al. JAMA. 2022;327(21):2104–2113.

Favipiravir may help patients <60 years with COVID-19 to recover

Although early intervention with favipiravir did not improve clinical outcomes for the overall population of hospitalised patients with COVID-19, a phase 3 study displayed that the agent may induce health benefits for patients under 60 years of age.

"Re-using existing agents for a different purpose is faster than developing novel drugs," argued Dr Christopher Orton (Royal Brompton Hospital, UK) [1]. Following this rationale, the phase 3 PIONEER trial (NCT04373733) was designed to test favipiravir, a medicine that demonstrated activity against various RNA viruses in individuals with COVID-19 (n=503). Patients who were hospitalised due to COVID-19 were randomised 1:1 to receive a 10-day treatment with favipiravir or placebo. The primary objective of the trial was to assess whether early intervention with favipiravir reduced the time to significant improvement in the health status of the participants. For this purpose, a 7-category ordinal scale was used, ranging from 1 'not hospitalised with resumption of normal activities' to 7 'death'.

The intervention was not significantly different from placebo when the whole study population was investigated (P=0.73). However, the favipiravir arm was superior to the placebo arm in participants under 60 years of age (P=0.03). Similarly, secondary outcomes demonstrated that participants under 60 benefitted from favipiravir versus placebo in terms of 'mechanical ventilation-free survival' (P=0.02).

Dr Orton added that these results implicate that a wider evaluation of anti-viral medications, including their age-stratified effects, should be considered in patients who are hospitalised with COVID-19.

1. Orton CM, et al. A randomised controlled trial of early intervention with oral favipiravir in patients hospitalised with COVID-19 (PIONEER Trial). ALERT 3, RCT2882, ERS International Congress 2022, Barcelona, Spain, 4–6 September.

Brensocatib fails in severe COVID-19

Brensocatib did not improve the health status of patients with severe COVID-19, even though there was an association between neutrophilic inflammation and mortality in COVID-19, and active neutrophil elastase was decreased.

A randomised-controlled trial investigated whether the oral dipeptidyl peptidase-1 (DPP1) inhibitor brensocatib delivered clinical benefits for patients with hospitalised COVID-19 [1]. The included patients (n=404) received brensocatib or placebo for 28 days. The primary endpoint was the improvement participants made on a 7-point WHO ordinal scale representing clinical status after 4 weeks of therapy. Ms Holly Keir (University of Dundee, UK) presented the results.

At day 29, 18.7% of the participants in the placebo arm and 14.7% of the participants in the brensocatib arm had reached the most favourable score on the ordinal scale: 'not hospitalised, no limitations on activities'. In addition, 10.7% and 15.3% of the participants had died in the placebo arm and the intervention arm, respectively. Thus, there appeared to be a small benefit for the placebo arm over the brensocatib arm (adjusted OR 0.72; P=0.008).

The adverse event rates were similar for the brensocatib arm (44.8%) and the placebo arm (46.3%), with no significant differences in skin disorders or infections between the 2 groups. Ms Keir added that the research team demonstrated that active neutrophil elastase levels were in fact reduced in participants receiving brensocatib (P<0.0001), but that this did not lead to a positive treatment effect.

1. Keir HR, et al. Dipeptidyl Peptidase-1 Inhibition in Patients Hospitalized with COVID-19: a Multicentre Randomized Double-Blind Placebo Controlled Trial. ALERT 3, RCT2883, ERS International Congress 2022, Barcelona, Spain, 4–6 September.

Inhaled agent under investigation for COVID-19

Inhaled interferon beta-1a did not meet its primary endpoint in patients who were hospitalised with COVID-19 but may improve clinical outcomes in patients with more severe disease or risk factors for disease progression, subgroup analyses of the SPRINTER trial displayed. Suggested is to evaluate inhaled interferon beta-1a in patients with severe viral lung infections in general, and in hospitalised patients with COVID-19 that have a more severe disease in particular.

"Inhaled interferon beta-1a has demonstrated anti-viral activity against a range of respiratory viruses, including SARS-CoV-2," outlined Prof. Tom Wilkinson (University of Southampton, UK) [1]. Moreover, inhaled delivery optimises the exposure of this agent to the tissue it should target, without ample systemic exposure [2,3]. Positive phase 2 results of this agent in COVID-19 [4] led to the unfoldment of the phase 3 SPRINTER trial (NCT04732949). The trial randomised 623 patients who were hospitalised with moderate COVID-19 1:1 to a 14-day course of inhaled interferon beta-1a plus standard care or placebo plus standard care. The primary endpoints were the time to hospital discharge and the time to recovery to 'no limitations of activities' up to day 28.

No difference was observed in time to hospital discharge between the 2 arms of the study (HR 1.06; 95% CI 0.89–1.27; P=0.509). Key secondary endpoints did not demonstrate a benefit of inhaled interferon beta-1a over placebo either but trended towards a benefit for the intervention arm: progression to severe disease or death (interferon beta-1a 10.7% vs placebo 14.4%; OR 0.71; P=0.161). Furthermore, in patients with O2 saturation ≤92% or respiratory rates ≥21 breaths per minute, the per-protocol analysis did show a trend towards a reduced risk of severe disease or death in those who were treated with inhaled interferon beta-1a instead of placebo (3.4% vs 12%; P=0.046).

The safety profile of inhaled interferon beta-1a was favourable and consistent with previously reported data. The rates of serious treatment-emergent adverse events were 12.6% and 18.2% in the experimental arm and placebo arm, respectively.

Prof. Wilkinson concluded that the favourable trends for inhaled interferon beta-1a over placebo that were observed in the current trial provide a clinical rationale to investigate the effect of this agent on the endpoint of progression of disease or mortality in hospitalised patients with COVID-19 and in patients with severe viral lung infections.

1. Wilkinson TMA, et al. SPRINTER: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Determine the Efficacy and Safety of Inhaled Interferon Beta-1a (SNG001) for the Treatment of Patients Hospitalised Due to COVID-19. ALERT 3, RCT2884, ERS International Congress 2022, Barcelona, Spain, 4–6 September.
2. Djukanović R, et al. Am J Respir Crit Care Med. 2014;190(2):145–54.
3. Filipi ML, et al. Int J MS Care. 2014;16(1):55–60.
4. Monk PD, et al. Lancet Respir Med. 2021;9(2):196–206.

Accurate voice-based COVID-19 diagnostic test in development

A long short-term memory (LSTM) model incorporating speech recognition demonstrated to provide a potentially cheaper, faster, and more precise diagnostic test for COVID-19 than a rapid antigen test (RAT).

Ms Wafaa Aljbawi (Maastricht University, the Netherlands) and colleagues aimed to develop and implement an effective, automated, and non-invasive diagnostic system for COVID-19 [1]. The research team used a database of Cambridge University that included data on the demographics, medical history, symptoms, and COVID-19 test results of registered participants. Furthermore, voice recordings were obtained from 893 participants, who recorded the sentence 'I hope my data can help to manage the virus pandemic.' Of these voice recordings, 308 belonged to COVID-19-positive individuals. After the noise was removed from the recordings, the edited audio files were entered into an LSTM model, predicting COVID-19 status based on these recordings.

The LSTM model had an accuracy of 89%, a sensitivity of 89%, and a specificity of 83%. Ms Aljbawi emphasised that the sensitivity of 89% is high compared with that of a RAT test, which has an average sensitivity of 56.2%. In other words, the LSTM model may miss 11 out of 100 cases of COVID-19, whereas a RAT may miss 44 out of 100 cases. In contrast, the specificity of a RAT test is higher at 99.5%, compared with 83% of the LSTM model. This means that only 1 out of 100 individuals would be wrongly diagnosed with COVID-19 if they used a RAT, whereas the current LSTM model may wrongly detect COVID-19 in 17 out of 100 non-infected individuals.

"We would rather misdiagnose patients with COVID-19 than to miss cases of COVID-19," commented Ms Aljbawi. Although the LSTM model needs to be validated with more data and in independent cohorts, it has the potential to provide a more precise test than a RAT.

1. Aljbawi W, et al. Developing a multivariate prediction model for the detection of COVID-19 from crowd-sourced respiratory voice data. Digital medicine for COVID-19, OA1626, ERS International Congress 2022, Barcelona, Spain, 4–6 September.

Novel scoring tool for post-COVID syndrome aids clinicians and researchers

A post-COVID syndrome (PCS) scoring tool was developed, including the entire clinical spectrum of PCS in 12 binary questions. The tool was validated and could potentially be used for the diagnosis and stratification of patients with PCS. Also, the scoring tool could serve as a possible endpoint for clinical studies.

PCS is characterised by the persistence of symptoms for more than 3 months or the post-acute onset of symptoms, and/or the deterioration of pre-existing comorbidities [1]. "There is however no efficient scoring tool to diagnose PCS and to stratify the severity of the disease," according to Prof. Thomas Bahmer (University of Kiel, Germany) [2]. The COVIDOM population-based cohort study aimed to develop a PCS scoring tool [2,3].

In total, 667 patients with PCR-confirmed SARS-CoV-2 infections were included in the training cohort, and 459 and 316 patients were included in 2 validation cohorts. Standardised interviews and on-site examinations 6 and 12 months post-infection were conducted to gather information on symptoms of PCS. Based on 12 long-term symptom complexes, such as fatigue, cough/wheezing, neurological ailments, and joint and muscle pain, the authors designed a PCS scoring tool with weighted PCS scores for different symptoms (see Table).

Notably, higher scores on the PCS validation scoring tool were related to lower health-related quality-of-life scores, as was assessed by the EQ-5D-5L-VAS/-index (P<0.001), increased blood inflammatory markers (P<0.01), and decreased lung function (P<0.01). The number of acute symptoms and personal resilience, as determined by the Brief resilience scale, were predictive of higher PCS scores 9–12 months after the acute infection.

Table: Weighted post-COVID syndrome scoring tool [2]

No.	Symptom complex	Cluster centre			Registration coefficient	PCS score weight
		I (n=198)	II (n=287)	III (n=95)		
2	Fatigue	0.07	0.89	0.97	7.234	7
6	Cough, wheezing	0.02	0.02	0.38	6.881	7
9	Neurological ailments	0.15	0.86	0.96	6.434	6.5
4	Joint and muscle pain	0.02	0.04	0.57	6.366	6.5
5	ENT ailments	0.02	0.02	0.46	5.455	5.5
8	Gastrointestinal ailments	0.00	0.01	0.29	5.064	5.0
12	Sleeping disturbance	0.18	0.81	0.85	4.828	5.0
3	Excercise intolerence	0.05	0.50	0.93	4.033	4.0
11	Infection signs	0.02	0.14	0.47	3.372	3.5
1	Chemosensory deficits	0.17	0.16	0.53	3.318	3.5
7	Chest pain	0.02	0.05	0.28	3.259	3.5
10	Dermatological ailments	0.03	0.03	0.29	1.782	2.0

Prof. Bahmer emphasised that this easy-to-use tool may be used to diagnose PCS, evaluate the disease burden of patients, and may serve as a clinical endpoint in future trials.

1. Nalbandian A, et al. Nat Med. 2021;27(4):601-615.
2. Bahmer T, et al. Severity score-based study of predictors and clinical correlates of Post-COVID Syndrome (PCS) in Germany. Long COVID and rehabilitation, ERS International Congress 2022, Barcelona, Spain, 4–6 September.
3. Bahmer T, et al. EClinicalMedicine. 2022;51:101549.

COPD: Therapies and Innovations

Icenticaftor achieves results on top of triple inhalation therapy in COPD

After 24 weeks, the use of icenticaftor on top of triple inhalation therapy resulted in a clear dose-response on 5 endpoints in patients with COPD and chronic bronchitis. The 300 mg, twice-daily dose of the drug showed an encouraging benefit-risk profile and should be investigated in further trials.

A phase 2b trial (NCT02449018), conducted by Prof. Frits Franssen (Maastricht University, the Netherlands) and co-investigators, assessed the dose-response relationship of

the orally-active, CFTR channel potentiatior icenticaftor on top of a triple therapy of long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS) in patients with COPD (severity class GOLD 2 & 3) and chronic bronchitis (n=974) [1]. The trial included 5 icenticaftor arms, with doses ranging from 25 mg, twice daily, to 450 mg, twice daily, and a placebo arm. The primary endpoint was the change in trough forced expiratory volume in 1 second (FEV_1) from baseline to week 12.

The 450 mg arm of the study discontinued early for meeting a pre-specified, exposure-based stopping criterion. The 300 mg arm displayed the best efficacy results. Although the primary endpoint was not met, the 300 mg arm outperformed placebo with respect to trough FEV_1 levels at 24 weeks (least-squares mean 35 mL; 90% CI 0.0008–0.062). Other endpoints showed similar results for the 300 mg arm after 24 weeks of therapy: change in EXACT-Respiratory Symptoms (E-RS) cough and sputum score (-0.40), E-RS total score (-0.85), fibrinogen (-0.332), and number of daily puffs of rescue medication (-0.30).

No major safety concerns were observed for any of the treatment arms. Approximately 61% of the participants experienced at least 1 adverse event (AE), the most common being COPD exacerbations, diarrhoea, nausea, and nasopharyngitis.

Prof. Franssen emphasised that these results were obtained on top of maximum inhaled triple therapy. "The positive benefit-risk profile of the 300 mg, twice daily dose of icenticaftor supports further evaluation of this agent in patients with COPD and chronic bronchitis. Furthermore, we should look for a biomarker that helps us to select patients that are likely to benefit from additional icenticaftor."

1. Franssen FME, et al. Dose response of icenticaftor in patients with COPD and chronic bronchitis on triple inhaled therapy. ALERT 1, RCT710, ERS International Congress 2022, Barcelona, Spain, 4–6 September.

STARR2: A new approach for treating COPD exacerbations

A point-of-care, eosinophil-guided prescription of prednisolone was non-inferior to standard-of-care prescription of prednisolone in the treatment of COPD exacerbations, the multicentre, randomised STARR2 trial showed. Personalised, endotype-based prednisolone treatment is possible for patients with COPD and should be implemented in the clinical guidelines, argued the research team.

"Corticosteroids are known to increase harm in our patients," said Prof. Mona Bafadhel (King's College London, UK) [1]. Evidence suggests that eosinophil-directed oral corticosteroid (OCS) treatment is non-inferior to standard-of-care OCS [2,3]. The multicentre, double-blind, randomised, placebo-controlled STARR2 trial (NCT04458636) aimed to confirm these results [1]. Patients with COPD (n=203) were randomised to standard-of-care OCS or blood-eosinophil-directed OCS in the treatment of exacerbations. In the experimental condition, participants received a placebo if their eosinophil count was <2% and prednisolone if eosinophil count was ≥2%. The primary outcome was treatment failure at day 30.

In the intention-to-treat analysis, eosinophil-directed care was non-inferior to standard-of-care (RR 0.82; 95% CI 0.54–1.23; P=0.34), with 27% and 34% of failed treatments in the experimental arm and the control arm, respectively. The per-protocol analysis confirmed the non-inferiority of the experimental treatment compared with the control arm in terms of treatment failure (19% vs 32%; RR 0.60; 95% CI 0.33–1.04; P=0.07). In addition, forced expiratory volume in 1 second (FEV_1) results, COPD Assessment Test (CAT) scores, and Visual Analogue Score (VAS) symptom scores did not display significant differences between the 2 treatment arms.

This large, primary care, COPD study showed that point-of-care eosinophil-guided prescription of OCS is safe and not associated with worse outcomes than standard-of-care prescription of OCS, concluded Prof. Bafadhel. "This new approach should be implemented in the guidelines, because it offers a more precise treatment and may reduce harmful events in our patients."

1. Bafadhel M, et al. Point of care blood eosinophil guided oral prednisolone for COPD exacerbations: a multi-centre double blind randomised controlled trial (The STARR2 trial). ALERT 1, RCT711, ERS International Congress 2022, Barcelona, Spain, 4–6 September.
2. Bafadhel, M, et al. Am J Respir Crit Care Med. 2012;186(1):48–55.
3. Sivapalan P, et al. BMJ Open Respir Res. 2019;6(1):e000407.

COPD medication not effective in symptomatic smokers with preserved spirometry

Long-acting bronchodilators do not appear to improve respiratory symptoms in symptomatic tobacco-exposed individuals, data from the RETHINC trial indicated. These results suggest that the widespread use of COPD medications in these individuals should be reconsidered.

"Current and former smokers with spirometric values within the normal range are frequently treated with bronchodilators

or inhaled corticosteroids (ICS)," explained Prof. MeiLan Han (University of Michigan, MI, USA) [1–3]. These individuals are however not included in current GOLD guideline recommendations and a benefit of these medications is not established.

The multicentre, randomised, phase 3 RETHINC study (NCT02867761) compared a 12-week treatment of inhaled indacaterol/glycopyrrolate with placebo in current and former smokers with preserved spirometry and respiratory symptoms as defined by a COPD Assessment Test score of at least 10 (n=535) [1]. The primary endpoint was a 4-unit improvement on the St. George's Respiratory Questionnaire (SGRQ) without experiencing treatment failure during the treatment period. The results have been published in the *New England Journal of Medicine* [4].

The primary outcome was achieved by 56.4% and 59.0% of the participants in the intervention arm and placebo arm, respectively (P=0.65). This result was consistent across subgroups. "COPD drugs may not alleviate symptoms in symptomatic individuals with preserved pulmonary function, because these participants do not have the typical small airway disease that is targeted by COPD medication," argued Prof. Han.

"It is essential that individuals with suspected COPD are being tested with spirometry to select patients that may benefit from bronchodilators. Also, we need to investigate the drivers of symptoms in individuals with respiratory symptoms and preserved spirometric values," concluded Prof. Han.

1. Han MK, et al. Bronchodilators in Symptomatic Tobacco-exposed Persons with Preserved Spirometry for the RETHINC Study Group. ALERT 1, RCT712, ERS International Congress 2022, Barcelona, Spain, 4–6 September.
2. Woodruff PG, et al. N Engl J Med. 2016;371:1811–1821.
3. Kesimer M, et al. N Engl J Med. 2017;377(10):911–922.
4. Han MK, et al. N Engl J Med. Sep 4, 2022. Doi: 10.1056/NEJMoa2204752.

Do digital tools improve physical activity in COPD?

Compared with usual care, a web-based, self-management support tool improved the physical activity levels of patients with COPD, preliminary results of a randomised-controlled trial showed.

Physical activity has been associated with clinical benefits for patients with COPD, however, it is unclear which type of intervention results in the largest behavioural change [1]. The current randomised-controlled trial, presented by Prof. Andre Nyberg (University of Umeå, Sweden), included 146 patients with COPD to evaluate the effect of a web-based support tool on physical activity [2]. In the control arm, participants received usual care, a folder about physical activity in COPD, and a step counter. In the intervention arm, the participants received the options from the control arm plus access to the so-called COPD Web, including information on the benefits of physical activity, how to increase physical activity, exercises, and reminder messages.

After 3 months, the web-based intervention led to a clinically relevant improvement in physical activity compared with the control arm (mean change +1,227 steps/day; 95% CI 90–2,365). In addition, 50% versus 28% of the participants in the experimental arm and the control arm achieved a minimal clinically important difference of >600 steps per day.

"These preliminary results show that a web-based, self-management support tool may lead to an objective, clinically relevant improvement in physical activity in the short term compared with usual care," concluded Prof. Nyberg. "Furthermore, interview-based information teaches us that patients in the intervention arm felt an increased sense of control to improve their physical activity level by being able to use the web-based tool we developed."

1. Burge AT, et al. Cochrane Database Syst Rev. 2020;4(4):CD012626.
2. Stenlund T, et al. Clinically relevant effects on physical activity with web-based self-management support in people with COPD: a randomized controlled trial. ALERT 2, RCT2160, ERS International Congress 2022, Barcelona, Spain, 4–6 September.

Hyperpolarised gas MRI ready for clinical use

Hyperpolarised gas MRI showed to be a promising prognostic biomarker for patients with asthma and COPD. In addition, it is useful for monitoring disease and guiding localised therapy. The approval for clinical use has been established in the UK and is pending in the USA.

"Hyperpolarised gas MRI directly measures static ventilation, capturing information from the whole lung," explained Dr Sarah Svenningsen (McMaster University, Canada) at the start of her presentation [1]. The ventilation defect percent (VDP) is the relevant outcome of this method. Dr Svenningsen emphasised that hyperpolarised gas MRI showed that ventilation defects in patients with asthma and COPD are regionally heterogeneous and patient-specific [2,3]. Moreover, this method has demonstrated to be sensitive to disease-specific pathologic changes, such as smooth muscle dysfunction, mucus plugs, and cells in lumen in patients with

asthma [4,5], or emphysema in patients with COPD [6]. "Thus, hyperpolarised gas MRI can deliver high-resolution, visually appealing images, sensitive to disease pathology in asthma and/or COPD," summarised Dr Svenningsen.

Predict clinical outcomes

"How can we use this tool in the clinical management of patients with asthma and COPD?" asked Dr Svenningsen. Predicting clinical outcomes is one of the applications of hyperpolarised gas MRI. In patients with mild-to-moderate COPD, baseline MRI VDP was predictive of the longitudinal change in the St. George's Respiratory Questionnaire (SGRQ) and of annual forced expiratory volume in 1 second (FEV_1) change [7]. Another study showed that MRI VDP was the only measure to predict exacerbations requiring hospitalisation in patients with mild-to-moderate COPD [8]. Similarly, VDP was a significant predictor of 2-year exacerbation rate in patients with severe asthma [9]. "In summary, VDP measured with hyperpolarised gas MRI is a promising prognostic biomarker for patients with asthma and COPD," concluded Dr Svenningsen.

Monitoring disease and guiding localised therapy

In a similar fashion, MRI VDP has demonstrated to be a sensitive measure of treatment response in asthma and COPD populations and may be more sensitive than the gold-standard spirometry measurements of airflow obstruction [10,11]. This technique may also be used to guide localised therapies in asthma and COPD. For example, a study demonstrated that bronchial thermoplasty treatment guided by hyperpolarised gas MRI achieved the same clinical outcomes as the standard bronchial thermoplasty sessions without guidance, resulting in a reduced procedure time, decreased costs, and fewer adverse events [12].

"Next to these useful applications, regulatory approval for the clinical use of hyperpolarised gas MRI has been established in the UK and is pending in the USA. Also, initial clinical experiences of this highly sensitive, safe, objective, and non-invasive measure are being collected at this moment," concluded Dr Svenningsen.

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All About Asthma

Tezepelumab in asthma: mucus plugging down, lung function up

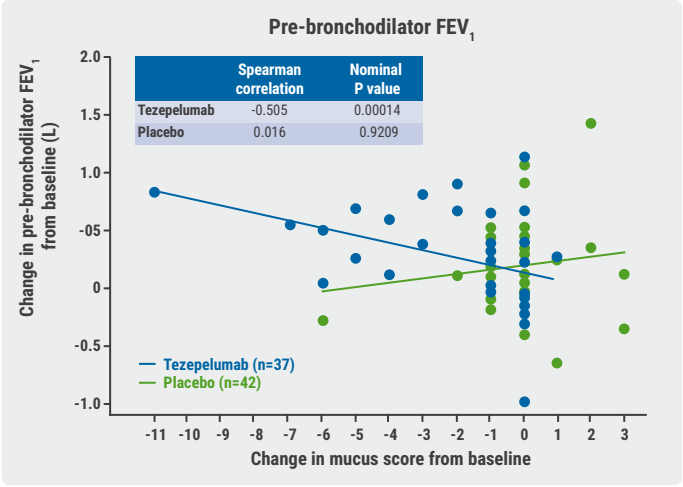
Tezepelumab reduced mucus plugging in patients with moderate-to-severe asthma. Moreover, reductions in mucus scores correlated with improvements in lung function. Tezepelumab is the first biologic agent to demonstrate these results in a randomised-controlled trial, emphasised the authors of the study.

Mucus plugging is a common disease characteristic in patients with asthma and is associated with eosinophilic airway inflammation and airway obstruction [1]. "However, the effect of biologic treatment on mucus plugs in patients with severe asthma had not been assessed until the execution of the phase 2 CASCADE study (NCT03688074)," said Prof. Christopher Brightling (University of Leicester, UK). This trial randomised 116 patients with uncontrolled, moderate-to-severe asthma 1:1 to tezepelumab or placebo. The primary analysis of CASCADE demonstrated a reduced submucosal eosinophil count for patients receiving tezepelumab compared with those receiving placebo [2]. The current, exploratory, post-hoc analysis examined mucus plugging before and after treatment using CT imaging [3]. In total, 82 patients had CT scans at baseline and at the end of treatment.

Baseline mucus scores were similar to those of comparable populations in previously published studies [1]. At baseline, blood eosinophil count was positively correlated with mucus score (ρ=0.24; nominal P=0.0006). In addition, pre-bronchodilator forced expiratory volume in 1 second (FEV_1)

scores were negatively related with mucus score (ρ=-0.325; nominal P=0.0017). After treatment, mucus scores were reduced in participants receiving tezepelumab but not in participants receiving placebo (mean change -1.7 vs 0.0; P=0.0007). Interestingly, post-treatment reductions in mucus scores correlated with improvements in lung function: change in pre-bronchodilator FEV_1 (ρ=-0.505; nominal P=0.00014; see Figure) and pre-bronchodilator forced expiratory flow (FEF) at 25–75% (ρ=-0.535; nominal P=0.0006).

Figure: Change from baseline in lung function parameters correlates with change from baseline in mucus score [3]



"This is the first, randomised-controlled trial to demonstrate the beneficial effect of a biologic agent on mucus plugging in patients with uncontrolled, moderate-to-severe asthma," concluded Prof. Brightling.

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Digital asthma intervention improves health and reduces costs

A pharmacy-supported, digital, medicine programme improved adherence to therapy and inhalation technique in patients with uncontrolled asthma, ultimately resulting in improved asthma control. Next to health benefits for the patients, the results suggest a potential for significant cost reductions.

"Adherence to therapy and an adequate inhaler technique are essential for optimal asthma control," explained Mr Luca Ponti (Amiko Digital Health, Italy). The current study compared a pharmacy-supported, digital, medicine programme, including inhaler sensors, mHealth apps, and in-person pharmacy-based counselling, with a traditional, pharmacy-based, patient-support programme in 68 participants with uncontrolled asthma [1].

The adherence to therapy was 82% in the experimental arm and 30–50% in the control arm. Furthermore, the digital intervention appeared to improve the rate of correct inhalation technique as compared with the control arm (64% vs 31%). At the end of the study, asthma control scores had improved by an average of 5.9 points in the intervention arm compared with 2.9 points in the control arm (P=0.007). Moreover, the digital intervention was associated with a larger annual cost saving than the control arm (€466; P=0.04).

"The combination of inhaler sensors, mHealth applications, and pharmacist counselling may improve adherence and inhalation technique in patients with uncontrolled asthma, leading to improved asthma control and cost savings," concluded Mr Ponti.

1. Onnis C, et al. Effect of pharmacy-supported digital medicine program on asthma control. ALERT 2, RCT2162, ERS International Congress 2022, Barcelona, Spain, 4–6 September.

Digitally enhanced therapy lowers treatment burden and costs in severe asthma

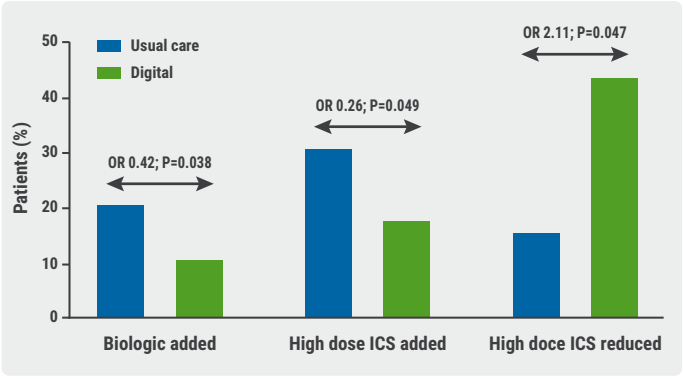
The treatment burden for patients with severe asthma was significantly reduced by using a digital tool set informing evidence-based care, including data on medication adherence, inhaler technique, and peak flow. Importantly, the lower treatment burden in the digital care group was not associated with a hampered asthma control.

"Medical adherence, inhaler technique, and underlying comorbidities are practical challenges in the assessment of patients with asthma," stated Prof. Richard Costello (Bon Secours Hospital Dublin, Ireland) [1]. Objective measures are needed to separate patients with difficult-to-treat asthma from those with severe asthma. The INCA-SUN trial (NCT02307669) randomised 216 patients with severe, uncontrolled asthma to the experimental arm, in which participants received personalised biofeedback on inhaler adherence, technique, and peak expiratory flow, with treatment decisions being informed by digital data, or to usual care.

At week 32, 11% of participants in the experimental group and 21% of the participants in the usual care arm required add-on biologic therapy (OR 0.42; P=0.038). In addition, participants in the usual care arm more often received added

high doses of inhaled corticosteroids (ICS) compared with the experimental arm (OR 0.26; P=0.049). A reduction in high-dose ICS was more frequently reported in the digital arm than in the usual care arm (OR 2.11; P=0.047; see Figure).

Figure: Digitally-informed decisions lead to better outcomes [1]



OR, odds ratio.

The authors showed that adherence was approximately 10% higher in the digital arm than in the control arm. Importantly, asthma control rates, lung function, T2 inflammation, and exacerbation rates were comparable between the 2 study arms, indicating that the digital approach achieved asthma control more frequently by improving the current therapy instead of escalating therapy.

Finally, Prof. Costello said that the direct medical costs for 1 individual were €3,000 less in the digital arm than in the usual arm.

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Mepolizumab beneficial for patients with severe eosinophilic asthma

In patients with severe eosinophilic asthma, continued reductions in clinically significant exacerbations were reported with the administration of mepolizumab after 2 years of follow-up. The current, real-world study confirmed the benefits of this IL-5 inhibitor in everyday practice.

The prospective, observational, single-arm REALITI-A study investigated the real-world benefits of mepolizumab in patients with severe eosinophilic asthma (n=823). Participants received 12 months of pre-treatment prior to enrolment, consisting of standard-of-care plus mepolizumab, and were subsequently followed for 24 months. Outcomes included the rate of clinically significant exacerbations, the use of maintenance oral corticosteroids (OCS), and exacerbations leading to hospital or emergency department admissions. The results after 1 year of follow-up were reported previously [1]. Dr Rupert Jakes (GSK, UK) presented the trial results after an additional 12 months of follow-up [2].

After 2 years of follow-up, 73% of the study population still received mepolizumab. Of those who had discontinued the study drug, 9% did this because of a perceived lack of efficacy. The clinical benefits of mepolizumab that had been reported after 1 year of follow-up were maintained after 2 years of follow-up. Compared with the pre-treatment period, the rate of clinically significant exacerbations (rate ratio 0.26; P<0.001) and the rate of exacerbations requiring hospitalisations or emergency department visits (rate ratio 0.21; P<0.001) were reduced significantly. Moreover, a 100% reduction in the daily median maintenance OCS dose was recorded at 2 years of follow-up; 57% of the participants using maintenance OCS at baseline had discontinued this therapy by week 101–104. According to Dr Jakes, no unexpected safety issues were observed.

In total, 90 treatment-related adverse events were reported, of which 18 led to the discontinuation of the study drug. One of the 7 treatment-related serious adverse events, a case of diffuse liver malignancy, resulted in the death of a patient.

Overall, the 2-year follow-up results of the REALITI-A trial confirmed the clinical benefits of mepolizumab in patients with severe eosinophilic asthma.

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Progress in Paediatrics

Antibiotics cause increased risk of wheezing in severe RSV bronchiolitis

The antibiotic agent azithromycin was associated with an increased risk for subsequent recurrent wheezing in patients with early-life, severe respiratory syncytial virus (RSV) bronchiolitis. Other antibiotics are likely to have the same harmful effect. "Leave the kids alone," pleaded the authors of the study.

Recurrent wheezing and asthma often occur after severe RSV bronchiolitis [1]. Aiming to solve this clinical problem, Prof. Avraham Beigelman (Schneider Children's Medical Center of Israel, Israel) and co-investigators developed a randomised trial to analyse whether azithromycin outperformed placebo with respect to recurrent wheezing in hospitalised patients with RSV bronchiolitis (n=200; 1–18 months of age). The primary results did not demonstrate a difference between placebo and azithromycin on recurrent wheezing after an RSV infection [2]. Prof. Beigelman presented the results of a post-hoc analysis of this trial, investigating the influence of non-macrolide antibiotics on the effect of azithromycin on recurrent wheezing [3].

In participants receiving other antibiotics next to azithromycin (30%), there was no difference in the risk for recurrent wheezing between the azithromycin arm and the placebo arm (HR 0.94; 95% CI 0.43–2.07; P=0.88). In contrast, in the no-other-antibiotic-stratum, participants receiving placebo performed better than participants receiving azithromycin (HR 1.79; 95% CI 1.03–3.1; P=0.037). In fact, the study showed that the use of any antibiotic may increase the risk of recurrent wheezing compared with placebo (HR 1.65; 95% CI 1.00–2.72; P=0.048).

"These results indicate that azithromycin, and likely other antibiotic agents, should be avoided during early-life, severe, RSV bronchiolitis," emphasised Prof. Beigelman. "In our next project, we will investigate whether the harmful effect of antibiotics is due to the impact these medications have on the gut microbiome."

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Inhaled corticosteroids useful in preterms with decreased lung function

The use of inhaled corticosteroids (ICS) improved the lung function of prematurely born children in a randomised-controlled trial. The results suggest that bronchodilator responsiveness may be used to screen eligible infants for this approach.

Preterm-associated lung disease is a common complication and evidence indicates that the lung function of patients that were born preterm worsens over time [1,2]. A randomised, clinical trial demonstrated that ICS may be administered to improve lung function in preterm-born children [3]. The current PICSI study, conducted by Prof. Shannon Simpson (Curtin University, Australia) and colleagues, randomised 170 survivors of very preterm birth (≤32 weeks gestation) to a 12-week course of the ICS fluticasone propionate or to placebo [4].

A modest but significant difference in % forced expiratory volume in 1 second (FEV_1)-change was observed between the fluticasone arm (5.93%) and the placebo arm (1.75%; P=0.01). Changes in FEV_1/forced vital capacity (FVC) also favoured the intervention arm over the placebo arm (3.69% vs -0.79%; P=0.013), as did changes in fractional exhaled nitric oxide (FeNO) (-4.92 vs 0.11; P=0.01). Prof. Simpson added that 21.3% of the participants had a clinically significant improvement in FEV_1. Finally, multivariate analysis showed that bronchodilator responsiveness was an independent predictor of the efficacy of ICS in these participants (P<0.001).

"Although our study observed only a modest improvement in lung function after a course of ICS, a significant proportion of patients was highly responsive to this treatment," according to Prof. Simpson. "Bronchodilator responsiveness may be used to screen for these patients, but further studies are needed to predict which children are most likely to benefit from ICS."

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Fish oil or vitamin D during pregnancy can prevent croup

Taking fish oil and/or high-dose vitamin D supplements during pregnancy has a protective effect on childhood croup, demonstrated a randomised-controlled trial. If this finding is confirmed in other trials, 2 cheap micronutrient supplies could be efficiently used in the prevention of this common childhood respiratory disease.

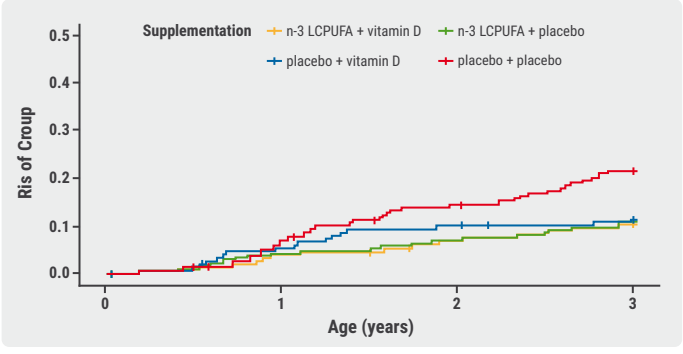
Croup is a common respiratory disease among children aged 6 months to 3 years [1]. Mostly, the disease is mild, but it can lead to hospitalisations in severe cases [2,3]. Furthermore, it has been suggested in various studies that fish oil and vitamin D play a role in the development of the immune system and lung tissue [4,5]. Dr Nicklas Brustad (University of Copenhagen, Denmark) and co-investigators designed a randomised-controlled trial to examine the influence of fish oil and vitamin D supplements during pregnancy on the incidence of childhood croup [6]. Pregnant Danish women (n=623) were allocated to 1 of the 4 study arms:

- High-dose vitamin D (2800 IU/day) and fish oil;
- Standard-dose vitamin D (400 IU/day) and fish oil;
- High-dose vitamin D and placebo; or
- Standard-dose vitamin D and placebo.

After their birth, children were followed from age 0 to 3 years during planned visits to measure any experienced acute respiratory symptoms.

A significantly beneficial effect was observed for the intake of fish oil versus the intake of placebo on the risk of croup (11% vs 17%; HR 0.62; 95% CI 0.41–0.93; P=0.02). Interestingly, high-dose vitamin D significantly reduced the risk of croup compared with standard-dose vitamin D (11% vs 18%; HR 0.60; 95% CI 0.38–0.93; P=0.02). There was no interaction effect between the supplements on the risk of croup ($P_{interaction}$=0.56).

Figure: No evidence of interaction between supplements [6]



n-3 LCPUFA, fish oil supplement.

"Observing the Kaplan-Meier curves, we can clearly see that there is no additive effect from 1 intervention to the other, suggesting that there is a ceiling effect of the 2 interventions (see Figure)," clarified Dr Brustad.

In summary, this is the first randomised-controlled trial to demonstrate protective effects of both fish oil and high-dose vitamin D supplements during pregnancy on the occurrence of childhood croup.

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Encouraging results of nintedanib in children with fibrosing ILD

With an acceptable safety profile and promising efficacy data, nintedanib is a potential candidate for treating children and adolescents with fibrosing interstitial lung disease (ILD).

There is a clear medical need to find treatment options for childhood ILD. Nintedanib could be a potential candidate due to its shown benefits in adults with fibrosing ILD and the existing similarities in the pathophysiology of fibrotic lung remodelling in adults and children [1,2]. To investigate nintedanib in children, Dr Robin Deterding (Children's Hospital Colorado, CO, USA) and colleagues designed the phase 3 InPedILD trial (NCT04093024) [3,4].

Patients aged 6–17 with fibrosing ILD (n=39) were randomised 2:1 to nintedanib or placebo in the 24-week, double-blind period. Hereafter, all participants received nintedanib in the open-label phase of the trial. Nintedanib dose was based on weight, ranging from 50 mg, twice daily, for patients between 13.5 and 23 kg, to 150 mg, twice daily, for patients ≥57.5 kg. The co-primary endpoints were area under plasma concentration-time curve at steady state and treatment-emergent adverse events after 24 weeks of therapy.

The exposure achieved with weight-based dosing was within the range observed in adults who were treated with nintedanib 150 mg, twice daily. Regarding safety, 84.6% of the participants experienced at least 1 adverse event, irrespective of treatment arm. As expected by the authors, diarrhoea was the most common adverse event in the

nintedanib arm (38.5%). In the control arm, only 15.4% of the patients experienced diarrhoea. Other frequently reported adverse events were vomiting, dental caries, nausea, and abdominal pain, with comparable rates for the 2 study arms.

Although the study was not powered to assess efficacy, the trends favoured the experimental arm: adjusted mean change in forced vital capacity (FVC) predicted at week 24 was 0.3% for nintedanib versus -0.9% for placebo; adjusted mean change in peripheral capillary oxygen saturation (SpO_2) at rest after 24 weeks of therapy was 0.07% for nintedanib versus -2.25% for placebo.

"These data support a positive benefit-risk assessment for the use of nintedanib in children and adolescents with fibrosing ILD," concluded Dr Deterding.

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Focus on Interventional Pulmonology

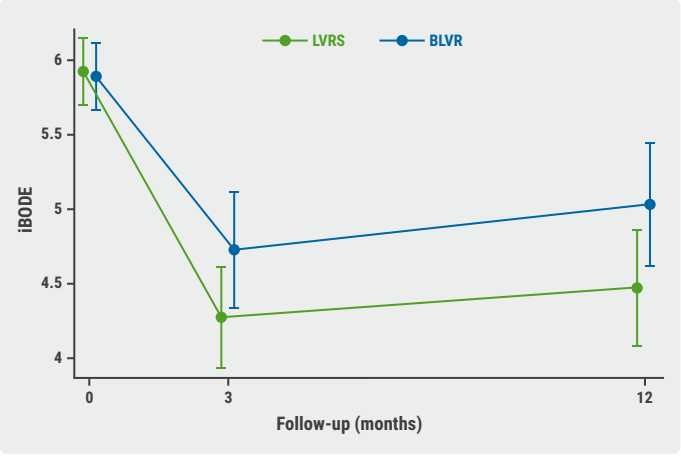
Head-to-head: lung volume reduction surgery vs endobronchial valves

Lung volume reduction surgery (LVRS) was not significantly superior to bronchoscopic lung volume reduction (BLVR) with valve placement in patients with emphysema who were eligible for both treatment options. These important findings to guide treatment decisions are currently being evaluated in a larger trial.

Although LVRS and endobronchial valves (EBVs) have both demonstrated to improve lung function, exercises capacity, and quality-of-life for patients with emphysema, no existing clinical trials have directly compared LVRS with the use of EBVs [1,2]. The randomised, single-blind CELEB trial (ISRCTN19684749) assessed whether LVRS was superior to BLVR in patients with emphysema who were suitable for both procedures (n=88) [3]. The primary endpoint was the Body-mass index, airflow Obstruction, Dyspnea, and Exercise index (i-BODE) score at 12 months, a measure that includes forced expiratory volume in 1 second (FEV_1) % predicted, exercise capacity, dyspnoea, and BMI. Ms Sara Buttery (Royal Brompton and Harefield NHS Foundation Trust, UK) presented the results.

The improvements on the i-BODE score at 12 months were comparable for LVRS and BLVR (-1.10 vs -0.82; P=0.54; see Figure). Analysis of the single components of the i-BODE score did not reveal a significant advantage of 1 treatment over the other. Moreover, the residual volume % (RV%) predicted was similar in the LVRS arm and BLVR arm (-36.1% vs -30.1%; P=0.81). Finally, the safety of the procedures appeared to be similar, with 1 death at 12 months in each arm of the study.

Figure: Primary outcome of the CELEB trial [3]



i-BODE, Body-mass index, airflow Obstruction, Dyspnea, and Exercise index; LVRS, lung volume reduction surgery; BLVR, bronchoscopic lung volume reduction.

Ms Buttery concluded that LVRS was not substantially superior to BLVR in the current trial. A larger trial (NCT04537182) is underway to confirm these findings and to evaluate the cost-benefit of the 2 treatments.

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Durable effect of endobronchial valves in severe emphysema

The randomised-controlled EMPROVE trial demonstrated long-term added clinical benefits of bronchoscopic placement of endobronchial one-way valves with the Spiration® Valve System (SVS) over medical management alone in treating hyperinflation in patients with severe heterogenous emphysema.

Minimally-invasive, bronchoscopic placement of endobronchial one-way valves has demonstrated to improve pulmonary function, reduce hyperinflation, and improve dyspnoea severity in patients with COPD and emphysema [1]. However, it is not established whether this treatment is superior to 'no intervention' in the long term. The EMPROVE trial (NCT01812447) randomised 174 patients with severe, heterogenous emphysema 2:1 to active treatment with the SVS on top of medical management or to medical management alone. Assessed were several quality-of-life endpoints to compare the 2 arms of the trial. The positive primary results of the trial were published in 2019 [2]. Prof. Gerard Criner (Temple University, PA, USA) presented the results after 24 months of follow-up [3].

The results displayed significant benefits of the intervention arm over the control arm in terms of severe dyspnoea (P<0.01), St. George's Respiratory Questionnaire (SGRQ) total score (P<0.05), the COPD assessment test score (P<0.05), and forced expiratory volume in 1 second (FEV_1) (P<0.05). Although the intervention arm was associated with a higher rate of serious adverse events in the short term (0–6 months; 28.3% vs 8.5%; P=0.003), this pattern was no longer significant in the long term (12–24 months; 29.6% vs 20.5%; P=0.309), indicating durability of the procedure.

"The EMPROVE trial demonstrated that SVS treatment provides a long-term clinical benefit in disease-specific, health-related quality-of-life, dyspnoea, and lung function in patients with severe heterogenous emphysema," concluded Prof. Criner.

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Cone beam CT-guided ENB improves detection of pulmonary nodules

Cone beam CT (CBCT) guidance to electromagnetic navigation bronchoscopy (ENB) for the diagnosis of pulmonary nodules significantly increased the diagnostic yield and diagnostic accuracy of transbronchial biopsy for small size nodules, compared with ENB without CBCT guidance.

The diagnostic yield for detecting lung nodules via 'classical' forceps transbronchial biopsy is low, with only a 14% success rate if it concerns peripheral nodules less than 2 cm in diameter [1]. ENB increases the diagnostic yield of transbronchial biopsy to 52–72.9% [2–3]. However, this procedure lacks real-time confirmation of the position of the catheter and biopsy tools [4]. "CBCT guidance of ENB allows for real-time control of the position of the catheter, enhanced fluoroscopy, and trans-parenchymal access," added Prof. Benjamin Bondue (Université Libre de Bruxelles, Belgium) [5]. Therefore, a randomised-controlled trial was designed to evaluate the benefit of CBCT guidance to ENB for the diagnosis of peripheral nodules [5].

The study group randomised 49 patients with pulmonary nodules that were a maximum of 30 mm in diameter to ENB or to CBCT-guided ENB. The primary outcome was the diagnostic yield and the diagnostic accuracy for malignancy.

The CBCT arm outperformed the regular ENB arm with respect to diagnostic yield (80% vs 42%; P=0.023) and diagnostic accuracy (83% vs 52%; P=0.025). The duration of the CBCT procedure was longer than that of the non-guided ENB procedure (80 vs 61 minutes; P=0.001). Pneumothorax occurred in 8% of the participants in the non-guided ENB arm and in 4% of the participants in the CBCT arm (P=0.819). In addition, moderate bleeding occurred in 17% and 4% of the participants in the non-guided ENB arm and the CBCT arm, respectively (P=0.143).

In summary, the use of CBCT guidance during ENB significantly increased the diagnostic yield and accuracy of transbronchial biopsy for small size nodules. Although the analysis did not reveal significant differences with regard to safety due to the limited numbers of participants included in this trial, CBCT may come with additional safety benefits. "This is an issue that should be investigated in the future. Also, subgroup analyses should be performed to examine which patients would benefit from CBCT guidance and which patients would not necessarily need this procedure," concluded Prof. Bondue.

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Confirmatory mediastinoscopy not needed in resectable NSCLC

After a well performed, negative, systematic endosonography, confirmatory mediastinoscopy could be omitted in patients with resectable non-small cell lung cancer (NSCLC), the randomised-controlled MEDIASTrial demonstrated. Since mediastinoscopy is associated with morbidity and a delay in the treatment of patients with NSCLC, these findings are of clinical importance.

"The guidelines tell us to perform endosonography and confirmatory mediastinoscopy in advance of anatomical resection and lymph node dissection in patients with resectable NSCLC," said Prof. Jouke Annema (Amsterdam UMC, the Netherlands) [1,2]. However, the role of confirmatory mediastinoscopy is under debate due to the upcoming experience and accuracy of endosonography as well as the negative impact that this surgical procedure may have on patients. Dr Annema and colleagues conducted the non-inferiority MEDIASTrial to assess whether confirmatory mediastinoscopy could be omitted after tumour-negative, systematic endosonography [2].

In total, 346 patients with resectable NSCLC were randomised 1:1 to immediate lung tumour resection or to mediastinoscopy. Unforeseen N2 disease after lymph node dissection was the primary outcome, with a non-inferiority margin of 8%.

In the intention-to-treat analysis, unforeseen N2 disease was observed in 8.8% of the participants in the immediate intervention group compared with 7.7% in the mediastinoscopy group (non-inferiority P=0.014). Likewise, in the per-protocol analysis, unforeseen N2 disease was identified in 9.0% of the participants in the immediate resection arm and in 8.2% of the participants in the mediastinoscopy arm (non-inferiority P=0.016). Major morbidity rates were comparable between the 2 groups, with 12% and 13% in the immediate resection and mediastinoscopy arm respectively. Finally, 30-day mortality data displayed that 2 deaths had occurred in the immediate resection arm and that 5 deaths had occurred in the mediastinoscopy arm (P=0.27).

The MEDIASTrial demonstrated that confirmatory mediastinoscopy could be omitted after negative systematic endosonograpy in patients with resectable NSCLC, concluded Prof. Annema.

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Sleep and Breathing Disorders

In the spotlight: Cancer trends in obstructive sleep apnoea

A large, Swedish cohort study showed that obstructive sleep apnoea (OSA)-mediated intermittent hypoxia was related to cancer prevalence. Notably, lung cancer, prostate cancer, and malignant melanoma displayed independent associations with the number of breathing events per hour in patients with OSA.

"Nocturnal intermittent hypoxia in OSA is associated with increased prevalence of cancer," claimed Dr Andreas Palm (Uppsala University, Sweden) [1]. The current, population-based, prospective, observational DISCOVER study assessed the relation between several OSA measures and cancer prevalence. Information on 62,811 patients who were treated with continuous positive airway pressure (CPAP) was retrieved from various Swedish registries, such as the Swedish Cancer Registry, the Swedish National Patient Registry, and the Swedish Prescribed Drug Registry [2]. In total, 44,197 CPAP-treated participants with OSA did not have a cancer diagnosis within 5 years prior to CPAP, whereas 2,093 participants did have a cancer diagnosis. Propensity score matching was performed, controlling for anthropometric data, comorbidities, and socioeconomic factors.

Participants with cancer had a higher number of breathing events per hour than those without cancer, the apnoea hypopnoea index (AHI) demonstrated (32 vs 30; P=0.002). Also, the Epworth sleepiness scale (ESS) displayed that those with cancer were slightly more sleepy than those

without cancer (10.0 vs 9.6; P=0.020). Next to these findings, it was shown that participants in the highest quartile of the oxygen desaturation index were relatively more likely to have cancer (25.7% vs 20.8%; P<0.001). Interestingly, certain types of cancer were specifically linked to an increased number of events per hour on the oxygen desaturation index compared with those without cancer: lung cancer (38 vs 27 events; P=0.012); prostate cancer (28 vs 24 events; P=0.005); and malignant melanoma (32 vs 25 events; P=0.015).

Overall, Dr Palm concluded that OSA-mediated intermittent hypoxia was independently related with cancer prevalence in the current cohort study. "We aim to investigate the possible influence of OSA treatment on cancer incidence in future, longitudinal studies," said Dr Palm at the end of his presentation.

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Impact of CPAP on cardiac endpoints in OSA

Prof. Anita Simonds (National Heart & Lung Institute, UK) critically reviewed the available data on the link between continuous positive airway pressure (CPAP) therapy and cardiovascular outcomes in patients with obstructive sleep apnoea (OSA). Also, she painted a picture on how to synchronise randomised-controlled trial (RCT) data with clinical practice.

Evidence from RCTs

Nocturnal heart rate changes, sleep arousal burden, hypoxic burden, total sleep time with oxygen saturation <90%, and duration of obstructive events are established risk factors for cardiovascular diseases (CVD) in patients with OSA [1]. "But what is the impact of CPAP therapy on cardiac outcomes in these patients?" asked Prof. Simonds. To answer this question, she discussed data from important trials that investigated the use of CPAP for the secondary prevention of CVD in patients with OSA [2].

The SAVE trial (NCT00738179) randomised 2,717 patients with OSA and prevalent CVD to CPAP therapy or the control group. After a follow-up of 43 months, there was no benefit for the participants who had received CPAP compared with those who had not received this therapy (HR 1.10; 95% CI 0.91–1.32). However, there was an effect for participants who had a higher adherence to CPAP therapy (>4 hours per night; HR 0.52; 95% CI 0.30–0.90) [3]. Interestingly, the RICCADSA trial (NCT00519597) and the ISAACC trial (NCT01335087) demonstrated a similar pattern: participants with a better adherence to CPAP therapy appeared to have a benefit in terms of cardiovascular outcomes [4,5]. "Thus, the consensus from clinical trials is that the use of CPAP is not associated with a reduction in cardiovascular events, except for patients who use CPAP therapy >4 hours per night," summarised Prof. Simonds.

The way forward

"This is however not the end of the story," commented Prof. Simonds. A post-hoc analysis of the SAVE trial demonstrated that participants with cerebrovascular disease and diabetes mellitus were more likely to benefit from CPAP therapy in terms of stroke reduction than participants with cerebrovascular disease alone, participants with CVD and diabetes mellitus, or participants with CVD alone [6]. Also, younger participants, participants with greater desaturation, or participants with increased obesity were more likely to achieve cardiovascular benefits from CPAP therapy [7]. "These results indicate that phenotyping and clustering is important," stressed Prof. Simonds.

Next, it has been shown that hypoxic burden and T90 are more closely linked to cardiovascular outcomes than the apnoea hypopnoea index (AHI) or the oxygen desaturation index (ODI), notwithstanding that these last 2 measures have been used to stratify participants in clinical trials [8]. Furthermore, less than 20% of the patients in the clinic meet the criteria for randomised-controlled trials, displaying a large discrepancy between trial results and clinical practice [9]. "Therefore, we need to incorporate new evidence, preferably real-world evidence," argued Prof. Simonds. "These studies should also include more women and patients from various ethnic backgrounds and report on patient-related outcome measures. In this way, we can start to synchronise the results from randomised clinical trials with everyday clinical practice."

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Sustained hypoxaemia predicts unprovoked VTE in OSA

In patients with obstructive sleep apnoea (OSA), the number of minutes during a night of sleep where a patient's oxygen saturation is 90% or lower (T90) was associated with the incidence of unprovoked venous thromboembolism (VTE). In contrast, the apnoea hypopnoea index (AHI), reflecting intermittent hypoxaemia in patients with OSA, was not a good predictor for VTE.

Several pathophysiological studies suggest that OSA might be a risk factor for VTE [1]. However, a recent cohort study showed that the AHI may not be as good as a predictor for VTE as for sustained hypoxaemia [2]. Prof. Wojciech Trzepizur (University of Angers, France) and his research team evaluated the relation between several measures of nocturnal hypoxaemia and unprovoked VTE in patients with OSA, to confirm the results of this recent study [3]. Between 2007 and 2018, the disease profile of 7,355 patients with suspected OSA was composed via OSA severity markers, AHI, T90, the oxygen desaturation index (ODI), and the hypoxic burden (total area under the respiratory event-related desaturation curve).

Participants who experienced an unprovoked VTE (n=142) were generally older, had a higher BMI, and were more likely to have comorbidities. The unadjusted analysis showed a significant effect of T90 on the incidence of VTE (log T90; HR 1.10; P<0.0001). Likewise, a higher hypoxic burden was related to an increased occurrence of VTE. AHI and ODI did not demonstrate a link with the incidence of VTE. After adjustment for demographic factors and comorbidities, T90 was still associated with an increased risk of VTE events (log T90; HR 1.06; P=0.0216). Moreover, in participants who had an oxygen saturation below 90% for more than 6% of their total sleep time, the risk of unprovoked VTE was doubled (HR 1.98; P=0.0359). Hypoxic burden was no longer a significant predictor of VTE after controlling for confounding factors. Finally, the authors did not find an association between CPAP adherence and the risk of VTE.

"T90 was the only independent predictor of VTE in this study," stressed Prof. Trzepizur. "These findings are consistent with the results that were reported by Genuardi et al. [2], confirming that T90 plays an important role in the occurrence of VTE events in patients with OSA."

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CPAP therapy in the prevention of cardiovascular risk in patients with OSA

Continuous positive airway pressure (CPAP) therapy is not always beneficial in the prevention of cardiovascular events in patients with obstructive sleep apnoea (OSA), due to low CPAP usage, inclusion of non-sleepy patients, and the usage of wrong selection criteria. New markers, such as hypoxic burden, are showing potential in stratifying patients with OSA for cardiovascular risk. For non-sleepy patients with OSA, there is a need still for specific cardiovascular-associated markers to demonstrate the benefit of CPAP therapy on cardiovascular risk.

"We should not forget that the main target of CPAP therapy is to treat sleepiness in patients with OSA," said Prof. Raphael Heinzer (Lausanne University Hospital, Switzerland) at the start of his presentation on the future of sleep science [1]. For this clinical outcome, CPAP has demonstrated to be an effective therapy [2]. In addition, excessively sleepy patients with OSA are at increased risk for cardiovascular diseases [3]. However, the majority of patients with OSA does not report sleepiness [4]. "So how do we treat the non-sleepy patients? And which patients are likely to benefit from CPAP in terms of cardiovascular risk reduction?"

The SAVE study did not show a clear benefit of CPAP therapy in the secondary prevention of adverse cardiovascular events in patients with OSA [5]. "Why did we not see an effect of this intervention in these patients?" asked Prof. Heinzer. Possible explanations are the low CPAP usage (<3 hours per night) in these trials or the fact that these trials included non-sleepy patients. Irreversible cardiovascular damage and the use of the apnoea hypopnoea index (AHI) as an inadequate selection criterion are other potential explanations. "Indeed, patients with AHI <15/hour and patients with AHI >15/hour did not differ with respect to their risk for cardiovascular incidences," stated Prof. Heinzer [6]. Fortunately, other markers that might have potential in stratifying patients with OSA for cardiovascular risk are emerging. Hypoxic burden was a significant predictor of cardiovascular death and cardiovascular events in 2 cohorts [7,8]. Next to this measure, the sleep apnoea-specific pulse-rate response as well as pulse-wave amplitude drops have been associated with the risk for cardiovascular events [4,9]. "Pulse-wave amplitude drops reflect peripheral vasoconstriction resulting from sympathetic activation," clarified Prof. Heinzer. Interestingly, low pulse-wave amplitude drops were linked to a higher

incidence of cardiovascular events. Prof. Heinzer argued that endothelial dysfunction or a blunted autonomic reactivity may be the underlying causes that explain this association.

"We need prospective primary prevention studies including patients with OSA stratified to more specific cardiovascular-associated markers, to demonstrate the benefit of CPAP therapy on cardiovascular risk in non-sleepy patients with OSA," continued Prof. Heinzer. "However, randomised trials are not feasible in primary prevention for ethical reasons." Follow-up of prospective clinical real-world cohorts appears to be the most suitable study design. Propensity score matching, inverse probability of treatment weighting, and other inventive techniques should be applied to gain reliable well-balanced data.

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Other Remarkable Research

Excellent results for high-flow nasal cannula oxygen therapy in acute respiratory failure

In patients with acute hypoxemic respiratory failure, high-flow nasal cannula (HFNC) oxygen therapy was superior to non-invasive ventilation (NIV) in preventing progression to invasive mechanical ventilation. Furthermore, the HFNC technique was very well tolerated by most patients, supporting its use in this population.

Prof. Gamal Agmy (Assiut University, Egypt) and colleagues conducted a randomised clinical trial (NCT03788304) to compare HFNC (n=50) with standard NIV (n=50) in patients who were admitted to the intensive care unit (ICU) with type 1 respiratory failure [1,2]. The primary endpoint was the rate of endotracheal intubation.

Progression to this invasive mechanical ventilation was 50.0% in the NIV arm versus 18.0% in the HFNC arm (P<0.001). The most distinctive causes of progression to mechanical ventilation were retained secretions (48.0% vs 0.0%; P=0.010) and worsening conscious level (12.0% vs 0.0%; P=0.042); both results that favoured the HFNC arm. Importantly, duration of ICU stay (6.0 vs 4.0 days; P=0.001), duration of hospital stay (9.5 vs 7.0 days; P=0.002), and duration of device usage (3.0 vs 2.0 days; P=0.057) were all shorter in the HFNC arm compared with the NIV arm. Prof. Agmy pointed out that HFNC was extremely well tolerated by most patients and that complications such as nasal bridge ulceration (48.0% vs 0%), leak (84.0% vs 0%), asynchrony (74.0% vs 0%), claustrophobia (40.0% vs 0%), retained secretions (32.0% vs 0%), and facial laceration (32.0% vs 0%) were only observed in the NIV arm. Finally, survival rates (52.0% vs 82.0%) displayed a substantial advantage for patients in the HFNC arm over patients in the NIV arm.

Prof. Agmy concluded that these results add to the growing body of evidence that HFNC oxygen therapy is better tolerated than NIV and is associated with lower mortality rates and lower rates of treatment failure. "HFNC is a more physiological technique. The delivery of heated, humidified oxygen at high-flow rates leads to a number of positive effects on the airways and respiratory function, potentially changing the management for patients with acute and chronic respiratory failure."

1. Agmy G, et al. High-flow nasal cannula versus noninvasive ventilation in the prevention of escalation to invasive mechanical ventilation in patients with acute hypoxemic respiratory failure. ALERT 1, RCT715, ERS International Congress 2022, Barcelona, Spain, 4–6 September.
2. Agmy G, et al. Egypt J Chest Dis Tuberc. 2022;71(1):81.

Antifibrotic therapy may slow down FVC decline in RAILD

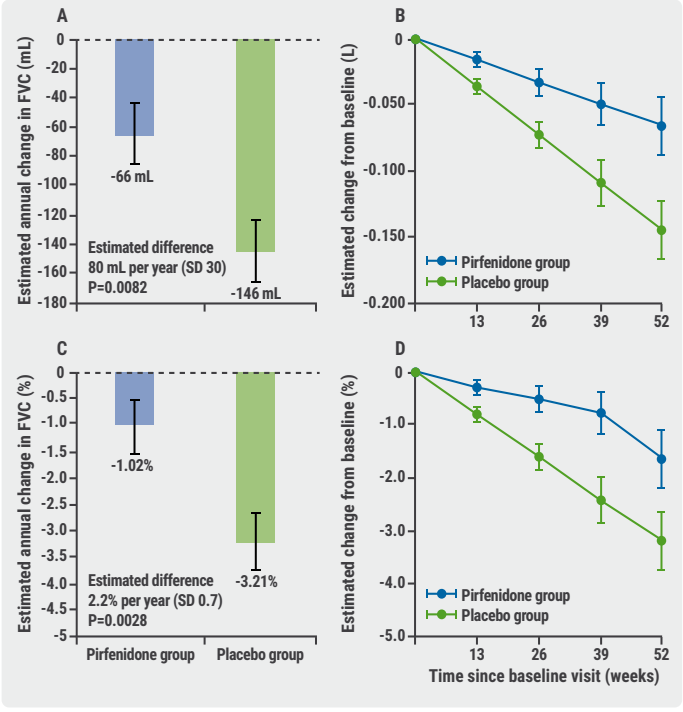
The TRAIL1 study examining pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease (RAILD) did not meet its primary endpoint. Nonetheless, a trend was observed towards a beneficial effect for

the agent under investigation, especially for patients with RAILD who displayed a pattern of usual interstitial pneumonia (UIP) on CT imaging.

Rheumatoid arthritis (RA) is the most common connective tissue disease, with a prevalence of 0.75% in the USA [1]. In addition, interstitial lung disease (ILD) can occur in up to 60% of the patients with RA [1]. To target RAILD, Prof. Ivan Rosas (Baylor College of Medicine, TX, USA) and colleagues designed the phase 2 TRAIL1 study (NCT02808871), which randomised 123 patients with RAILD to the antifibrotic agent pirfenidone or placebo [2]. The primary endpoint was a decline in percent predicted forced vital capacity (FVC) by 10% or more, or death.

Although Prof. Rosas mentioned that the primary endpoint was not met, a positive effect of pirfenidone on the estimated annual change in FVC was reported (pirfenidone -66 mL vs placebo -146 mL; P=0.0082; see Figure). When the investigators looked at estimated annual change in FVC by high resolution CT pattern, it was noted that those with UIP benefitted from pirfenidone compared with placebo (-43 mL vs -169 mL; P=0.0014), whereas those without UIP may not (-85 mL vs -68 mL; P=0.57). The safety analysis did not show unexpected issues. The serious adverse event rates were comparable for the experimental and placebo group (15% vs 13%), with nausea being more common in the intervention arm (53% vs 18%).

Figure: Estimated change in FVC for pirfenidone versus placebo [2]



FVC, forced vital capacity; SD, standard deviation.

Prof. Rosas emphasised that although the trial was underpowered due to recruitment issues, the use of pirfenidone was associated with clinically relevant improvements of FVC decline compared with placebo. "Our study adds to the emerging evidence that patients with ILD with progressive disease may benefit from antifibrotic therapy. A phase 3 trial is needed to support the findings of the current phase 2 trial."

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Intravenous N-acetylcysteine performs well in hospitalised patients

Intravenous N-acetylcysteine demonstrated mucolytic and expectorant efficacy in hospitalised patients with respiratory diseases and abnormal mucus secretion. The agent outperformed placebo in a large, randomised-controlled study.

N-acetylcysteine is an established mucolytic and anti-oxidant medicine for acute and chronic respiratory conditions [1]. In severely ill patients, intravenous administration of this agent may be the preferred route. However, no large-scale trials have studied the efficacy of intravenous N-acetylcysteine as a mucolytic and expectorant therapy.

To address this gap in the literature, Prof. Alberto Papi (University of Ferrara, Italy) and co-investigators randomised 333 patients with acute respiratory conditions and abnormal mucus secretion 1:1:1 to standard-of-care plus a 7-day course of intravenous N-acetylcysteine (600 mg, twice daily), standard-of-care plus intravenous ambroxol hydrochloride (30 mg, twice daily), or standard-of-care plus placebo. Prof. Papi presented the results of the primary endpoints, which were the change from baseline to day 7 in mean sputum viscosity score and expectoration difficulty score, comparing the N-acetylcysteine arm with the placebo arm [2]. The primary endpoints were measured at 4-point ordinal scales.

The sputum viscosity score had improved significantly more in the N-acetylcysteine arm than in the placebo arm (-1.2 vs -1.0; P<0.001). Similarly, the expectoration difficulty score had dropped with 1.4 points in the N-acetylcysteine arm and with 1.1 points in the placebo arm, significantly favouring the experimental arm (P=0.002). Prof. Papi added that the observed safety profile was in line with the good tolerability

of intravenous N-acetylcysteine (600 mg, twice daily) that had been reported in previous smaller studies [3].

"This is the first, large, randomised-controlled trial to demonstrate clinical benefits of intravenous N-acetylcysteine in patients with respiratory diseases and abnormal mucus secretion," decided Prof. Papi.

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Men and women respond differently to diesel exhaust

Sex-related differences in response to diesel exhaust (DE) were reported in a plasma proteomics analysis. The differences could be translated to the level of 'functional groups', such as inflammation, oxidative stress, and cardiovascular disease. It is essential to take sex-related differences into account when it concerns pollution-driven, biological effects in humans.

"Exposure to inhaled DE has been associated with inflammatory and metabolic changes, and is linked to respiratory and cardiovascular diseases," outlined Dr Mahadevappa Hemshekhar (University of Manitoba, Canada) [1]. "Furthermore, the severity and prevalence of these diseases are different in men and women." However, the underlying, traffic-related, air pollution-mediated protein changes have not been thoroughly investigated. The current study aimed to assess sex-related differences in response to real-world concentrations of DE. For this purpose, participants were randomised to 4 hours exposure to filtered air (n=5) or to 4 hours exposure to DE (20, 50, or 150 µg PM2.5/m^3; n=5 each), with a 4-week washout period and a random cross-over after which another 4-hour exposure followed [1]. After 24 hours of exposure, plasma was obtained for proteomic profiling through liquid chromatography with tandem mass spectrometry.

The results displayed that 97 proteins in men and 46 proteins in women were altered after exposure to DE. Interestingly, sex was an effect modifier of 57 proteins that were related to DE. These proteins could be organised in functional groups, such as inflammation, oxidative stress, cardiovascular diseases, and host defence peptides, and it was demonstrated that different patterns of expression could be observed for men and women. According to Dr Hemshekhar, this data demonstrates the importance of sex as a modifier of host response to air pollution and that sex is an essential factor in the understanding of the effect of traffic-related air pollution on humans.

1. Hemshekhar M, et al. Plasma proteomics analysis reveals sex-related differences in response to diesel exhaust. Impact of the external and internal exposome on chronic lung disease, PA591, ERS International Congress 2022, Barcelona, Spain, 4–6 September.

New trends in cystic lung diseases

The progress of 3 common diffuse cystic lung diseases (DCLDs) was discussed, including lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), and Birt-Hogg-Dubé syndrome (BHD). LAM cells were found that could serve as a diagnostic marker and VEGF-D has proven to be a distinctive biomarker for LAM. *BRAF* mutations in patients seem an indicator for PLCH and smoking cessation is an important intervention. *FLCN* mutations may offer a lead into the pathogenic mechanisms to be targeted in BHD. Finally, future research should focus on the common pathogenesis in DCLDs.

"DCLDs are pathophysiologically distinct entities that share a common phenotypic manifestation of thin-walled cysts on chest radiology," explained Prof. Cormac McCarthy (University College Dublin, Ireland) at the start of his presentation titled 'New trends in cystic lung diseases' [1]. The thin-walled cysts are usually less than 2 mm thick and are interfaced with normal lung tissue. In general, high-resolution CT imaging is needed to analyse the cyst characteristics [2]. "Recently, data that may improve prognostication and guidelines for patients with DCLD has become available," said Prof. McCarthy. "Today I will be discussing the progress we have made in 3 of the more common DCLDs, namely LAM, PLCH, and BHD."

Underlying causes of DCLDs

It is important to distinguish between the underlying causes of DCLDs, because of the different approach that is required for the different conditions; family screening is indicated for BHD, neoplastic monitoring is indicated for LAM and BHD, various lifestyle modifications are recommended for patients with LAM or PLCH, and the prognoses of the diseases are different. Prof. McCarthy added that measuring VEGF-D levels and detecting *FLCN* mutations are non-invasive lab tests to distinguish LAM and BHD, respectively, from other DCLDs. "The use of these lab tests may avoid invasive testing in our patients with DCLDs."

How to handle pneumothorax

Spontaneous pneumothorax is common in patients with LAM

(>50%), BHD (25–75%), and PLCH (15–30%). Importantly, after the first presentation of pneumothorax, the recurrence rate of spontaneous pneumothorax is >70% in patients with LAM and BHD, and approximately 60% in patients with PLCH. If pleurodesis is offered, the recurrence rates drop to 30–35% in patients with LAM or BHD and to 15–20% in patients with PLCH, resulting in a cost benefit and a mortality benefit [3–5]. "Therefore, it is crucial that pleurodesis is offered on the first presentation of spontaneous pneumothorax in patients with these conditions," emphasised Prof. McCarthy. In addition, a study by Gupta et al. showed that screening for DCLDs in patients with spontaneous pneumothorax via high-resolution CT is a cost-effective approach to detect patients with DLCDs [6].

Lymphangioleiomyomatosis

LAM involves systemic, low-grade metastasising neoplasm and may occur sporadic or in association with tuberous sclerosis complex (TSC-LAM). Furthermore, *TSC* mutations lead to mTOR activation, which drives clonal, neoplastic proliferation of smooth muscle-like cells [7]. Recently, it has been demonstrated that LAM cells, migrating to the lungs, are likely to come from the uterus [8]. "The uniquely identified LAM cells in this study may serve as a diagnostic marker and therapeutic target in the future," added Prof. McCarthy.

An important development is the investigation of serum VEGF-D in women with TSC as a biomarker for the presence of LAM. On CT imaging, conditions like LAM, PLCH, and Sjögren's syndrome may mimic each other, but VEGF-D is a distinctive biomarker for LAM, saving biopsies and other invasive tests in 70% of patients [9,10]. In addition, it has been demonstrated that LAM and angiomyolipomas occur more frequently in women with *TSC* and *TSC2* mutations compared with those harbouring *TSC1* mutations [11]. Furthermore, higher VEGF-D levels (>600 pg/mL), lower baseline diffusing capacity of the lungs for carbon monoxide (DLCO), and a pre-menopausal status have been associated with a faster disease progression [12,13]. Finally, regarding the treatment of this condition, sirolimus has been approved as the first therapy for patients with LAM, based on the results of the MILES trial (NCT00414648) [14]. Recently, it has been demonstrated that administration of this agent reduces the 5-year probability of pneumothorax recurrence with 80% [15].

Pulmonary Langerhans cell histiocytosis

"It has been shown that 50% of patients with the smoking-related disease PLCH harbour *BRAF* mutations in the myeloid/monocyte lineage," continued Prof. McCarthy." This finding is pathologically relevant for the molecular mechanisms behind the disease and may lead to treatment targets for this disease in the future. Also, smoking cessation is the most important intervention to treat this condition [16–18]. Although a recent French study has demonstrated that the survival of patients with PLCH is comparable with that of the general French population, those with pulmonary hypertension and/or chronic respiratory failure had a worse prognosis [19]. "Therefore, screening for pulmonary hypertension is important in patients with PLCH," argued Prof. McCarthy. Finally, a study showed that, like in patients with LAM, loss of heterozygosity for TSC2 was common in patients with PLCH, indicating that this may be a treatment target in the future [20].

Birt-Hogg-Dubé syndrome

BHD is a genetic syndrome, characterised by diffuse cystic lung disease and an increased risk for renal tumours. "Approximately 30% of patients will develop a renal tumour in their lifetime," added Prof. McCarthy. Recently, several *FLCN* mutations have been associated with the risk of pneumothorax, offering a lead into pathogenic mechanisms that may be targeted in patients with BHD. Also, it has been reported that younger patients with a first spontaneous pneumothorax are at higher risk for recurrent pneumothorax than older patients [21].

Finally, constitutive activation of transcription factor EB (TFEB) by mTORC1 may be the missing link between BHD, TSC, and other DCLDs, a recent study in *Nature* displayed [22]. "Are TSC and the mTOR pathway the key in understanding the common pathogenesis in DCLDs?," wondered Prof. McCarthy at the end of his presentation. Answering this question is an important target for future research and may lead the field to new heights.

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