Journal club

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PROGNOSTIC VALUE OF DIFFUSING CAPACITY FOR CARBON MONOXIDE IN MILD COPD: WORTH MEASURING MORE THAN JUST SPIROMETRY

Phenotyping patients with Chronic Obstructive Pulmonary Disease (COPD) is of increasing importance to clinicians to support personalised medicine. There is particular interest in identifying patients with early disease at higher risk of progression to inform management decisions. A low diffusing capacity for carbon monoxide (DLCO) is associated with increased mortality in patients with severe COPD but the relationship in mild disease is not clear. de-Torres *et al* (Chest 2021;160:872) retrospectively analysed 360 patients with a clinical diagnosis of COPD and Global Initiative for Obstructive Lung Disease (GOLD) stage 1 (FEV1:FVC <0.7, FEV1%≥80%) to determine if a low DLCO leads to a worse mortality. This was a multicentre, retrospective, observational study over a mean 9-year follow-up, using three different prospectively recruited cohorts. The authors compared different cut-off values for DLCO %, adjusted for age, body mass index (BMI), sex and smoking status, to select the highest threshold which demonstrated a statistically significant difference in all-cause mortality: <60% predicted (DLCO ≥60%–9% vs DLCO <60% 23%, p=0.01). It was found that at the same Charlson score and FEV1% predicted those with DLCO <60% had more severe clinical manifestations and an increased risk of death over the follow-up period (HR 3.37, 95%CI 1.35 to 8.39; p=0.09). A difference in their overall clinical profile was also identified with 'low DLCO' cohort more likely to be female, with lower BMI and higher pack year history. While the study identifies a group at risk of worse outcomes to assist with treatment optimisation, the underlying mechanisms of this increased mortality were not elucidated within this work and should be the focus of future studies.

INHALED TREPROSTINIL IN PATIENTS WITH INTERSTITIAL LUNG DISEASE AND ASSOCIATED PULMONARY HYPERTENSION: POTENTIAL IMPACT ON LUNG FUNCTION

There has been evidence suggesting treprostinil, an analogue of prostacyclin, has anti-fibrotic properties. Nathan *et al* (Lancet Respir Med 2021, doi.org/10.1016/S2213-2600(21)00165X) performed a post hoc analysis on the data from the INCREASE study to explore the effect of inhaled treprostinil in patients with interstitial lung disease (ILD) and associated pulmonary hypertension (PH) on FVC. INCREASE was a 16-week, multicentre randomised, double-blind, placebo controlled, phase 3 trial of inhaled treprostinil in patients with ILD and PH. Between 2017 and 2019, 326 patients were recruited (146/326; 45% had idiopathic interstitial pneumonia including 92/326; 28% had idiopathic pulmonary fibrosis; IPF). When compared with placebo, inhaled treprostinil was associated with a non-significant improvement in FVC of 44.4 mL (35.4 mL; −25.2 to 114.0; p=0.21). Subgroup analysis demonstrated an FVC difference of 168.5 mL (64.5 mL; 40.1 to 297.0; p=0.011) compared with baseline at week 16 in patients with IPF and a difference of 108.2 mL (46.9 mL; 15.3 to 201.1, p=0.023) at week 16 for those with idiopathic interstitial pneumonia. While the impact on FVC was consistent across baseline severity of DLCO impairment and severity of PH, the effect was lost in patients on established antifibrotic therapy (although confounded by small subgroups). The study serves as a proof of concept that inhaled treprostinil may preserve lung function in patients with ILD and associated PH. However, it is important to remember this study was conducted over a 16-week period and it is unclear whether the results will be sustained in the longer term. A current clinical trial into this is under way (NCT04708782) aimed at addressing this question.

LUMACAFTOR–IVACAFTOR IN CHILDREN AGED 6–11 YEARS WITH CYSTIC FIBROSIS HOMOZYGOUS FOR THE *F508DEL*: SAFE AND EFFECTIVE IN LONGER-TERM USE

Lumacafor–ivacaftor combination treatment has been demonstrated in the earlier trials to improve lung function and reduce pulmonary exacerbations in patients with cystic fibrosis (CF) who are homozygous for F508del-CFTR aged 12 years and older. The efficacy and safety of this combination had not been studied for longer than 24 weeks in children ages 6–11 years. Chilvers *et al* (Lancet Respir Med 2021;9:721) undertook a phase 3, open-label, multicentre extension study examining long-term safety and efficacy of lumacaftor–ivacaftor in patients pooled from two phase 3 parent studies. The study was conducted in 61 clinics internationally from 2015 to 2018. Children aged 6–11, homozygous for F508del-CFTR mutation and who had completed study visits in their parent study up to week 26 were enrolled and all received active treatment (n=239). The primary endpoint focused on safety and tolerability, with secondary endpoints looking at BMI and change in lung clearance index 2.5%. Of those enrolled 90% completed 96 weeks of treatment, with a low rate of adverse events. Most frequent adverse events reported were expected and could be attributable to CF itself, cough (65%) and pulmonary exacerbation (49%), with no new safety concerns identified. The event rates were similar but slightly lower than the original studies, with the exception of nasopharyngitis and positive bacterial tests. Efficacy results indicated a similar impact in patients switching from placebo to active treatment in chloride sweat test, lung clearance index and quality of life questionnaires as reported in the original trials. Combination therapy with lumacafor–ivacaftor was generally well tolerated and safe with sustained efficacy for up to 120 weeks in children aged 6–11 years.

GLOBAL BURDEN OF RESPIRATORY TRACT CANCERS 2010–2019: SMOKING REMAINS MAJOR FACTOR

Lung, tracheal and bronchus cancers remain the leading cause of cancer deaths worldwide and therefore early prevention, control and treatment of these respiratory tract cancers is vital. The Global Burden of Diseases, Injuries and Risk Factors Study and the Respiratory tract Cancers collaborators (Lancet Respir Med 2021;9:1030) reviewed the global burden of respiratory cancers over the last decade from 1990 to 2019 with particular focus on 2010–2019. The results showed an increase in numbers of cases and deaths from lung, tracheal, bronchial and laryngeal cancers in the last decade. From 2010 to 2019, the number of new lung, bronchial and tracheal cancer cases increased globally by 23.3% (95% uncertainty interval; UI 12.9 to 33.6), with 2.26 million (95% UI 2.07–2.45) new diagnoses and 2.04 million (95%UI 1.88 to 2.19) deaths in 2019. Smoking was found to contribute to 64.2% (95% UI 61.9–66.4) of all deaths from respiratory cancers and was the leading risk factor identified in males. While clear progress was noted in reducing smoking attributable respiratory tract cancer burden at the global level, there was significant regional variation. In addition, in females, household air pollution from solid fuels was the leading specific risk factor in the lower sociodemographic index countries. The authors concluded that the findings within this study provide motivation for policy-makers to enact stricter air quality guidelines, culturally responsive smoking cessation programmes and to expand access to clean sources of cooking and heating energy worldwide.

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