JOURNAL CLUB

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ELEXACAFTOR IN CYSTIC FIBROSIS: TWO DRUGS GOOD, THREE DRUGS BETTER

For cystic fibrosis (CF) patients homozygous for the *F508del* mutation of the transmembrane conductance regulator (CFTR) protein, a combination of a CFTR potentiator and a corrector has been shown to be beneficial. This pharmaceutical funded double-blinded randomised control trial (Heijerman *et al*, *Lancet* 2019;394:1940) examined the clinical outcomes with the addition of elexacaftor (a further corrector) or placebo to tezacaftor and ivacaftor on percent predicted forced expiratory volume in one second (ppFEV$_1$) after four weeks of therapy. The study randomised 107 participants with stable CF. The addition of elexacaftor was associated with a significant improvement in ppFEV$_1$ (10%, 95% CI 7.4 to 12.6; p<0.0001) and reduction in sweat chloride concentration (−45.1 mmol/L, 95% CI −50.1 to −40.1; p<0.0001). The regime was well tolerated. Although the trial was limited to four weeks, similar improvements in lung function and sweat chloride tests over this duration have previously been associated with sustained positive outcomes in areas such as exacerbation rates. In addition, the group published data on patients heterozygous for *F508del* (Middleton *et al*, *NEJM* 2019;381:1809) demonstrating similar physiological improvements. These two trials represent a significant development for patients with at least one *F508del* mutation — almost 90% of patients.

E-CIGARETTE OR VAPING-ASSOCIATED LUNG INJURY (EVALI): VITAMIN E ACETATE AS A POTENTIAL TRIGGER

First reported in April 2019, e-cigarette or vaping-associated lung injury (EVALI) has affected more than 2400 patients in the USA, with 52 deaths. The addition of vitamin E acetate to tetrahydrocannabinol-containing products is a recent development which temporally coincides with the onset of the EVALI outbreak. Blount *et al* (*NEJM* 2019 doi.org/10.1056/NEJMoa1916433) analysed bronchoalveolar lavage (BAL) fluid from 51 patients with EVALI in comparison with previously collected fluid from 99 healthy comparators. Cases of EVALI had recent e-cigarette use, pulmonary infiltrates and no plausible alternative diagnosis. In patients with EVALI, vitamin E acetate was present in all e-cigarette fluid and 94% (48 cases) of BAL fluid. It was not detected in BAL fluid in any of the healthy comparators. No alternative toxicants were found in BAL fluid of patients with EVALI. This study could not assess the timing or burden of vitamin E acetate exposure in relation to presentation. Sample collection was not standardised, and data for the healthy comparators were collected from a previous study. Furthermore, there is no diagnostic test for EVALI, resulting in the potential for misdiagnosis using the broad clinical definition. However, there is a biologically plausible mechanism whereby vaping products can deliver vitamin E acetate to respiratory epithelium lining fluid, leading to lung injury.

AMBIENT OZONE AND RESPIRATORY MORBIDITY: THE IMPORTANCE OF THE AIR THAT WE BREATHE

Ozone is generated when pollutants react with sunlight, and higher levels are found in urban areas. While the relationship between respiratory outcomes and short-term increased ozone exposure is established, there are limited data on the effect of prolonged exposure on smokers. In this cross-sectional study, Paulin *et al* (*JAMA* 2020;180:106) analysed respiratory outcomes of 1874 predominantly white (79%) participants with more than 20 smoking pack years in relation to ozone exposure, estimated based on home address using pollution prediction models. Adjusting for smoking history and other environmental exposures, this study found a significant decrease in ppFEV$_1$ (−2.5%, p=0.01) with an increase in percentage emphysema (0.94, p=0.007) and air trapping (1.6, p=0.03) in patients with five parts per billion (ppb) historical increase in ozone exposure (median 10-year mean ozone concentration 25.1 (21.8–28.1) ppb). This patient group also had significantly worse scores on quality of life and symptom questionnaires (1.47 in St George's Respiratory Questionnaire, 0.65 in Chronic Obstructive Pulmonary Disease (COPD) Assessment Test and 0.1 in modified Medical Research Council dyspnoea, all p<0.05) and increased risk of reporting an exacerbation in the previous 12 months (OR 1.37, p=0.002). No association was found between exposure and chronic bronchitis, COPD, airway wall thickness or six-minute walk test results. Sensitivity analysis indicated increased impact in those who spent longer outdoors, suggesting a causal impact of air pollutants. This study highlights a public health need to review long-term ozone standards.

EFFECT OF MAINTENANCE AZITHROMYCIN ON ASTHMA EXACERBATIONS

Macrolides are recommended in the Global Initiative for Asthma guidelines as add-on therapy in severe asthma despite the paucity of supportive published data. Hiles *et al* (*ERJ* 2019;54:1901381) conducted an individual patient data meta-analysis of randomised double-blind placebo-controlled trials on the effects of at least eight weeks of azithromycin treatment on exacerbation rate over six months in asthmatic adults. Exacerbations could be defined as temporary or increased oral corticosteroid (OCS) use, antibiotic use for respiratory infection or hospitalisation/emergency department (ED) visit. Preplanned subgroup analyses of eosinophilic, non-eosinophilic and severe asthma were conducted. Only three of 1864 identified studies met the inclusion criteria. Azithromycin was associated with reduced exacerbation rate over six months (incidence rate ratio 0.61, p<0.001, n=529) in the entire cohort and in all subgroups. However, OCS use was significantly reduced only in the eosinophilic cohort. While antibiotic use was significantly reduced overall, the effect was only significant in the non-eosinophilic group. There was no change in hospitalisation or ED visits. There was no significant impact on quality of life, asthma control or lung function. Azithromycin was well tolerated, although details on study population exclusions were not reported. The differential effect on exacerbation populations requires further investigation to elucidate the possible mechanisms. These results support the use of azithromycin to reduce asthma exacerbation frequency in patients with both eosinophilic and non-eosinophilic asthma.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Smith DJF. *Thorax* 2020;**75**:360.

Thorax 2020;**75**:360.
doi:10.1136/thoraxjnl-2020-214676