JOURNAL CLUB

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Cormac Mee

ICS/LABA/LAMA SINGLE INHALER TRIPLE THERAPY IN ASTHMA: 3 IN 1 BETTER THAN 2 IN 1 BUT NOT BETTER THAN 3 IN 2…

Combined inhaled corticosteroid and long-acting beta-agonist (ICS/LABA) therapy is well established for long-term asthma control, with long-acting muscarinic antagonists (LAMA) being increasingly used as add-on therapy. Virchow *et al* (*Lancet Respir Med* 2019;394:1737) report on the first published study on patients with asthma on ICS/LABA/LAMA triple therapy with a single combination inhaler. Patients were enrolled in two double-blinded, phase III trials (TRIMARAN n=1155 and TRIGGER n=1437) evaluating combination therapy of beclomethasone dipropionate, formoterol fumarate and glycopyrronium in a single metered dose inhaler. Both trials recruited adult patients with asthma with reversible airway disease and at least one exacerbation per year. The TRIMARAN trial used ICS/LABA as an active control and TRIGGER used a 2:2:1 ratio of triple inhaler, ICS/LABA or ICS/LABA plus separately inhaled tiotropium. The co-primary endpoints were early morning FEV_1 and rate of moderate to severe exacerbations over 1 year. Both studies showed significant improvement in FEV_1 of triple combination inhaler over ICS/LABA alone: 57 mL (95% CI 15 to 99; p=0.0080) in TRIMARAN and 73 mL (CI 26 to 120; p=0.0025) in TRIGGER. TRIMARAN also showed a 15% reduction in moderate and severe exacerbations across 12 months (relative risk 0.85, CI 0.73 to 0.99, p=0.033). The TRIGGER trial showed no significant difference between triple therapy and ICS/LABA plus tiotropium. In the pooled analysis of both trials, ICS/LABA/LAMA patients had a 14% (p=0.0083) reduction in rate of moderate and severe exacerbations. These studies provide supporting evidence for the use of LAMAs to improve lung function and reduce exacerbation rates in patients with asthma.

DIFFERENTIATING COPD AND ASTHMA: USING INSPIRATORY AS WELL AS EXPIRATORY FLOWS MAY HELP

Diagnosing asthma in older patients with a smoking history can be challenging. Okazawa *et al* (*Journal of COPD* 2020;17;230) explored using spirometry to differentiate the patient populations in a Japanese outpatient clinic setting. Patients with COPD (n=143) and bronchial asthma (n=142) were identified from outpatient clinic data across 6 years. Patients with asthma–COPD overlap were excluded. All patients had spirometry with an emphasis on recording maximal inspiratory as well as expiratory flows. Parameters measured included peak inspiratory flow to peak expiratory flow ratio (PIF:PEF) and the ratio of peak inspiratory flow to maximal expiratory flow at 50% FVC predicted ($PIF:MEF_{50}$), as well as FEV_1:FVC ratio and PEF. Multivariate analysis showed that predictors of COPD were $PIF:MEF_{50}$ >3.29 (OR 4.6) and FEV_1:FVC <63.4% (OR 4.3). Being positive on both tests gave an 82% post-test probability of COPD in all patients, rising to 94% when only smokers (n=44) were analysed. $PIF:MEF_{50}$ can be easily obtained in clinical practice and may be a useful test to differentiate asthma from COPD. Given the small single-centre sampling, further data in more diverse populations are required for validation.

PREDICTING COPD EXACERBATIONS: CAN 'BIG DATA' PROVIDE PERSONALISED MEDICINE?

There are no tools to predict COPD exacerbations used in routine clinical practice as those studied so far lack sufficient granularity to inform treatment decisions. Adibi *et al* (*Lancet Respir Med* 2020; doi:10.1016/S2213-2600(19)30397-2) developed a model that aims to accurately quantify patient-specific risk of an acute exacerbation in the next 12 months. Data were pooled from three multicentre trials (n=2380) which had recruited patients with COPD with a history of at least one exacerbation in the last year. Predictors were prespecified by the research team and a joint logistic regression/accelerated failure time model was used to project the rate and severity of exacerbations. The model was then externally validated using data from an independent longitudinal study of COPD outcomes (ECLIPSE; n=1819). During external validation, the Acute COPD Exacerbation Prediction Tool (ACCEPT) was accurate in predicting exacerbations (all exacerbations predicted 1.31/year vs actual 1.20/year; severe exacerbations predicted 0.25/year vs actual 0.27/year). It was also superior to history alone in predicting at least two exacerbations (area under the curve $(AUC)_{ACCEPT}=0.88$ vs $AUC_{history}=0.79$, p<0.0001) and one severe exacerbation ($AUC_{ACCEPT}=0.77$ vs $AUC_{history}=0.66$, p<0.0001) over the 1-year period sampled for analysis. The ACCEPT tool is one of the few externally validated COPD risk models that predict an individualised exacerbation rate. The tool uses readily available demographic and clinical data but requires input into a data package or app for risk score calculation; however, given the ubiquity of electronic health records, this should not limit its incorporation into clinical practice.

COVID-19: SEVERITY AND MORTALITY IN COPD AND SMOKERS

As the SARS-CoV-2 continues to spread globally, understanding how it affects patients with pre-existing respiratory disease is vital. Alqahtani *et al* (*PLoS ONE* 2020;15(5);e0233147) conducted a meta-analysis to examine the severity and mortality of comorbid COPD or smoking during COVID-19 infection. They included papers published up to 24 March 2020. Non-English papers and studies not reporting COPD were excluded, leaving 15 studies (n=2473) in the final analysis. Majority of the data were from China, except for one study including 21 patients from the USA. Overall mortality was 7.4%. Severe COVID-19 was defined as intensive care unit admission, mechanical ventilation or death. Seven papers reported on severity in a minority of patients with COPD (n=35), showing a 63% risk of severe disease compared with 33% in those without (relative risk 1.88, CI 1.4 to 2.4). Mortality differences were not statistically significant. Eight of the studies (n=221) reported on smoking history, with current smokers comprising 9% (95% CI 4% to 14%) of the COVID-19 cases in these studies. Current smokers were 1.45 times (95% CI 1.03 to 2.04) more likely to have a severe complication than former or never smokers. This is one of the first published systematic reviews examining mortality risk of COVID-19 in patients with COPD and smokers, and indicates that these groups are at higher risk of severe disease. Larger studies involving a more diverse geographical area are required to provide more accurate estimates of attributable risk.

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Correspondence to Dr Cormac Mee, Lane Fox Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK; cormac.mee@gmail.com