Welcome to issue 66 of Respiratory Research Review.

One of the papers in this issue proposes that palliative care could play a key role in the management of people with chronic obstructive pulmonary disease (COPD). The study researchers suggest that integrating palliative care early in the disease trajectory, using a needs-based rather than prognosis-based approach to patient care, can improve outcomes for both patients and caregivers.

COPD is an independent risk factor for cardiovascular (CV) disease and another paper in this issue discusses the prognostic value of non-invasive CV risk markers in COPD patients. It suggests that the coronary artery calcium (CAC) score can be used to evaluate the risk of these patients experiencing a major CV event.

I hope you find the papers in this issue useful in your practice and I look forward to your comments and feedback.

Kind Regards,
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Tezepelumab in adults with uncontrolled asthma

Authors: Corren J et al.

Summary: This dose-ranging trial of tezepelumab recruited patients (18-75 years of age) whose asthma was uncontrolled with long-acting beta-agonist (LABA) therapy combined with medium- to high-doses of inhaled glucocorticoids. Patients were randomised to receive subcutaneous tezepelumab 70 mg every 4 weeks (low dose; n=145), 210 mg every 4 weeks (medium dose; n=145), or 280 mg every 2 weeks (high dose; n=146), or placebo (n=148), for 52 weeks. The primary efficacy end point was the annualised rate of asthma exacerbations (events per patient-year) at week 52. Treatment with tezepelumab was associated with lower exacerbation rates at week 52 of 0.26, 0.19, and 0.22 in the low-dose, medium-dose, and high-dose groups, respectively, as compared with 0.67 in the placebo group; thus, exacerbation rates were lower in the tezepelumab groups by 61%, 71%, and 66% than the rate in the placebo group (p<0.001 for all comparisons). Similar results were observed in patients regardless of blood eosinophil counts at enrolment. The prebronchodilator FEV1 at week 52 was lower in all tezepelumab groups than in the placebo group (difference, 0.12 L with the low dose [p=0.01]; 0.11 L with the medium dose [p=0.02]; and 0.15 L with the high dose [p=0.002]). Two patients in the medium-dose group, 3 in the high-dose group, and 1 in the placebo group discontinued study treatment due to adverse events.

Comment: Tezepelumab is a human monoclonal antibody that blocks action of thymic stromal lymphopoietin (TSLP). It affects lymphocyte maturation and acts upstream to other monoclonal antibodies. The study was a phase 2 trial and used three doses of tezepelumab. All three doses reduced asthma exacerbation rates by over 60%. Effects of treatment were seen as early as at 4 weeks. Both blood eosinophil counts and FeNO levels were reduced. No anaphylactic reactions were noted. Overall, treatment was well tolerated but there were three serious adverse events including pneumonia, stroke and Guillaumin-Barré syndrome. The study shows that targeting TSLP can reduce the type 2 inflammatory response in asthma but the risk of immune modulation and adverse effects need further study.


Abstract

Change the path of IPF*1,2

*Pooled analysis of INPULSIS®-1 and -2: significantly reduced annual rate of decline in FVC in the OFEV® group vs placebo

Before prescribing, please review PBS and Product information available on page 4

Evaluation of a rapid molecular drug-susceptibility test for tuberculosis

Authors: Xie Yi, et al.

Summary: These researchers assessed the accuracy of an automated, cartridge-based molecular assay for the detection, directly from sputum specimens, of Mycobacterium tuberculosis with resistance to fluoroquinolones, aminoglycosides, and isoniazid. They enrolled 405 adults in South Korea and China who had symptoms of pulmonary tuberculosis (TB). One investigational assay and one Xpert MTB/RIF test were performed directly on the same sputum specimen from each participant. M. tuberculosis isolates were subjected to phenotypic drug-susceptibility testing and DNA sequencing of the genes katG, gyrA, gyrB, and of the eis and embB promoter regions. 308 participants were culture-positive for M. tuberculosis. When phenotypic drug-susceptibility testing was used as the reference standard, the sensitivities of the investigational assay for detecting resistance were 85.3% for isoniazid, 88.4% for ofloxacin, 87.6% for moxifloxacin at a critical concentration of 0.5 μg/mL, 88.2% for moxifloxacin at a critical concentration of 2.0 μg/mL, 71.4% for kanamycin, and 70.7% for amikacin. The specificity of the assay for the detection of phenotypic resistance was ≥94.3% for all drugs except moxifloxacin at a critical concentration of 2.0 μg/mL (specificity, 84.0%). When DNA sequencing was used as the reference standard, the sensitivities of the investigational assay for detecting mutations associated with resistance were 98.1% for isoniazid, 95.8% for fluoroquinolones, 92.7% for kanamycin, and 96.8% for amikacin, while the specificity was ≥99.6% for all drugs.

Comment: One of the challenges in treating resistant TB is sometimes the difficulty in undertaking drug susceptibility testing and the delay in getting results. Xpert MTB/RIF (Cepheid) is already used for rapid detection of rifampin resistance. This study evaluated the efficacy of a new test able to detect mutations associated with resistance to fluoroquinolones, aminoglycosides, and isoniazid. The sensitivity and specificity, respectively, of the investigational assay for the detection of resistance mutations were 98.1% and 100.0% for isoniazid, 95.8% and 100.0% for fluoroquinolones, 92.7% and 99.6% for kanamycin, and 96.8% and 100.0% for amikacin. The investigational assay met the WHO sensitivity targets for isoniazid, fluoroquinolones, and amikacin, but not kanamycin. There were some cases of phenotypic-genotypic discrepancy related to mechanisms other than mutations causing drug resistance. The advantage of the assay is that the test is done directly on sputum and results are available in 2 hours, which can aid decision-making on drug regime selection.


Abstract

Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993–2012)

Authors: Etmeller S et al.

Summary: This analysis collated age-standardised country-specific asthma mortality rates in the 5–34-year age group from the online WHO Mortality Database for 46 countries worldwide (36 high-income countries and 10 middle-income countries). A locally weighted scatter plot smoother (LOESS) curve, weighted by the individual country population in the 5–34-year age group, was used to illustrate the global trends in asthma mortality rates with time. The LOESS estimate of the global asthma mortality rate was 0.44 deaths per 100,000 people in 1993 and 0.19 deaths per 100,000 people in 2006. The researchers found evidence for further reductions in some countries and regions of the world, but no appreciable change in global asthma mortality rates from 2006 through to 2012, with a LOESS estimate of 0.19 deaths per 100,000 people.

Comment: This study looks at the asthma mortality trends over the last decade. The study found that while there was a 57% reduction globally in asthma mortality between 1995 and 2006, there has been no significant change from 2006 to 2012. The study limited the analysis to people aged 5–34 years. In Australia, most asthma-related mortality occurs in the older age groups. The study unfortunately could not evaluate case fatality rates, which would have provided more information on risk of death in people with asthma. The global trends seem to reflect some countries showing greater gains in asthma mortality vs very little improvement in other countries. The reasons for this plateau in asthma mortality rates do seem to be complex. Medications may be more affordable and available, but factors such as ongoing cigarette smoking, psychosocial dysfunction and poor health literacy continue to have a large impact on patient compliance and asthma control.

Reference: Lancet 2017; 390: 935–45

Abstract

Independent commentary by Dr Alpna Marissa Antony, MBBS, MRCP, FRACP.

Dr Antony is a Respiratory and Sleep Physician currently working at St. George Hospital, Sydney as a Staff Specialist in General Medicine. Her areas of clinical interest include respiratory infections, interventional pulmonology and respiratory failure.

CHANGE THE PATH OF IPF

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*Pooled analysis of INPULSIS*-1 and -2: significantly reduced annual rate of decline in FVC in the OFEV® group vs placebo; *Refer to the PBS Schedule for full authority information

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Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease

Authors: Maddocks M M et al.

Summary: These researchers highlight the substantial multimorbidity experienced by patients with advanced chronic obstructive pulmonary disease (COPD), who often have limited understanding of their disease and it is recognised that few access palliative care services. This article makes the case for expert multidisciplinary palliative care, which incorporates assessment and management of symptoms and concerns, patient and caregiver education, and sensitive communication to elicit preferences for care towards the end of life. It describes the substantial illness burden of patients with advanced COPD, summarises current evidence on how their symptoms and concerns can be addressed by palliative care interventions, and considers models of integrated palliative care in COPD and evidence for their effectiveness in high-income countries.

Comment: This is an interesting study exploring the physical and psychosocial symptoms in COPD, current evidence to manage these symptoms and models to integrate palliative care in COPD management. Most COPD patients report a median of 11–14 symptoms, comparable to patients with advanced lung cancer. But studies show that only 10–20% of patients with advanced COPD have accessed palliative care services. The study emphasises the advantages of palliative care services early in course of illness and recommends that it should be needs-based, rather than prognosis based.

Reference: Lancet 2017; 390: 988-1002

Cardiovascular and neuropsychiatric risks of varenicline and bupropion in smokers with chronic obstructive pulmonary disease

Authors: Koiz D et al.

Summary: This analysis examined real-life data from the UK CORD study (a research database (CORD)), to determine whether varenicline and bupropion are associated with serious adverse cardiovascular (CV) and neuropsychiatric events in smokers with COPD. The study researchers identified patients with COPD who received a prescription of nicotine replacement therapy (NRT, n=10,426, reference group), bupropion (n=350) or varenicline (n=3574) and followed them up for 6 months to compare incident CV (i.e. ischaemic heart disease, stroke, heart failure, peripheral vascular disease and cardiac arrhythmias) and neuropsychiatric (i.e. depression and self-harm) events using Cox proportional hazards models, adjusted for potential confounders. Neither bupropion nor varenicline increased the risk of adverse events compared with NRT. Varenicline was associated with a significantly reduced risk of heart failure (HR 0.56, 95% CI, 0.34 to 0.92) and depression (HR 0.73; 95% CI, 0.61 to 0.86). A propensity score analysis yielded similar results. Modelling the effects of possible unmeasured confounders reiterated the likelihood of any increased risk of these adverse events.

Comment: Varenicline and bupropion have been shown to be effective drugs in aiding smoking cessation but there were concerns raised regarding increased CV and neuropsychiatric risk associated with the medications, which led to the FDA including boxed warnings. Subsequently the warnings have been removed following a large randomized controlled trial that showed no increased risk of CV or neuropsychiatric events compared to nicotine replacement or placebo. As COPD patients are known to have higher risk of CV morbidity, this study was done as a retrospective study in COPD patients, with a total of 14,355 patients included. The study found no increased risk of CV or neuropsychiatric events.

Reference: Thorax 2017; 72(10):905-11

Cardiovascular risk in patients with alpha-1-antitrypsin deficiency

Authors: Fährndörft S et al.

Summary: This German investigation analysed the clinical phenotype of patients with α-1-antitrypsin deficiency (AATD) within the German COPD cohort study COSYCONET ("COPD and Systemic consequences: COSMOrbilities NETwork"). Records were obtained for 2,645 COSYCONET patients, including 139 AATD patients (110 with and 29 without augmentation on therapy). The prevalence of CV comorbidities was significantly lower in the AATD cohort compared with the non-AATD COPD patients. In regression analysis correcting for age, pack years, BMI, and sex, the between-group differences remained significant for coronary artery disease (p = 0.002) and the prevalence of peripheral artery disease as determined by an ankle-brachial-index <0.9 (p = 0.033). The distribution of other comorbidities such as bronchiectasis also differed between AATD and non-deficient COPD.

Comment: COPD patients are known to have increased risk of CV morbidity but little is known about the CV risk profile in patients with AATD. This study found that, as expected, patients with AATD had worse lung function compared to other COPD patients, with evidence of emphysema in >75% of lung on chest CT. They also had a higher prevalence of asthma. Surprisingly, AATD patients had a lower prevalence of hyperension, congestive cardiac failure, ischaemic heart disease and diabetes. They also had lower serum triglyceride and HDL levels and higher HDL cholesterol levels compared to other COPD patients. The exact mechanisms for this lower CV risk profile seen in patients with AATD are unclear, but could be an advantage conferred by the SERPINA1 mutation.

The impact of cognitive impairment on self-management in chronic obstructive pulmonary disease: A systematic review

Authors: Baird C et al.

Summary: These researchers examined the evidence from 13 studies in English published between 1 January 2000 and 20 February 2016 describing the relationship between cognition and COPD self-management domains in older community-dwelling persons with dementia or cognitive impairment. None of the studies grouped populations by recognised dementia subtypes.

Comment: Patients with COPD are known to have a higher prevalence of other medical comorbidities. Previous studies have shown that cognitive impairment has a prevalence of 32% in COPD patients. This can have an impact on older patients’ ability to self-manage their condition, medication compliance and symptom perception. This was a meta-analysis with 13 studies included in the review. The aims of studies and tools for detection of cognitive impairment were very varied, but the majority evaluated inhaler device competency. Most studies showed that a Mini Mental State Examination (MMSE) score of less than 23 – 24 was associated with poor inhaler competency, especially with impaired executive function and praxis. Education on inhaler technique was unsuccessful. Capsule and dry powder inhaler devices were associated with highest competency rates. Cognitive impairment was shown to be associated with lower disability status and even small changes in MMSE scores were shown to be associated with poor symptom recall. The review clearly shows that cognitive impairment poses challenges to patients’ ability for self-management. There is lack of data on how best to support these patients.

Reference: Respir Med. 2017;129:130-9

Abstract

Prospective comparison of non-invasive risk markers of major cardiovascular events in COPD patients

Authors: Zagaeta J et al.

Summary: These researchers assessed the prognostic value of non-invasive CV risk markers in 287 patients with COPD. Markers included the Framingham score, Systematic Coronary Risk Evaluation (SCORE) charts, coronary arterial calcium (CAC), epicardial adipose tissue (EAT), and various clinical, biochemical and physiological variables. During a median 65 months of follow-up, 44 CV events were recorded. 12 acute myocardial infarctions (27.3%), 10 ischaemic heart disease/angina (22.7%), 12 peripheral artery disease events requiring surgery (27.3%) and 10 strokes (22.7%). Thirty-five CV deaths occurred during follow-up. In univariate analysis, age, hypertension, C-reactive protein, total cholesterol, LDL cholesterol, Framingham score and CAC were independently associated with CV events. In multivariate analysis, CAC was the only variable that predicted CV events (HR 1.32; 95% CI, 1.19 to 1.46; p<0.001).

Comment: COPD patients are known to have much higher risk of CV morbidity and mortality. Most of the CV risk assessment tools have not been specifically validated in COPD patients. This study compared the predictive power of Framingham score, SCORE charts, CAC, EAT, as well as clinical, biochemical and physiological variables in COPD patients. The CAC was found to be the best independent predictor of CV risk. Although SCORE and EAT are well-validated tools to predict CV events in the general population, they were not found to be useful in COPD patients. The study had mostly mild-moderate COPD patients and mostly men. Their findings will need to be confirmed in larger studies with more diverse populations of COPD patients, but computed tomography of coronary arteries provides an easy non-invasive method to detect patients at high risk of CV events.

Reference: Respir Res. 2017;18(1):175

Abstract

PBS listed for the treatment of IPF*

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OFEV® nintedanib (as nintedanib esilate) 100 mg and 150 mg soft capsules. MINIMUM PRODUCT INFORMATION. INDICATION: Treatment of Idiopathic Pulmonary Fibrosis (IPF).

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