American Thoracic Society International Conference (ATS) 2015 Conference Review™

Making Education Easy

15-20 May 2015, Denver, Colorado, USA

In this review:

Abbreviations used in this review:

CF = cystic fibrosis; **FVC** = forced vital capacity; **HRCT** = high-resolution computed tomography; **IPF** = idiopathic pulmonary fibrosis; **OSA** = obstructive sleep apnoea; **PCI** = percutaneous coronary intervention; **PFT** = pulmonary function test; **SSc** = systemic sclerosis

Follow **RESEARCH REVIEW** Australia on Twitter now

@ResearchRevAus

Visit https://twitter.com/ResearchRevAus

Conference Reviews are prepared with an independent commentary from relevant specialists.

To become a reviewer please email geoff@researchreview.com.au

Research Review Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including Government depts., health product companies, insurers and other organisations with an interest in health. Journal content is created independently of sponsor companies with assistance from leading local specialists. **Privacy Policy:** Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time. **Disclaimer:** This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

Research Review publications are intended for Australian health professionals.

RESEARCH REVIEW the Australian perspective

Welcome to this review of the American Thoracic Society International Conference (ATS), held in Denver, Colorado, USA.

The ATS International Conference is dedicated to topics related to pulmonary, critical care and sleep medicine as well as other fields including Behavioural Science, Allergy/Immunology, Environmental & Occupational Health, Cardiology & Cardiac Surgery, Infectious Disease, Hospitalists, Paediatric Pulmonary, Critical Care and Sleep, Nursing and Thoracic Surgery. The event is attended by pulmonary, critical care and sleep clinicians and researchers from around the world.

Professor Peter Wark is a senior staff specialist in Respiratory and Sleep Medicine at John Hunter Hospital, Newcastle and a conjoint Associate Professor with the University of Newcastle, New South Wales. He attended this Congress and selected the presentations included in this review.

We hope you enjoy these selections and look forward to your comments and feedback.

Kind Regards,

Dr Janette Tenne

Medical Research Advisor

janette.tenne@researchreview.com.au

Allergen-induced asthmatic responses modified by a GATA3-specific DNAzyme

Authors: Krug N et al.

Summary: These researchers developed a GATA3-specific DNA enzyme (DNAzyme) SB010 that has the ability to cleave and inactivate GATA3 messenger RNA. SB010 was then tested in a multicentre clinical trial involving 40 patients with allergic asthma with sputum eosinophilia (>3%) and who also had early and late asthmatic responses after allergen provocation testing. Twenty-one patients received 10 mg of SB010; 19 patients received placebo. Each treatment was administered by inhalation once daily for 28 days. The primary end point was late asthmatic response quantified by the area under the curve (AUC) of FEV_1. At 28 days, as compared with baseline measurements of the AUC for FEV_1, SB010 attenuated the mean early and late asthmatic responses by 11% and 34%, respectively. In contrast, placebo increased the early and late asthmatic response by 10% and 1%, respectively ($p<0.05$ for both comparisons). Furthermore, SB010 was associated with attenuation of allergen-induced sputum eosinophilia, lower levels of tryptase in sputum and lower plasma levels of interleukin-5.

Comment: This is the first report of a novel non-corticosteroid-based agent that can be taken by inhalation and inhibits the TH2 immune response in asthma, attenuating the associated bronchial reactivity seen with allergen challenge. It is an exciting new class of agent, with the next step presumably being to move to phase three trials to compare efficacy to inhaled corticosteroids.

Reference: N Engl J Med. 2015;372:1987-95

Abstract

High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure

Authors: Frat JP et al.

Summary: This open-label trial recruited 310 patients with nonhypercapnic acute hypoxaemic respiratory failure and a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2:FIO2) of ≤300 mm Hg. Study participants were randomised to receive high-flow oxygen therapy through a nasal cannula (n=106), standard oxygen therapy delivered through a face mask (n=94), or noninvasive positive-pressure ventilation (NIV; n=110). The primary outcome, the proportion of patients intubated at day 28, was lower in the high-flow oxygen group compared with the groups treated with standard oxygen therapy or NIV, but the rates did not differ significantly (38% vs 47% and 50%, respectively; p=0.18 for all comparisons). The mean number of ventilator-free days at day 28 was significantly higher in the high-flow oxygen group (24 days vs 22 in the standard-oxygen group and 19 in the NIV group; p=0.02 for all comparisons). The hazard ratio for 90-day mortality was 2.01 (95% CI, 1.01 to 3.99) with standard oxygen versus high-flow oxygen (p=0.046) and 2.50 (95% CI, 1.31 to 4.78) with NIV versus high-flow oxygen (p=0.006).

Comment: High-flow oxygen is now widely available throughout Australian hospitals. While its use has been embraced by clinicians and patients as it is relatively comfortable and easy to use, there has been little evidence in regard to its place in treatment. This trial identifies it as being superior to both standard high-flow oxygen and NIV when given to patients with hypoxic respiratory failure, but with no evidence of hypercapnoea. While further work will need to be done here, it seems to indicate its utility in this group of patients, providing it with a different niche from that of NIV, which is now very clear and established in the acute setting.

Reference: N Engl J Med. 2015;372(23):2185-96

Abstract

Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del *CFTR*

Authors: Wainwright CE et al.

Summary: Data are reported from two phase III trials that examined the effects of lumacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) corrector, in combination with ivacaftor, a CFTR potentiator, in patients aged ≥12 years who had cystic fibrosis and were homozygous for the Phe508del *CFTR* mutation. In both trials, 1108 such patients were randomly assigned to receive either lumacaftor (600 mg once daily or 400 mg every 12 hours) in combination with ivacaftor (250 mg every 12 hours) or matched placebo for 24 weeks. The primary endpoint was the absolute change from baseline in the percentage of predicted FEV_1 at week 24. At baseline, the mean FEV_1 was 61% of the predicted value. In both trials, significant improvements were observed in the primary endpoint in both lumacaftor-ivacaftor dose groups; the difference between active treatment and placebo with respect to the mean absolute improvement in the percentage of predicted FEV_1 ranged from 2.6–4.0 percentage points (p<0.001), which corresponded to a mean relative treatment difference of 4.3–6.7% (p<0.001). In pooled analyses, the lumacaftor-ivacaftor groups had reductions in the rate of pulmonary exacerbations (by 30–39% vs placebo), with accompanying decreases in the numbers of events leading to hospitalisation or intravenous antibiotic treatment. The incidence of adverse events was generally similar in the lumacaftor-ivacaftor and placebo groups. The rate of discontinuation due to an adverse event was 4.2% with lumacaftor-ivacaftor and 1.6% with placebo.

Comment: This is the first clinical study that applies a CFTR potentiator and a CFTR corrector, to attempt to reverse the underlying defect in patients with the most common mutation in *CFTR*. The magnitude of change that was seen here was not as great as was seen when the CFTR potentiator ivacaftor was used alone in patients with type III *CFTR* gating mutations. Why was the therapy not as effective? This remains unclear. It may relate to the fact that the defect of the mis-folded protein is not directly improved by lumacaftor. In addition, the lumacaftor-ivacaftor combination results in *in vitro* antagonistic effects on each other and the need to combine and time the doses may not be ideal. This is a start that brings treatment that finally deals with the underlying disease process in those with the most common *CFTR* mutation.

Reference: N Engl J Med. 2015 May 17. [Epub ahead of print]
Abstract

Predictive value of serial HRCT analyses and concurrent lung function tests in systemic sclerosis

Authors: Hoffmann-Vold AM et al.

Summary: This Norwegian study assessed the use of serial lung fibrosis measurements and paired pulmonary function tests (PFTs) as outcome prediction tools in a cohort of patients with systemic sclerosis (SSc). Data were evaluable from paired PFTs and high-resolution computed tomography (HRCT) images obtained at baseline and follow-up (mean 3.1 years) in 305 SSc patients. At baseline, lung fibrosis was scored on 10 sections from every HRCT and expressed as percentage of total lung volumes. Three SSc groups were categorised by baseline HRCT analyses: Group 1, >20% lung fibrosis (n=40); Group 2, 1–20% fibrosis (n=157); and Group 3, no fibrosis (n=108). At follow-up HRCT, all patients in Group 3 remained fibrosis-free. Among the patients in Group 2, 146 remained at 1–20% (group 2a) while 11 patients, marked by short disease duration (1.3 years) progressed to >20% (2b). Annual fibrosis progression rates differed across the 4 groups (Group 1, 0.9%; Group 2a, 0.7%; Group 2b, 5.9%; and Group 3, 0%) and correlated with declines in forced vital capacity (FVC) (7.1%, 5.7%, 8.7% and 2.9%, respectively), but not with the decline in diffusing capacity of the lung for carbon monoxide (DLCO) (8.6%, 7.7%, 7.7% and 8.4%, respectively). In multivariate analyses, anti-centromere antibodies (odds ratio [OR] 4.7) and baseline DLCO (OR 1.04) were identified as predictors for no fibrosis at follow-up, while baseline fibrosis (OR 1.3) and FVC (OR 0.96) were predictors for >20% fibrosis.

Comment: Progressive interstitial lung disease is a major cause of mortality in systemic sclerosis. The disease course, however, varies widely between individuals. This study clearly defines a practical system for assessing patients with SSc at baseline for risk of progression of interstitial lung disease. It will allow more accurate advice on prognosis for patients. Unfortunately, at this stage, effective interventions are limited.

Reference: Arthritis Rheumatol. 2015 Apr 27. [Epub ahead of print]
Abstract

A bronchial genomic classifier for the diagnostic evaluation of lung cancer

Authors: Silvestri GA et al.

Summary: Data are reported from two multicentre studies (AEGIS-1 [n=298] and AEGIS-2 [n=341]) involving current or former smokers undergoing bronchoscopy for suspected lung cancer. These studies assessed the clinical performance of a bronchial-airway gene-expression classifier in lung cancer diagnosis, using epithelial cells collected from the normal-appearing mainstem bronchus. A total of 43% of bronchoscopic examinations were nondiagnostic for lung cancer, and invasive procedures were performed after bronchoscopy in 35% of patients with benign lesions. In AEGIS-1, the classifier had an AUC of 0.78 (95% CI, 0.73 to 0.83), a sensitivity of 88% and a specificity of 47%. Corresponding values in AEGIS-2 were 0.74 (95% CI, 0.68 to 0.80), 89% and 47%, respectively. The combination of the classifier plus bronchoscopy had a sensitivity of 96% (95% CI, 93 to 98) in AEGIS-1 and 98% (95% CI, 96 to 99) in AEGIS-2, regardless of lesion size and location. In 101 intermediate-risk patients with a nondiagnostic bronchoscopic examination, the negative predictive value of the classifier was 91%.

Comment: Patients at risk of lung cancer will frequently undergo bronchoscopy and CT surveillance when lung cancer is suspected. However, a bronchoscopy will frequently be negative in those with lesions that are not directly accessible from the large airways. The option then is for continued surveillance, usually by CT, or progression to more invasive investigations, including fine needle aspiration biopsy (FNAB) under CT guidance or surgical biopsy. In all cases, the risk of adverse events increases.This study shows that a sample of brushed epithelium from normal proximal airways, when run through a panel of genes in the gene-expression classifier, had high sensitivity across different lesion sizes, locations, stages, and cell types to detect the presence of lung cancer in the distant lesion that could not be sampled directly. The combination of the classifier plus bronchoscopy had a sensitivity of 96% and 98% in both studies. A negative result could then safely support a more conservative approach in these patients, rather than proceed onto invasive investigations.

Reference: N Engl J Med. 2015 May 17. [Epub ahead of print]
Abstract

Validation of predictors for fall asthma exacerbations in inner city children

Presenter: Dr H.E. Hoch, University of Colorado School of Medicine, Colorado, USA

Summary: The placebo-controlled PROSE study evaluated the effect of omalizumab on preventing fall asthma exacerbations in a cohort of children (aged 6–17 years) with asthma at risk for an exacerbation in the NIAID Inner City Asthma Consortium (ICAC). Prior ICAC studies identified the following risk factors for a fall exacerbation: younger age, increased number of positive allergen skin tests, lower FEV_1/FVC ratio, higher exhaled nitric oxide (eNO), and higher serum immunoglobulin (Ig)E. The study researchers assigned a risk score to each of these attributes, to develop a seasonal exacerbation predictive index score by assigning statistical cut-off values to 8 risk variables, rounding these values to clinically meaningful numbers, combining IgE and skin test positivity to get an allergy score, and assigning point values to the risk variable range (low risk=0 points, medium risk=1 point, high risk=2 points) with a composite score ranging from 0 to14. Variables considered included age, allergic potential (total IgE and allergen skin test positivity), blood eosinophils, exacerbation in the prior season, treatment step, FEV_1/FVC and fractional eNO. The 23 (26%) placebo-treated participants who had an exacerbation were more likely to be younger (8 years vs 10 years; p=0.01), have a higher total eosinophil count (380 cells/mL vs 265 cells/mL; p<0.01), higher IgE (410 kU/L vs 242 kU/L; p=0.01) and tended to have a higher eNO (34.0 ppb vs 19.8 ppb; p=0.11), as compared with those without an exacerbation. There was no difference in number of positive allergen skin tests or FEV_1/FVC. A strong statistical association was observed between the seasonal exacerbation index score and risk of an exacerbation.

Comment: Predicting which children will exacerbate with asthma is essential to target those who will require add on and regular asthma therapy. This cohort of children with persistent asthma was assessed to determine risk of exacerbations. Similar to what has been seen in adults, those who went on to exacerbate had evidence of uncontrolled TH2-associated inflammation, with elevated blood eosinophils and increased exhaled nitric oxide. They were also more likely to have allergic disease.

Reference: Am J Respir Crit Care Med. 2015;191:A2639
Abstract

ATS 2015
Conference Review™

Independent commentary by Professor Peter Wark, who is a senior staff specialist in Respiratory and Sleep Medicine at John Hunter Hospital, Newcastle and a conjoint Associate Professor with the University of Newcastle, New South Wales.

Efficacy and safety of electronic cigarettes for smoking cessation: a systematic review

Authors: Allehebi RO et al.

Summary: This systematic review of the published literature regarding the efficacy and safety of electronic-cigarettes (e-cigarettes) identified 4569 abstracts, 297 of which underwent full-text review. Four studies (2 randomised trials, 2 uncontrolled before-and-after studies) met inclusion criteria for efficacy analyses (these studies enrolled current smokers and compared e-cigarettes to placebo, active control or no therapy). Twenty-two studies were included for safety analyses (they reported any adverse events associated with e-cigarette use). In a meta-analysis, point-prevalence abstinence rates were significantly higher for e-cigarettes than for placebo at 1 month (RR 1.71; 95% CI, 1.08 to 2.72). However, this between-group difference was no longer statistically significant at 3 months (RR 1.95; 95% CI, 0.74 to 5.13) or 6 months (RR 1.32; 95% CI, 0.59 to 2.93). However, substantial heterogeneity between studies rendered the validity of these pooled estimates uncertain. Only 1 study evaluated continuous abstinence; it reported low rates at 6 months, with no significant differences seen between e-cigarettes versus placebo (7.3% vs 4.1%; RR 1.77; 95% CI, 0.54 to 5.77) or open-label nicotine patch (7.3% vs 5.8%; RR 1.26; 95% CI, 0.68 to 2.34). Respiratory adverse effects among e-cigarette users included dry cough (incidence range 26–32%), throat irritation (7–32%), and shortness of breath (2–20%), although incidence of these events tended to decrease over time. Case reports have documented serious adverse events in e-cigarette users including death, lipoid pneumonia, and recurrent atrial fibrillation. In comparative studies, incidence of serious adverse events did not differ between e-cigarettes and placebo e-cigarettes (19.7% vs 13.9%; RR 1.36; 95% CI, 0.54 to 3.42), but were more frequent with e-cigarettes than open-label nicotine patch (19.7% vs 11.8%; RR 1.97; 95% CI, 1.05 to 3.68).

Comment: E-cigarettes have emerged as a very popular alternative to conventional cigarettes, with manufacturers claiming their improved safety profile and also they can be used to aid smoking cessation. However, case reports of adverse events have led to concerns about their real safety and the magnitude of any benefit. This meta-analysis looks at this emerging evidence and is of great interest in this area. While e-cigarettes were of value in the short-term in aiding with smoking cessation, the effect was not sustained beyond a month. This is not surprising, as even with medicated nicotine replacement, cessation usually requires other supports. Adverse events, especially in the short-term, were also relatively high, though the majority were not severe or sustained.

Reference: Am J Respir Crit Care Med. 2015;191:A3715
Abstract

Obstructive sleep apnea (OSA) and excessive daytime sleepiness (EDS) are independently associated with depression in a community based population of Australian men

Authors: Lang CJ et al.

Summary: The Men Androgen Inflammation Lifestyle Environment & Stress Study (MAILES) involved 1875 community-dwelling Australian men aged 35–83 years who were assessed for depression using Beck's Depression Inventory (BDI)/Centre for Epidemiological Studies Depression Scale (CES-D) at two time points over a 5-year period. A random sample of 857 men without previously diagnosed obstructive sleep apnoea (OSA) underwent at home polysomnography (PSG) and completed the Epworth Sleepiness Scale questionnaire. 1660 men without depression at baseline were included in the longitudinal analysis of incident depression. In cross-sectional analyses, previously undiagnosed severe OSA was associated with depression prevalence, even after adjustment for potential confounders and excessive daytime sleepiness (EDS) (adjusted OR 1.9; 95% CI, 1.07 to 3.70). EDS was also associated with depression (adjusted OR 2.4; 95% CI, 1.40 to 3.95). The risk of developing depression in men with previously undiagnosed OSA and EDS was 4.2 times higher than in men without OSA and EDS and 3.5 times higher than in men with either OSA or EDS alone. Both previously diagnosed OSA (OR 2.0; 95% CI, 1.15 to 3.45) and previously undiagnosed severe OSA (Apnoea-Hypopnoea Index [AHI] ≥30) (OR 2.9; 95% CI, 1.19 to 6.92) at follow-up were significantly associated with depression onset over a 5-year period. Other PSG parameters including O_2 saturation, O_2 desaturation and arousal index were not associated with depression prevalence or incidence.

Comment: This trial clearly determines that depression is linked to OSA and clinicians should be mindful to check for both comorbid diseases that may adversely impact on each other.

Reference: Am J Respir Crit Care Med. 2015;191:A3934
Abstract

High prevalence of obstructive sleep apnea in patients treated with percutaneous coronary intervention: a multicenter observational study

Authors: Furlan SF et al.

Summary: This analysis included data from 1305 participants (mean age 58 years) from the multinational Sleep and Stent Study, which examined the associations between obstructive sleep apnoea (OSA) and cardiovascular outcomes in adult patients aged 18–80 years who underwent successful percutaneous coronary intervention (PCI). All patients underwent an overnight sleep study before being discharged from hospital. The patients were divided into 2 groups based on apnoea-hypopnoea index (AHI) score: OSA (AHI ≥15) and non-OSA (AHI <15). Indications for PCI were ST-segment elevation myocardial infarction (STEMI) in 32.8%, non-STEMI in 19.9%, unstable angina in 16.2% and stable angina in 31%. The prevalence of OSA was 45% (21.8% presented with severe OSA, AHI ≥30 events/hour). Excessive daytime sleepiness (Epworth Sleepiness Scale >10) was found in only a quarter (24.5%) of the patients with OSA and just half (54.3%) of all patients were identified by the Berlin Questionnaire as being at high risk for OSA, suggesting that these sleep questionnaires may not be useful for screening OSA in patients with cardiovascular diseases.

Comment: This is another large study that emphasises the high prevalence of OSA in patients with active coronary heart disease. This association is well known and it is recommended that these patients be screened for OSA. Unfortunately, the interesting feature of this abstract was that neither the Epworth sleepiness score nor the Berlin Questionnaire appeared to detect disease with adequate sensitivity. While treatment with continuous positive airway pressure (CPAP) may improve non-sleep-related outcomes in these patients this effect is clearly best for those who are symptomatic. This interesting finding deserves more attention as to how to detect these individuals, but will need to also detect those who will benefit most from treatment of OSA.

Reference: Am J Respir Crit Care Med. 2015;191:A6107
Abstract

Consistent effect of nintedanib on decline in FVC in patients across subgroups based on HRCT diagnostic criteria: results from the INPULSIS® trials in IPF

Authors: Raghu G et al.

Summary: This post-hoc subgroup analysis pooled data from the two replicate, randomised, placebo-controlled, 52-week INPULSIS® trials, which assessed the efficacy and safety of nintedanib 150 mg twice daily in patients with idiopathic pulmonary fibrosis (IPF). In both trials, nintedanib significantly reduced the annual rate of FVC decline, consistent with a slowing of disease progression, in patients with different radiological patterns at baseline. This subgroup analysis compared outcomes between 723 patients (425 nintedanib, 298 placebo) with diagnosis based on honeycombing and/or confirmation of usual interstitial pneumonia (UIP) by biopsy and 338 patients (213 nintedanib, 125 placebo) with no honeycombing or biopsy for diagnosis of IPF. Demographics and baseline characteristics were similar between these subgroups. In patients with honeycombing and/or biopsy, the adjusted annual rate of decline in FVC was –108.7 mL/year with nintedanib and –225.7 mL/year with placebo (difference: 117.0 mL/year); in patients with no honeycombing or biopsy, it was –122.0 mL/year with nintedanib and –221.0 mL/year with placebo (difference: 98.9 mL/year). The treatment by subgroup interaction p-value was not significant for the primary endpoint (p=0.81) or for the key secondary endpoints of time to first acute exacerbation (p=0.37) or change from baseline in St. George's Respiratory Questionnaire total score at 52 weeks (p=0.67), indicating that the treatment effect of nintedanib was not statistically significantly different between the subgroups.

Comment: The INPULSIS trial demonstrated that nintedanib could slow decline in lung function in patients with IPF. Concerns remain, however, as to whether this effect would also be seen in those in whom the diagnosis was less clear, those with probable UIP, as opposed to definite UIP. This analysis confirms that a treatment effect was seen in both groups.

Reference: Am J Respir Crit Care Med. 2015;191:A1022
Abstract

Effect of continued treatment with pirfenidone following a clinically meaningful decline in percent predicted forced vital capacity in patients with idiopathic pulmonary fibrosis (IPF)

Authors: Nathan SD et al.

Summary: For this analysis, data were pooled from the phase III ASCEND and CAPACITY trials to assess the potential benefit of continued treatment with pirfenidone in patients with IPF who experience a ≥10% decline in percent predicted FVC (%FVC) during the first 6 months of treatment. Thirty-four and 68 patients in the pooled pirfenidone and placebo groups, respectively, experienced a ≥10% absolute decline in %FVC between baseline and month 6 (relative difference, 49.5%). During the subsequent 6-month interval, fewer patients in the pirfenidone group compared with placebo experienced a ≥10% decline in %FVC or death (2 [5.9%] vs 19 [27.9%]), and more pirfenidone-treated patients than placebo-treated patients had no further decline in %FVC (20 [58.8%] vs 26 [38.2%]). Pirfenidone was also associated with fewer deaths (1 [2.9%] vs 14 [20.6%] with placebo).

Comment: The CAPACITY and ASCEND trials demonstrated that pirfenidone slowed decline in lung function. It was not known though whether this beneficial effect would be lost in those who start to decline despite treatment. This post-hoc analysis that examined the effect of pirfenidone on those who did decline in FVC >10% despite the intervention demonstrated that this group still appeared to do better compared to placebo, with less further decline in FVC and reduced mortality. This implies that treatment should continue, even when IPF progresses.

Reference: Am J Respir Crit Care Med. 2015;191:A1016
Abstract