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Issue 76 - 2019

In this issue:

Abbreviations used in this issue:

6MWD = 6-minute walk distance; **BMI** = body mass index; **BP** = blood pressure; **CAP** = community-acquired pneumonia; **COPD** = chronic obstructive pulmonary disease; **CPAP** = continuous positive airway pressure; **ENDS** = electronic nicotine delivery systems; **h** = hours; **HR** = hazard ratio; **ICS** = inhaled corticosteroid; **IV** = intravenous; **LABA** = long-acting β_2 agonist; **LAMA** = long-acting muscarinic receptor antagonist; **MAC** = *Mycobacterium avium* complex; **MI** = myocardial infarction; **OR** = odds ratio; **OSA** = obstructive sleep apnoea; **PE** = pulmonary embolism; **SF-36** = Short Form-36; **VTE** = venous thromboembolism.

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Welcome to issue 76 of Respiratory Research Review.

One of the papers in this issue indicates that corticosteroid treatment may lower the rate of myocardial infarction in patients hospitalised with community-acquired pneumonia. Corticosteroids also appeared to be of greater benefit in patients with COPD, as compared with those without COPD. Perhaps having COPD increases the risk of thrombotic events?

In another study, annual influenza vaccination significantly reduced influenza-related hospitalisations in patients with COPD, highlighting the importance of influenza vaccination uptake in this vulnerable population.

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

Dr Janette Tenne

Medical Research Advisor

janette.tenne@researchreview.com.au

Thunderstorm asthma: revealing a hidden at risk population

Authors: Clayton-Chubb D et al.

Summary: These researchers surveyed staff and volunteers regarding the nature and extent of respiratory symptoms among healthcare workers during the Melbourne epidemic thunderstorm asthma event; the survey was completed by 511 respondents, mostly female, from a potential pool of ~9000. Symptoms suggestive of asthma during the Melbourne epidemic thunderstorm asthma event were reported by 25.6% of respondents, among whom most did not seek professional medical help. Among respondents reporting symptoms, 43.9% and 73.5% had histories of asthma and allergic rhinitis, respectively. Strong predictors of symptoms included a history of allergic rhinitis (OR 2.77; p<0.001), a history of asthma (1.67; p=0.037) and Asian ethnicity self-identification (3.24; p<0.001); predominantly being indoors did not protect against symptoms.

Comment: In November 2016, Australia recorded the worst episodic thunderstorm asthma (ETSA) event in history, with over 3,500 patients treated in hospitals across Melbourne and 10 fatalities. This study shows that these numbers are possibly an underestimate, as 25% of respondents in this survey had symptoms but did not seek medical help. As expected, participants with histories of allergic rhinitis and asthma were more likely to experience asthma-like symptoms, but interestingly, Asian ethnicity was shown to be an independent risk factor for thunderstorm asthma. They were shown to have triple the risk for ETSA. Asian Australians are known to have a higher prevalence of atopy and environmental factors may have a role as previous studies have shown a link between length of residency and risk of developing asthma.

Reference: Intern Med J. 2019;49(1):74-8

Abstract

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Effect of supplemental oxygen on blood pressure in obstructive sleep apnea (SOX): a randomized continuous positive airway pressure withdrawal trial

Authors: Turnbull CD et al.

Summary: The SOX trial investigated the role of intermittent hypoxia in daytime BP elevations in OSA in patients with moderate-to-severe OSA who had been treated with CPAP for >1 year, with average CPAP usage of over 4 h/night. They were initially randomised to receive overnight supplemental oxygen or air (sham) instead of CPAP for 2 weeks, followed by a 2-week washout back on CPAP, before crossing over to receive supplemental air of oxygen for another 2 weeks (instead of CPAP). Supplemental oxygen abolished elevations in home morning BP after CPAP withdrawal and, compared with air, significantly reduced the elevation in mean systolic BP (–6.6 mm Hg; p=0.008), mean diastolic BP (–4.6 mm Hg; p=0.006) and median Oxygen Desaturation Index (–23.8/h; p<0.001) after CPAP withdrawal. No significant differences were seen in terms of changes in Apnoea-Hypopnoea Index scores, subjective sleepiness (Epworth Sleepiness Scale score), or objective sleepiness (Oxford Sleep Resistance Test), for oxygen versus air.

Comment: This was a randomised, double-blind, crossover study comparing nocturnal oxygen therapy versus sham oxygen on BP. Patients had been on CPAP for at least a year and had a 2-week withdrawal period when they were randomised to oxygen therapy or sham oxygen. The study found that there was a statistically significant increase in morning systolic and diastolic BP in the group on sham oxygen. The study concludes that intermittent hypoxemia, rather than arousal-mediated sympathetic activation, is the cause for awake BP elevation. However, previous studies on supplemental oxygen have failed to show reduction in BP. It may be that short-term effects of OSA on BP are mediated through hypoxia, but chronic baroreceptor and chemoreceptor changes are less rapidly reversible. Treatment of OSA with oxygen is known to prolong apnoeas and hypercapnoea, and long-term effects are unknown. Oxygen therapy also had no effect on AHI or sleepiness, but its benefits in reducing cardiovascular risk needs further investigation.

Reference: Am J Respir Crit Care Med. 2019;199(2):211-9
Abstract

Capturing exacerbations of chronic obstructive pulmonary disease with EXACT: a subanalysis of FLAME

Authors: Frent SM et al.

Summary: The FLAME (Effect of Indacaterol Glycopyrronium vs. Fluticasone Salmeterol on COPD Exacerbations) study demonstrated superiority of the long-acting β_2 agonist (LABA)/long-acting muscarinic receptor antagonist (LABA) combination of indacaterol/glycopyrronium versus the LABA/inhaled corticosteroid (ICS) combination of salmeterol/fluticasone propionate on COPD exacerbation prevention, irrespective of baseline blood eosinophil count. This paper reports outcomes from a substudy of FLAME that used the Exacerbations of COPD Tool (EXACT) to capture symptom-defined exacerbations in 457 patients; this substudy also assessed differences between physician-confirmed exacerbations requiring healthcare resource use (HCRU) and symptom-defined exacerbations using the EXACT. The annualised rate of symptom-defined exacerbations using the EXACT was 17% lower with indacaterol/glycopyrronium versus salmeterol/fluticasone (rate ratio 0.83; 95% CI, 0.60 to 1.14; p=0.242) and LABA/LAMA treatment prolonged the time to first symptom-defined exacerbation (HR 0.76; 95% CI, 0.56 to 1.03; p=0.075). Around a quarter (23.5%) of the symptom-defined (EXACT) events corresponded with HCRU events; 22.2% of HRCU events were captured by EXACT (κ index, 0.24; 95% CI, 0.15 to 0.33).

Comment: This was an analysis of a subset of patients from the FLAME study that used the Exacerbations of COPD Tool (EXACT) to capture symptom-defined exacerbations. The study compared the effect of indacaterol/glycopyrronium versus salmeterol/fluticasone on symptom-defined exacerbations measured using EXACT, and to assess differences between these events and exacerbations requiring healthcare resource use (HCRU). The study found that there was a 17% reduction in annual symptom-defined (EXACT) exacerbation rates and a longer time to first exacerbation. There wasn't very good concordance between EXACT events and HCRU events and this finding is similar to previous studies. Of importance, irrespective of how exacerbations were defined, the use of long-acting β_2 agonists/long-acting muscarinic receptor antagonists was the preferred treatment option for patients at risk of future exacerbations.

Reference: Am J Respir Crit Care Med. 2019;199(1):43-51
Abstract

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References: 1. Bleecker ER, *et al. Lancet* 2016;388(10056):2115–27. 2. FitzGerald JM, *et al. Lancet* 2016;388(10056):2128–41.
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Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by *Mycobacterium avium* complex (CONVERT): a prospective, open-label, randomized study

Authors: Griffith DE et al.

Summary: In this study, adults with amikacin-susceptible *Mycobacterium avium* complex (MAC) lung disease and MAC-positive sputum cultures despite ≥6 months of stable guideline-based therapy (GBT) were randomised to receive once-daily amikacin liposome inhalation suspension (ALIS, supplied in single-use vials delivering 590 mg amikacin to the nebuliser) with GBT (ALIS+GBT; n=224) or GBT alone (n=112). At significantly higher proportion of patients receiving ALIS+GBT compared with those receiving GBT alone achieved culture conversion, defined as 3 consecutive monthly MAC-negative sputum cultures by month 6 (29.0% vs 8.9%; OR 4.22; 95% CI, 2.08 to 8.57; p<0.001). Patients in the ALIS+GBT arm vs GBT alone were more likely to achieve conversion (HR 3.90; 95% CI, 2.00 to 7.60). Respiratory adverse events (primarily dysphonia, cough, and dyspnoea) were reported in 87.4% of the ALIS+GBT cohort and 50.0% of those on GBT alone; rates were comparable between the groups for serious treatment-emergent adverse events (20.2% vs 17.9% of patients, respectively).

Comment: Treatment outcomes in patients with *Mycobacterium avium* complex (MAC) on current recommended treatment regimes have been poor. This study enrolled patients with MAC that were still sputum-positive after 6 months of guideline-based therapy (GBT) and randomised them to receive amikacin liposome inhalation suspension (ALIS) or continue on GBT. Culture conversion was achieved in 29% with ALIS + GBT compared to 8.9% with GBT alone. There were no significant differences in 6MWT or quality of life between the treatment groups. Adverse reactions were common, with 82.5% of treatment-emergent adverse events related to ALIS. However, treatment discontinuation was infrequent. Based on these findings, the FDA has approved ALIS for patients with treatment-refractory MAC. The question is whether use of ALIS earlier in the course of disease will limit the loss of lung function and translate to improvements in patients' function and quality of life.

Reference: Am J Respir Crit Care Med. 2018;198(12):1559-69
Abstract

Frailty and clinical outcomes in chronic obstructive pulmonary disease

Authors: Kennedy CC et al.

Summary: This retrospective analysis used data from the previously published National Emphysema Treatment Trial (NETT), which compared lung volume reduction surgery with medical management in COPD. For this analysis, 902 NETT participants were followed starting 12 months after study randomisation for an additional 24 months. The primary objective was to determine whether the frailty phenotype conceptual model (operationalised as ≥3 frailty parameters: a BMI decrease of ≥5% over 12 months, self-reported exhaustion, low 6MWD, or physical activity or respiratory muscle strength in the lowest quartile) is associated with mortality in patients with COPD. The incidence rate of frailty was 6.4 per 100 person-years. Compared with NETT patients with ≤2 frailty parameters, frail participants reported significantly worse disease-specific and overall quality of life on total St. George's Respiratory Questionnaire scores (mean difference of 11.6; 95% CI, 7.6 to 15.6; p<0.001), as well as lower (worse) scores for the SF-36 mental composite score (mean difference –6.8; 95% CI, –10.0 to –3.6; p<0.001) and SF-36 physical composite score (–16.7; –21.3 to –12.1; p=0.001). The frailty phenotype was associated with an increased incidence of hospitalisation (aHR 1.6; 95% CI, 1.1 to 2.5; p=0.02) and an 8.0-day increase in hospital length-of-stay (95% CI, 4.4 to 11.6; p<0.001), as well as a higher mortality rate (1.4; 0.97 to 2.0; p=0.07).

Comment: Frailty has been shown to be associated with worse outcomes in geriatric patients and in some other chronic diseases. Prevalence of frailty in elderly with COPD has been shown to be as high as 10.2%. Frailty in this study was conceptually based on the Fried frailty phenotype but modified for this cohort. In this study, the majority were male, with a median age of 67. The prevalence of frailty was 6%. The study found that frail patients had worse survival with a 2-year mortality rate of 36%. They also had an increased risk for hospitalisations and an 8-day increase in hospital stay compared to non-frail patients. In this study, the incidence of frailty was as high as 9% in the prefrail patients. But it is also important to note that during the study duration 23% of prefrail patients improved their frailty scores and became nonfrail. This implies that frailty factors can be modified to improve patient outcomes and further research is needed to address whether these benefits were related to pulmonary rehabilitation or other factors.

Reference: Ann Am Thorac Soc. 2019;16(2):217-24
Abstract

Corticosteroid use and incident myocardial infarction in adults hospitalized for community-acquired pneumonia

Authors: Cangemi R et al.

Summary: This retrospective Italian study analysed data from 758 adults (mean age, 71.7 years) hospitalised with CAP, 241 of whom were treated with systemic corticosteroids (methylprednisolone, betamethasone, or prednisone). In-hospital myocardial infarction (MI) occurred in 8.2% of the cohort (incidence, 0.72 per 100 person-days). The incidence of MI was lower in those patients administered corticosteroids (0.42 per 100 person-days) compared with those who were not (0.89 per 100 person-days). In propensity score-adjusted Cox modelling, corticosteroid use was associated with a lower incidence of MI (HR 0.46; 95% CI, 0.24 to 0.88; p=0.02).

Comment: CAP is known to increase the risk of cardiovascular morbidity and mortality. In this retrospective study of 758 patients, 32% were treated with oral corticosteroids. Those who were treated with corticosteroids had a lower incidence of MI than those not treated with corticosteroids. When the cohort was stratified based on pre-existing COPD, it was found that corticosteroid use was more prevalent in patients with COPD than in those without COPD and patients with COPD treated with corticosteroids had a lower incidence of MI, whereas there was no association between corticosteroid treatment and MI in those without COPD. The exact mechanisms by which corticosteroids reduce MI is unclear and also why COPD patients benefit more than those without COPD. It may reflect that COPD patients are at increased risk for thrombotic events. These are areas for future research.

Reference: Ann Am Thorac Soc. 2019;16(1):91-8
Abstract

Effectiveness of influenza vaccination on hospitalizations and risk factors for severe outcomes in hospitalized patients with COPD

Authors: Mulpuru S et al.

Summary: This Canadian research group analysed data from 4,198 patients with COPD and known vaccination status for influenza who were hospitalised with any acute respiratory illness or exacerbation between 2011 and 2015. All patients underwent influenza testing by nasopharyngeal swab with polymerase chain reaction. In multivariable logistic regression analyses adjusted for potential confounders, influenza vaccination was associated with a significant reduction in influenza-related hospitalisations (38%). The influenza-positive cohort (n=1,833) experienced higher crude mortality (9.7% vs 7.9%; p=0.047) and need for critical care (17.2% vs 12.1%; p<0.001) compared with the influenza-negative cohort. Risk factors for 30-day mortality in influenza-positive patients included age >75 years (OR 3.7; 95% CI, 0.4 to 30.3), cardiac comorbidity (2.0; 1.3 to 3.2), residence in long-term care (2.6; 1.5 to 4.5) and oxygen use at home (2.9; 1.6 to 5.1).

Comment: Annual influenza vaccination is recommended for patients with COPD, but the studies that influenced this recommendation were limited by small sample sizes. This study looked at the outcomes of 4,198 patients hospitalised between 2011 and 2015 with COPD. The seasonal influenza vaccine reduced influenza-related hospitalisations among patients with COPD by 37.5% compared with unvaccinated patients. Despite recommendations, the study found that only 66.5% of hospitalised COPD patients had been vaccinated during the season when hospitalisation occurred. The effectiveness of influenza vaccine ranged between 43–49%, except for the 2014–2015 influenza season, when it dropped to 6%, due to a vaccine/influenza strain mismatch. COPD patients with influenza had high mortality (8%) and critical illness rates (18%). The study shows that influenza vaccination can significantly reduce influenza-related hospitalisations in this group and more needs to be done to increase vaccination uptake in this at-risk group.

Reference: Chest. 2019;155(1):69-78
Abstract

Secondhand exposure to aerosols from electronic nicotine delivery systems and asthma exacerbations among youth with asthma

Authors: Bayly JE et al.

Summary: These researchers examined the relationship of secondhand electronic nicotine delivery systems (ENDS) aerosol exposure and asthma exacerbations among youth with asthma, using data from 11,830 youth (aged 11–17 years) who participated in the 2016 Florida Youth Tobacco survey with a self-reported diagnosis of asthma. Around one-fifth (21%) reported having an asthma attack in the past 12 months, and one-third (33%) reported secondhand ENDS aerosol exposure. In a multivariable logistic regression analysis controlling for covariates, secondhand ENDS aerosol exposure was associated with a higher likelihood of reporting an asthma attack (aOR 1.27; 95% CI, 1.11 to 1.47).

Comment: The effect of secondhand exposure to vapours from electronic nicotine delivery systems (ENDS), which include electronic cigarettes (e-cigarettes), is not well known. This study, done in a cohort of high school students, had a majority of females and were aged between 11–13 years. Compared to 4–6% reporting current cigarette or hookah use, 12% reported they were using ENDS. About a third of participants reported exposure to aerosols from ENDS. The study found that there was an association between exposure to ENDS aerosols and risk of asthma exacerbation. This highlights that vapours from ENDS are not benign and patients and families need to be educated on potential risks.

Reference: Chest. 2019;155(1):88-93
Abstract

Health-care cost impact of continued anticoagulation with rivaroxaban vs aspirin for prevention of recurrent symptomatic VTE in the EINSTEIN-CHOICE trial population

Authors: Wells PS et al.

Summary: These researchers used event rates from the Reduced-Dose Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN-CHOICE) trial and cost data from the published literature to assess the cost impact of continued anticoagulation therapy with rivaroxaban (10 and 20 mg daily) versus aspirin (100 mg daily). The event rate was multiplied by cost of care to calculate clinical event costs (in 2016 US dollars). Rivaroxaban was associated with lower per patient per month (PPPM) clinical event costs compared with aspirin ($US123 and $US243 vs $US381 for rivaroxaban 10 and 20 mg vs aspirin, respectively). However, the higher cost of rivaroxaban led to higher PPPM total healthcare costs compared with those for aspirin ($US24 higher for rivaroxaban 10 mg and $US143 higher for rivaroxaban 20 mg). When a 15% drug discount was applied to rivaroxaban 10 mg, the lower cost of clinical events for the rivaroxaban-treated patients offset the higher drug costs and yielded a $US19 lower total healthcare cost.

Comment: The EINSTEIN-CHOICE study compared the safety and efficacy of long-term anticoagulation with rivaroxaban 10 mg or 20 mg daily against aspirin and found that rivaroxaban significantly lowered VTE events, without any difference in bleeding rates. In this study, the unit pricing and healthcare costs were calculated based on the US healthcare system. However, it is clear that although rivaroxaban unit pricing may be more than aspirin, clinical event costs per patient were lower for all efficacy outcomes for rivaroxaban vs aspirin. Drug cost, rate difference of all-cause mortality, recurrent DVT and recurrent PE had the highest impact on the total healthcare cost difference, which was in favour of rivaroxaban 10 mg daily. The study had limitations, with no accurate costing available for treatment of major bleeds. Also, costings of loss of productivity and earnings associated with recurrent VTE events were not calculated.

Reference: Chest. 2018;154(6):1371-8
Abstract

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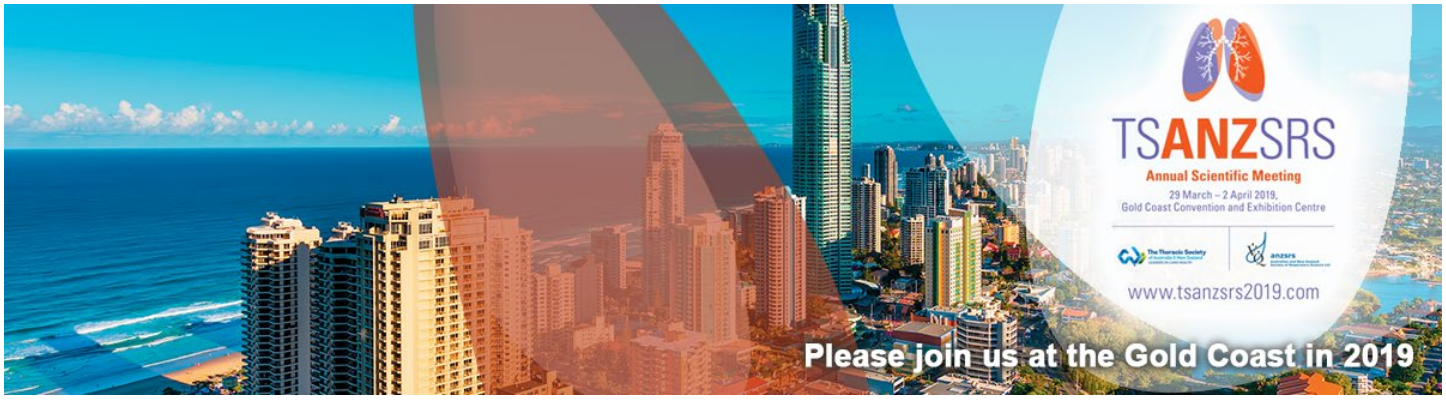

Omadacycline for community-acquired bacterial pneumonia

Authors: Stets R et al.

Summary: Intention-to-treat data are reported from this study in which adults with CAP were treated with IV omadacycline (100 mg every 12 h for 2 doses, then 100 mg every 24 h; n=386) or IV moxifloxacin (400 mg every 24 h; n=388). After 3 days, patients could transition to oral omadacycline (300 mg every 24 h) or moxifloxacin (400 mg every 24 h); the total treatment duration was 7–14 days. Omadacycline was non-inferior to moxifloxacin for the primary endpoint of early clinical response (survival with improvements in ≥2 of 4 symptoms [cough, sputum production, pleuritic chest pain, and dyspnoea] and no worsening of symptoms at 76–120 h, without any rescue antibacterial therapy), with rates of 81.1% and 82.7%, respectively; corresponding rates of investigator-assessed clinical response at a post-treatment evaluation 5–10 days after the last dose were 87.6% and 85.1%, respectively. After commencing treatment, adverse events were reported by 41.1% of the omadacycline arm and 48.5% of the moxifloxacin arm; the most commonly reported events were gastrointestinal (10.2% and 18.0%, respectively), with diarrhoea affecting fewer patients in the omadacycline group compared with the moxifloxacin group (1.0% and 8.0%, respectively).

Comment: Omadacycline is a new once-daily aminomethylcycline antibiotic agent that can be administered intravenously or orally. It belongs to the tetracycline class of antibiotics. In this randomised controlled trial, omadacycline was compared to moxifloxacin for the treatment of patients hospitalised with CAP. Omadacycline was found to be non-inferior to moxifloxacin. The mortality rate was noted to be higher in the omadacycline group compared to the moxifloxacin group (2.1% vs 1%). The reason for this is unclear. Omadacycline has the advantage of having activity against the common respiratory pathogens, but also to the atypical organisms *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*. Hence, omadacycline can be used as a single-agent alternative, either parenteral or oral, to empirical β-lactam–macrolide combination therapy or a respiratory fluoroquinolone for CAP. It is also many times more active than doxycycline and minocycline against *Enterobacteriaceae* and *Acinetobacter baumannii*.

Reference: N Engl J Med. 2019;380:517-27
Abstract

Independent commentary by Dr Alpana 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.

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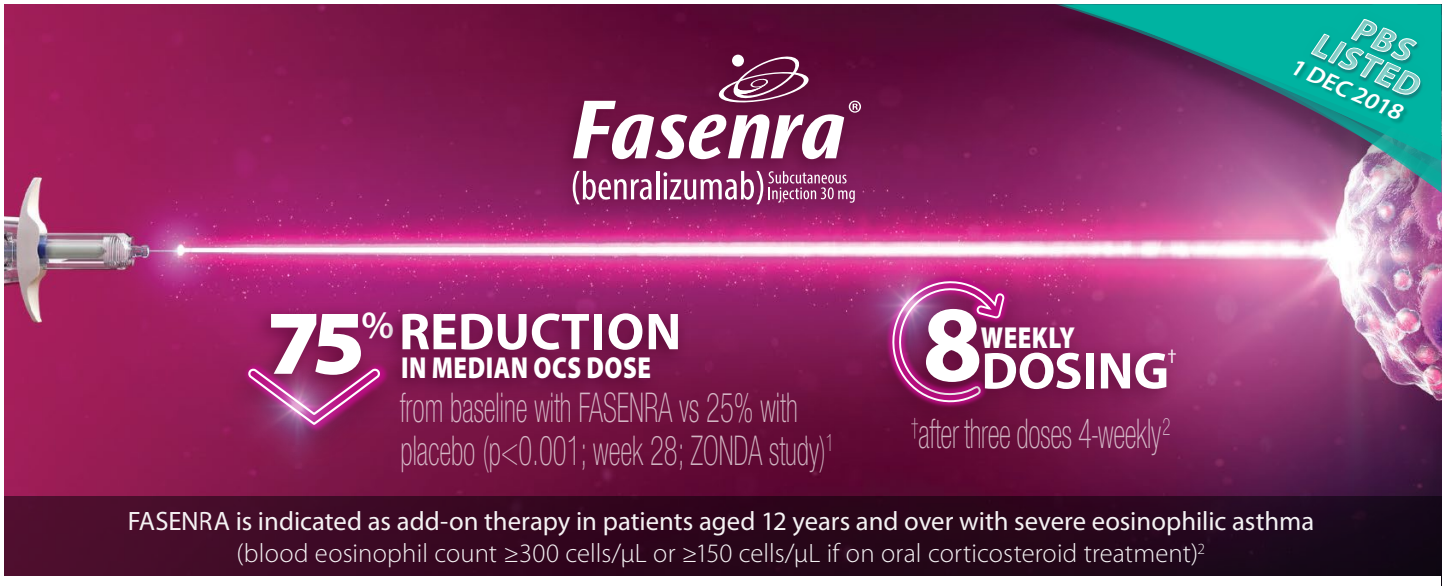

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OCS=oral corticosteroid. **References: 1.** Nair P, *et al. N Engl J Med* 2017;376(25):2448–58. **2.** Fasenra (benralizumab) Product Information. April 2018. FASENRA® is a registered trademark of the AstraZeneca group of companies. Registered user AstraZeneca Pty Ltd. ABN 54 009 682 311. 66 Talavera Road, Macquarie Park, NSW 2113. www.astrazeneca.com.au. For Medical Information enquiries: 1800 805 342 or medinfo.australia@astrazeneca.com. To report an adverse event: 1800 805 342 or via https://aereporting.astrazeneca.com. AU-3847 ASTR0105/3 Date of preparation: December 2018 AstraZeneca

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