WHY, WHEN, AND HOW? OPTIMISING THE MANAGEMENT OF PATIENTS WITH SEVERE EOSINOPHILIC ASTHMA

Summary of the symposium which took place on 5th September 2016 as a part of the European Respiratory Society (ERS) International Congress in London, UK

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Disclosure: Prof Pavord has received speaker's honoraria from AstraZeneca, Boehringer Ingelheim, Aerocrine, Respivert, Teva, and GSK; and advisory panel fees from Almirall, AstraZeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey, and Napp. Prof Pavord has also received sponsorship honoraria from Boehringer Ingelheim, GSK, AstraZeneca, and Napp. Prof Buhl has received speaker/consulting honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Roche, and Teva, and has received research support from Boehringer Ingelheim, GSK, Novartis, and Roche. Prof Costello is a speaker and advisory board member to Aerogen, Boehringer Ingelheim, GSK, Novartis, and Teva, and has received grant support from Aeorogen, Vitalograph, and GSK. Prof Costello has an active patent on use of acoustic analysis to assess inhaler technique of use. Prof Castro has received royalties from Elsevier, speaker fees from Boeringer Ingelheim, Boston Scientific, Genentech, and Teva and has received consulting fees from AstraZeneca, Boston Scientific, Holaira, NeoStem, Neutronic, Novartis, Roche, Sanofi Aventis, Teva, and Therabron. Prof Castro has also received funding from AsthmaNet, the American Lung Association, Severe Asthma Research Programme, Amgen, Boehringer Ingelheim, Genentech, Gilead, GSK, Invion, Johnson & Johnson, Medimmune/AstraZeneca, Novartis, Pfizer, Sanofi Aventis, Teva, and Vectura.
Acknowledgements: Writing assistance was provided by Mia Cahill of ApotheCom.
Support: The publication of this article and the symposium at the International Congress of the European Respiratory Society (ERS) were funded by Teva Pharmaceuticals B.V. The views and opinions expressed are those of the authors and not necessarily Teva Pharmaceuticals B.V. or the ERS.
Citation: EMJ Respir. 2016;4[1]:51-59.

MEETING SUMMARY

The main objectives of this symposium were to explore the challenges faced when treating patients with severe eosinophilic asthma, to evaluate the key clinical assessments that are available for early disease recognition, and to discuss the latest personalised treatment options that could shape future management strategies. Prof Ian Pavord opened the symposium by introducing uncontrolled severe asthma, focussing on the challenges and unmet needs of patients. Prof Buhl then delved into the basics of eosinophilic asthma from a molecular and physiological point of view, discussing the clinical relevance and characterisation of eosinophilic patients. Prof Costello focussed on the key clinical assessments (diagnosis, adherence, and phenotyping) and management of patients. Prof Castro summarised the latest evidence from studies of mepolizumab, benralizumab, reslizumab, anti-interleukin (IL)-4, and anti-IL-13 therapies, and how this relates to clinical practice.

A New Era for Patients with Uncontrolled Severe Asthma

Professor Ian Pavord

Patients with severe asthma are a small subgroup of patients, comprising 5–10% of the total asthma population (approximately 300 million patients worldwide). Despite taking appropriate treatments and adhering to therapies, ≤5% of patients have severe refractory asthma. Eosinophilic asthma is the cause of severe refractory asthma in 50–60% of patients, making them potential candidates for anti-IL-5 treatment.[1-3] Patients with severe asthma are a very important subgroup as they require high-intensity treatment; those receiving Global Initiative for Asthma (GINA) Step 4 (medium/high-dose inhaled corticosteroid or long-acting β-agonist) or Step 5 (add-on therapy e.g. mepolizumab) treatment to control their asthma or who remain uncontrolled despite treatment.[4] Severe asthma patients account for >80% of all direct healthcare costs in asthma and are therefore important from a health services point of view.[1-3]

The European Respiratory Society/American Thoracic Society (ERS/ATS) define severe asthma as requiring high-dose combination treatment, often with other therapies, for at least a year or that which requires systemic corticosteroids for at least half a year to prevent it from becoming uncontrolled, or which remains uncontrolled despite high-intensity treatment. Asthma can become uncontrolled because of poor symptom control (Asthma Control Questionnaire [ACQ] score >1.5 or Asthma Control Test score <20), frequent severe exacerbations (≥2 bursts of corticosteroids in previous year); the occurrence of one serious exacerbation resulting in hospitalisation; intensive care unit admission or mechanical ventilation in the previous year; persistent airflow limitation (post-bronchodilator forced expiratory volume in 1 second [FEV_1] <80% predicted); or if controlled asthma worsens on tapering of treatment.[5]

A survey conducted in patients with asthma highlighted that they are most concerned about exacerbations, episodes of asthma that do not respond to bronchodilators,[6] and the burden associated with oral corticosteroid therapy.[7,8] Severe asthma exacerbations are the most clinically important manifestations of asthma and result in death in 1,200 cases per year in the UK.

How Should We Approach the Clinical Assessment of Patients with Severe Asthma?

When assessing a patient for severe asthma it is critical to identify: i) those who have pseudo-asthma or comorbid asthma, in which another factor is responsible for the symptoms (i.e. dysfunctional breathing or upper airway problems); ii) patients who have not mastered inhaler technique, self-management, or have poor adherence; and iii) those with genuine severe disease. Assessment should centre on whether there is objective evidence of airway dysfunction and airway inflammation, and if there are other factors contributing to symptoms.

Phenotyping Disease

After carrying out basic measurements of spirometry, fractional exhaled nitric oxide (FeNO), and blood eosinophils, the phenotype of the patient can be determined. This is important as severe asthma is heterogeneous, particularly in the way eosinophilic airway inflammation relates to airway dysfunction. Two main groups of discordant patients exist, inflammation-predominant and symptom-predominant,[9] suggesting that a symptom-guided approach will not achieve optimum results in these patients. Measuring airway inflammation is the only way to assess for discordant phenotypes and there is clinical value in doing so; targeted treatment to normalise inflammation leads to improved patient outcomes.[10] This key conceptual insight provided the basis for successful pilot studies of anti-IL-5 treatment in severe eosinophilic asthma.[11,12]

Eosinophilic Inflammation Under the Lens

Professor Roland Buhl

Eosinophilic Asthma: The Basics

IL-5 mediates eosinophil maturation and mobilisation in the bone marrow as well as activation of the cells. Eosinophils are delivered to the lungs via the blood stream where they are involved in smooth muscle hypertrophy (eventually leading to airway hyper-responsiveness), matrix deposition (leading to remodelling in some patients), and goblet cell metaplasia and mucous production. Until relatively recently, it was thought that T helper 2 (Th2) cells, as part of the adaptive immune system, were the main source of IL-5 before it was discovered that innate lymphoid Type 2

cells (ILC-2) produce IL-4, IL-5, and IL-13 at higher concentrations compared to Th2 cells. The ILC-2 pathway is part of the innate immune system and as such, unlike in allergic asthma, is not triggered by allergens but rather by microbes, pollutants, and other epithelial danger signals, although both pathways eventually lead to similar inflammatory and functional changes in the asthmatic lung.[13] Asthma can therefore be categorised as Type 2 (T2) high or low asthma based on biomarkers reflecting the T2 cytokine signature, among them blood and sputum eosinophils, FeNO, and serum periostin.[14-16] T2 high asthma is characterised by high eosinophil numbers and/or high FeNO or periostin levels, indicating high concentrations of T2 cytokines IL-5 and IL-13. Approximately 40–60% of patients with severe asthma have eosinophilic asthma;[17] eosinophils, when activated, release various mediators that damage lung tissue and induce airway hyper-responsiveness and mucous hypersecretion. The number of sputum and blood eosinophils correlates with disease severity.

Clinical Relevance of Eosinophilic Disease

In a study by Malinovschi et al.,[18] an increasing number of blood eosinophils and increasing concentrations of nitric oxide (NO) in exhaled breath were correlated with a higher prevalence of asthma attacks and asthma-related emergency department visits. Similarly, a strong independent predictor of asthma mortality is blood eosinophilia; patients with blood eosinophils ≥450/µL have a 2-fold higher mortality risk.[19] The prognostic relevance of blood eosinophils was also demonstrated in a study of 130,248 patients aged 12–80 years in which blood eosinophils greater than or less than 400 µL were significantly correlated with acute respiratory events, severe exacerbations, and poor asthma control (Figure 1).[20]

How to Characterise a Patient with Severe Eosinophilic Asthma

When assessing blood cell differentials, it is important to use absolute numbers rather than percentages. This can be calculated simply by dividing leukocytes/µL of blood by 100 and multiplying by the percentage of eosinophils. Large clinical trials indicate that the probability and magnitude of a relevant clinical response to drugs inhibiting IL-5 increases with increasing eosinophil numbers, and that a threshold eosinophilia relevance may be around 300–400 eosinophils/µL. The importance of defining the severity of eosinophilia can be seen in a study by Corren et al.,[21] which explored the effects of reslizumab on lung function stratified by baseline eosinophil thresholds. The change from baseline in FEV_1 was not statistically significant in patients with <400 eosinophils/µL blood but showed meaningful improvement in those with severe eosinophilia (≥400 eosinophils/µL blood).[21]

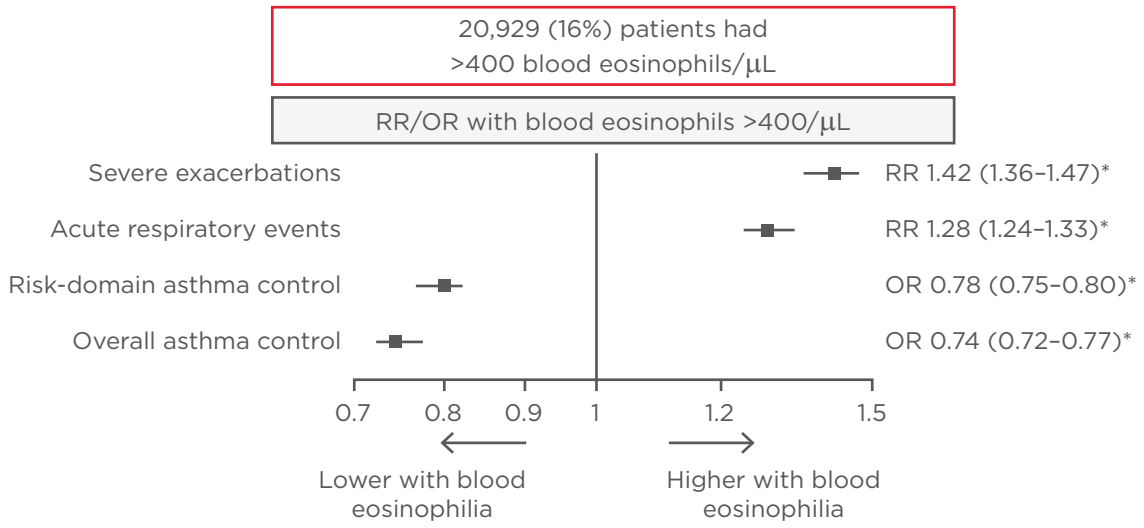

Figure 1: Relative risk of severe exacerbations, acute respiratory events, and overall asthma control in 21,000 patients with blood eosinophils levels >400/µL.[20]

*Adjusted for age, sex, BMI, smoking status, and Charlson comorbidity index score; p<0.0001 for all comparisons.

RR: relative risk; OR: odds ratio.

In Prof Buhl's opinion, typical patients with severe eosinophilic asthma have late-onset of disease, are highly symptomatic, and have frequent exacerbations and eosinophilia in their blood and sputum. Many patients have an increased NO concentration in each exhaled breath and some patients have upper airway complications, including nasal polyposis, compromised senses of smell and taste, and usually respond well to oral corticosteroids.

Exploring the Diagnostic Workup: Key Clinical Assessments

Professor Richard Costello

It is well established that eosinophils localise to the subepithelial space of the airways of patients with asthma.[22] In animal models, this is strongly associated with subepithelial thickness and it is postulated that subepithelial fibrosis leads to chronic fixed airway obstruction. Costello et al.[23] have shown interweaving nerve fibres co-localised with eosinophils, which perhaps mediates cough and sensations of chest tightness. Eosinophil infiltration correlates with the symptoms described; obstruction, reversibility during an exacerbation, and mucous production.

Mucous is very important in asthma as it plugs the airways in patients with fatal asthma,[24] and is frequently seen on imaging; multiple detector computed tomography (CT) scanning has shown that 58% of asthmatics had mucous in at least one segment.[25] Immunofluorescence microscopy reveals eosinophils in the subepithelial space and strands of mucous within mucous plugs that tether mucopolysaccharides together, making the mucous tenacious. When referring to mucous in the context of eosinophilic asthma, mucous plugging rather than a bronchitis phenotype must be thought about, from the occasional sighing-type feature sometimes described by patients to the acute ventilatory failure that occurs in an acute severe asthma attack or the regional heterogeneity that leads to an increase in alveolar–arterial gradient and dysfunctional ventilation.

Clinical Assessment and Management of Patients with Severe Eosinophilic Asthma

When assessing patients with asthma, certain features should be looked for to allow accurate identification of those who may be suitable for anti-IL-5 therapy. Firstly, the diagnosis of asthma must be confirmed; secondly, patient adherence to therapy should be reviewed; and thirdly, the patient should be ascribed to a phenotype.

Prof Costello described a case of a 55-year-old man with a 15-year history of asthma that was uncontrolled and had persistent symptoms, particularly in the last 5 years despite long-acting beta-2 agonist/inhaled corticosteroid (LABA/ICS) use. He presented with cough, wheeze, and breathlessness on moderate exertion, and had nasal congestion and loss of smell. The patient's diagnosis was confirmed with spirometry. According to the GINA recommendations, stepping up treatment should be considered if symptoms remain uncontrolled but inhaler technique and adherence must be checked first.[4] Adherence and technique can be checked by examining the patient's inhaler, asking them to demonstrate technique, checking for deposition of medication on the epiglottis, and checking pharmacy refill records.

If patients are to be funnelled through Stage IV treatment onto Stage V, adherence needs to be objectively assessed. Inhaler Compliance Assessment (INCA) technology can be utilised to record audio of inhaler use. An acoustic recording device is attached to the inhaler and each step of use is recorded. The recordings are then downloaded and signal processing analysis identifies when, how regularly, and how well the inhaler is used, which is presented as a calendar graph. The visual representation can be used for follow-up to identify if intervention helps asthma control and as feedback on inhaler technique.

The patient was placed on the INCA programme for 2 months, which confirmed good adherence and was ascribed by measuring peripheral blood count, which revealed 400 eosinophils/cm^3 with elevated immunoglobulin E (IgE). This phenotype suggested that the patient would benefit from anti-eosinophilic therapy.

Applying Evidence to Clinical Practice: Options for Patients with Uncontrolled Severe Eosinophilic Asthma

Professor Mario Castro

The ATS/ERS guidelines outline six clinical phenotypes with physiological associations and specifically-targeted therapies, even though

some associations and treatments have not been evaluated prospectively in randomised controlled trials. The eosinophilic asthma phenotype, however, has a preponderance of evidence demonstrating high serum IgE, recurrent exacerbations, high FeNO, and response to three different anti-IL-5 drugs that substantiate this unique phenotype.[5] Several determinants of an anti-IL-5 response should be considered: exposure to the drug; disease severity; level of baseline control; blood eosinophil level; prevention of further eosinophil infiltration; and other patient factors (e.g. associated comorbidities and allergy).

Mepolizumab: The DREAM Trial

The DREAM trial[26] compared the effectiveness of the anti-IL-5 drug mepolizumab at 75 mg, 250 mg, and 750 mg administered intravenously (IV) once a month over 1 year. The primary endpoint, clinically significant exacerbations, was dramatically reduced compared with placebo for all three doses (exacerbation rate: placebo=2.40/year; 75 mg=1.24/year; 250 mg=1.46/year; 750 mg= 1.15/year) (Figure 2). Secondary endpoints included a change in blood eosinophil count, sputum eosinophil count, pre-bronchodilator FEV_1, and ACQ score. Mepolizumab produced no significant effect on asthma control in all three doses and had variable effects across doses on lung function, but positive results were seen for the reduction of eosinophils ($p<0.001$ versus placebo for blood eosinophil counts). Dose discrepancies were observed for sputum eosinophil count: 75 mg and 250 mg mepolizumab were not significantly effective, whereas 750 mg mepolizumab demonstrated a significant reduction ($p=0.0082$). The side effect profile of mepolizumab was similar across the three doses and not significantly different compared with placebo.

Benralizumab

Benralizumab is a humanised monoclonal antibody that binds with high affinity to the IL-5 receptor alpha subunit and depletes eosinophils through antibody-dependent cell-mediated cytotoxicity.[27] Various doses of benralizumab have been explored for the treatment of asthma, and in a Phase II study by Castro et al.[28] patients were stratified by eosinophil phenotype (based on the ratio of blood eosinophils [E] to lymphocytes [L], the ratio of blood eosinophils [E] to neutrophils [N] [ELEN index], and FeNO) into either eosinophilic or non-eosinophilic groups. Eosinophilic patients were randomised to either 2 mg, 20 mg, or 100 mg of benralizumab versus placebo, and non-eosinophilic patients were randomised to 100 mg benralizumab or placebo. Patients were followed >1 year and the primary endpoint looked at asthma exacerbations. Results showed that the 20 mg and 100 mg doses reduced exacerbations in the eosinophilic group, with an annual exacerbation rate reduction (AERR) of 36% ($p=0.173$) and 41% ($p=0.096$), respectively; the non-eosinophilic group had an AERR of 22% ($p=0.284$). The degree of eosinophilia in enrolled patients ranged from 50 cells/µL to ≥500 cells/µL and was mapped against AERR relative to placebo. Data showed a significant reduction in exacerbations for eosinophil levels ≥300 cells/µL; for 100 mg benralizumab 43% ($p=0.049$) and 70% ($p=0.002$) AERR was achieved for ≥300 cells/µL and ≥400 cells/µL, respectively. Treatment with anti-IL-5 confirmed that there was a significant reduction in exacerbations for patients with baseline eosinophil levels ≥300 cells/µL. The side effect profile of benralizumab was favourable with adverse events comparable across all three doses and placebo.

Reslizumab

Reslizumab is a humanised anti-human IL-5 monoclonal antibody that is licensed for the treatment of severe asthma in the USA and European Union (EU) at an IV dose of 3 mg/kg. A Phase II study of 106 patients with uncontrolled asthma and elevated eosinophil counts explored the effects of reslizumab 3 mg/kg (administered at baseline and at Weeks 4, 8, and 12) on blood eosinophils levels.[29] Reslizumab effectively reduced blood and sputum eosinophil levels to below baseline and reductions were observed as early as Week 4. At the end of the study, median percentage reductions in eosinophils in sputum were 95.4% in the treatment group and 38.7% in the placebo group ($p=0.0068$). Exacerbations occurred in 8% in the reslizumab group versus 19% in the placebo group ($p=0.083$). Reslizumab did not show a consistent effect on the primary endpoint, the ACQ score. Overall, 59% of patients in the reslizumab group achieved improvement of at least 0.5 in ACQ score compared with 40% in the placebo group (95% confidence interval: 2.06 [0.88–4.86], $p=0.0973$), which is the minimal clinically significant change. Significant improvement in lung function, measured by FEV_1 change from baseline, was seen after one dose of study drug ($p=0.0364$).[29] Patients with a history of nasal polyposis showed a marked improvement in ACQ score (-1.0 reslizumab versus

-0.1 placebo, p=0.012) compared with those with no history of nasal polyposis (-0.5 reslizumab versus -0.4 placebo, p=0.7176).

Two Phase III trials explored the effect of reslizumab 3 mg/kg administered over 52 weeks in patients with exacerbation-prone uncontrolled eosinophilic asthma. The studies met the primary endpoint, reduction of clinical exacerbation rate, demonstrating a pooled reduction rate of 54% compared with placebo (p<0.0001) (Figure 3). Secondary endpoints of lung function, quality of life score, ACQ score, and asthma symptom utility index were also met. Reslizumab was efficacious in reducing asthma exacerbations regardless of treatment received at baseline. Reslizumab was well-tolerated across the two studies and had slightly fewer discontinuations due to adverse events compared with placebo.[30]

Reslizumab had a greater effect on asthma exacerbation rate in adults aged ≥65 years (67% reduction compared with placebo) compared with younger adults (53% reduction compared with placebo).[31] Patients with late-onset disease (aged ≥40 years) have a preferential reduction rate in asthma exacerbations (75% reduction compared with placebo) when compared with those with early-onset disease (42% reduction compared with placebo).[32] Reslizumab demonstrated greater efficacy in reducing frequency of asthma exacerbations in patients with a history of chronic sinusitis and/or nasal polyposis.[33]

Other Biologic Therapies: Anti-Interleukin-4 and Anti-Interleukin-13

Targeting the IL-4 alpha receptor impacts IL-4 and IL-13 binding and leads to in-organ effects of mucous cell metaplasia, inflammation, and airway hyperactivity. Dupilumab, a monoclonal antibody against the IL-4 alpha receptor administered every 2 weeks at doses of 200 mg and 300 mg, was efficacious in reducing asthma exacerbations in the overall asthma population (70% reduction compared to placebo for both doses) and in the high eosinophil population (≥300 cells/μL) (71% and 81% reduction compared with placebo, respectively).[34]

Lebrikizumab, an anti-IL-13 drug, improved FEV_1 in patients with high pretreatment serum periostin.[35]

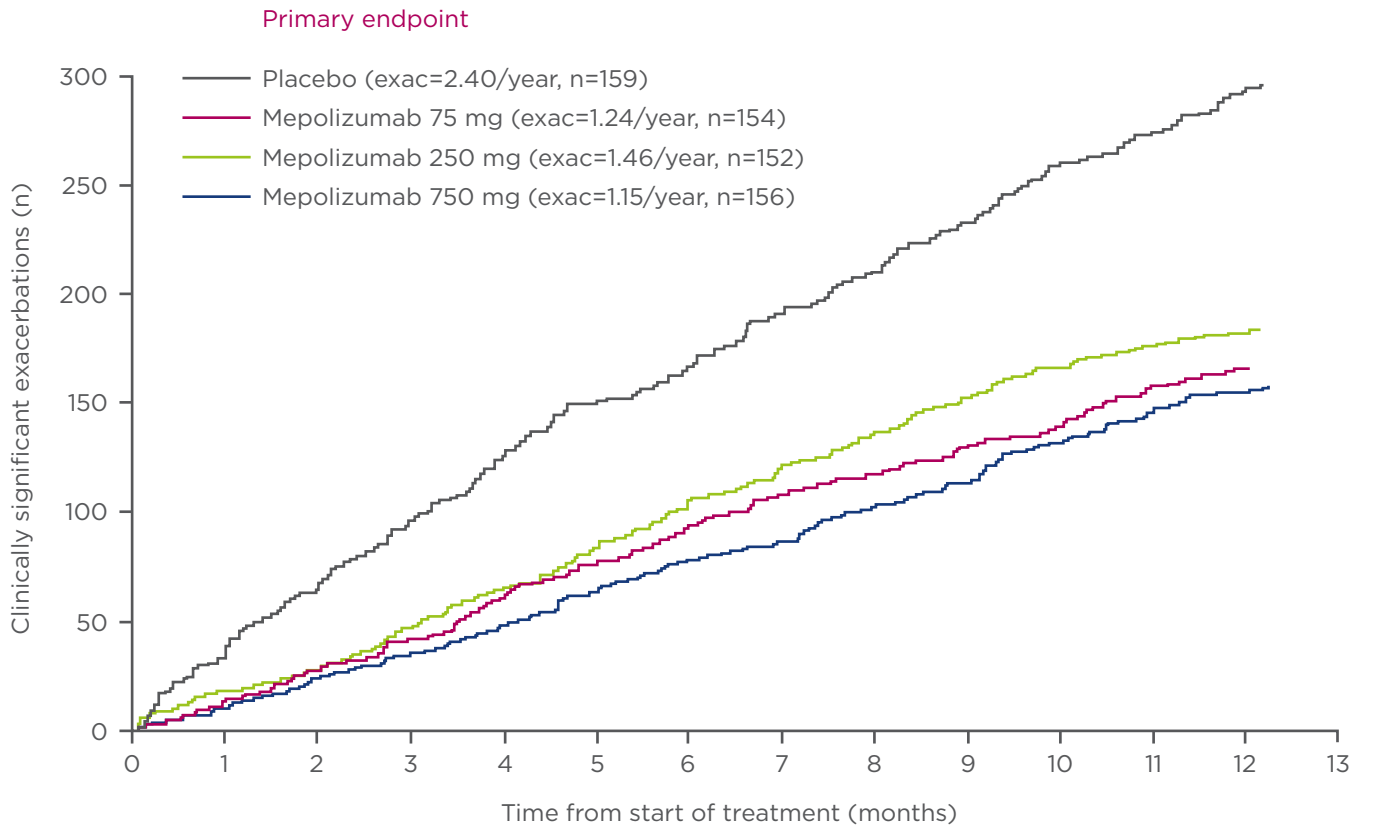

Figure 2: Efficacy of mepolizumab in reducing clinically significant asthma exacerbations in patients with severe eosinophilic asthma.[26]
exac: exacerbation rate.

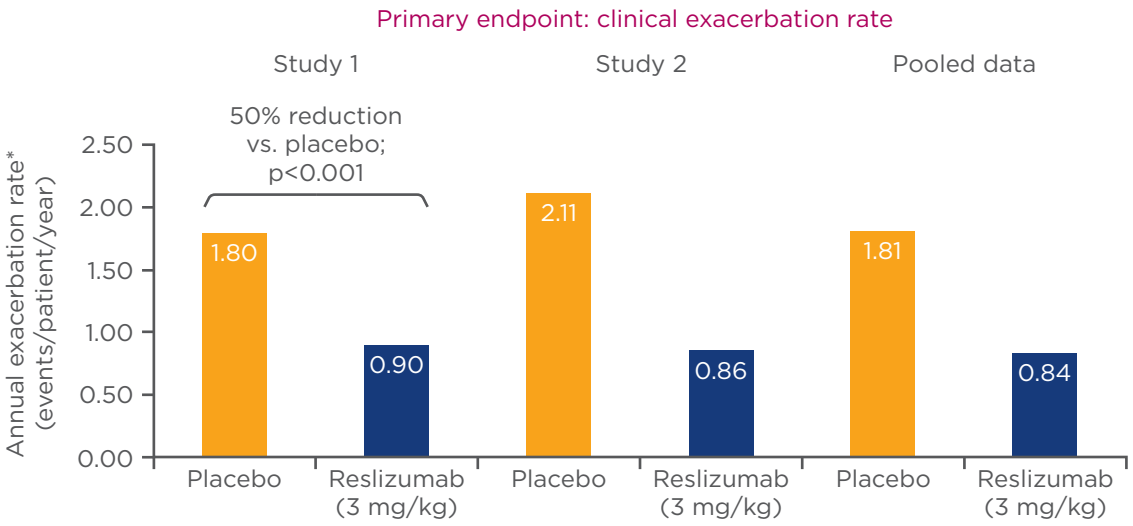

Figure 3: Data from two Phase III trials exploring the effect of reslizumab or placebo on annual exacerbation rate.[30]

*Exacerbations were defined as worsening asthma resulting in any of the following: use of systemic corticosteroids in steroid-naïve patients, a 2-fold increase in the dose of either inhaled corticosteroid or systemic corticosteroids for ≥3 days, or the need for asthma-related emergency treatment.

Tralokinumab is an anti-IL-13 drug that did not demonstrate significant reduction in asthma exacerbations in patients with severe asthma; however, patients with high serum dipeptidyl peptidase-4 levels showed improvements in FEV_1, ACQ score, and quality of life. Likewise, patients with high periostin concentrations showed improvements in asthma exacerbation rate, FEV_1, and ACQ score.[36] Omalizumab, an anti-IgE therapy, has retrospectively shown a 25% reduction in exacerbations compared with placebo in patients with high eosinophil and periostin levels.[37]

In conclusion, we are on the threshold of a new era for severe asthma. Anti-IL-5 treatment has demonstrated a positive effect on the reduction of asthma exacerbations and the requirement for oral corticosteroids in severe asthma. Biologic agents targeting IL-4, IL-13, and IgE show promise and are being explored in clinical studies. Blood eosinophil levels offer an excellent therapeutic and prognostic tool that help identify patient subgroups suitable for treatment with anti-IL-5 therapy. To further advance the field and make the most of anti-IL-5 and other biological treatments, new biomarkers and models of disease are necessary.

Question and Answer Session

Q: Is blood eosinophilia variable within patients, and if so, how many tests should be carried out before treatment is chosen?

Prof Pavord replied that blood eosinophilia can be triggered by viral infection of the upper airways. Therefore, a single measurement should never be relied on, instead, measurements should be taken over a period of 2–3 weeks. In patients taking systemic corticosteroids, a history of consistent eosinophilia is sufficient.

Q: Is there a need to reduce sputum eosinophils, as the clinical efficacy seems to be large with just a blood eosinophil reduction?

Prof Pavord replied that most clinicians do not measure sputum eosinophil levels in daily practice, although when it is used as a target the reduction in exacerbations is significant. Therefore, if sputum eosinophil levels are available they should be utilised to drive therapy.

Footnotes

Benralizumab was not approved at the time of the symposium and writing of this manuscript, and there may be other data available not covered by the faculty during the symposium. AstraZeneca published online in the Lancet on the 5th September 2016 two Phase III trials: CALIMA[38] and SIROCCO.[39] Benralizumab reduced annual exacerbation rates by 28% in CALIMA and 51% in SIROCCO (30 mg every 8 weeks). In conjunction with the DREAM trial, GSK published online 8th September 2014 in The New England Journal of Medicine the MENSA trial.[40] Asthma exacerbations were significantly alleviated by the administration of mepolizumab both IV and subcutaneously.

REFERENCES

1. Akinbami LJ et al. Asthma prevalence, health care use, and mortality: United States, 2005-2009. Natl Health Stats Report. 2011;12(32):1-14.

2. Masoli M et al. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004;59(5):469-78.

3. Rodrigo GJ et al. Acute asthma in adults: a review. Chest. 2004;125(3): 1081-102.

4. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2016. Available at: http://www.ginasthma.org. Last accessed: 13 September 2016.

5. Chung KF et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73.

6. Price D, Pearson M. What is success in asthma – the patient's view. Am J Respir Crit Care Med. 1998;157:A631.

7. Sarnes E et al. Incidence and US costs of corticosteroid-associated adverse events: a systematic literature review. Clin Ther. 2011;33(10):1413-32.

8. Elixhauser A et al. Health Cost Util Proj. 2007;1-12.

9. Haldar P et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008;178(3):218-24.

10. Green RH et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet. 2002; 360(9347):1715-21.

11. Haldar P et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009;360(10): 973-84.

12. Nair P et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009; 360(10):985-93.

13. Brusselle GG et al. Eosinophils in the spotlight: Eosinophilic airway inflammation in nonallergic asthma. Nat Med. 2013;19(8):977-9.

14. Robinson DS et al. Predominant TH2-like bronchoalveolar T-lymphocyte population in atopic asthma. N Engl J Med. 1992;326(5):298-304.

15. Bernink JH et al. The role of ILC2 in pathology of type 2 inflammatory diseases. Curr Opin Immunol. 2014;31: 115-20.

16. Wechsler ME. Combating the eosinophil with anti-interleukin-5 therapy. N Engl J Med. 2008;358(12):1293-4.

17. Zhang JY, Wenzel SE. Tissue and BAL based biomarkers in asthma. Immunol Allergy Clin North Am. 2007;27(4): 623-32.

18. Malinovschi A et al. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. J Allergy Clin Immunol. 2013;132(4):821-7.

19. Ali Z et al. Long-term mortality among adults with asthma: a 25-year follow-up of 1,075 outpatients with asthma. Chest. 2013;143(6):1649-55.

20. Price DB et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med. 2015;3(11):849-58.

21. Corren J et al. Phase 3 Study Of Reslizumab in Patients with Poorly Controlled Asthma: Effects Across a Broad Range Of Eosinophil Counts. Chest. 2016;150(4):799-810.

22. Thornton MA et al. Eosinophil recruitment to nasal nerves after allergen challenge in allergic rhinitis. Clin Immunol. 2013;147(1):50-7.

23. Costello RW et al. Localization of eosinophils to airway nerves and effect on neuronal M2 muscarinic receptor function. Am J Physiol. 1997;273(1 Pt 1):L93-103.

24. Filley WV et al. Identification by immunofluorescence of eosinophil granule major basic protein in lung tissues of patients with bronchial asthma. Lancet. 1982;2(8288):11-6.

25. Dunican E et al. Regional Ventilation Defects Measured On Hyperpolarized 3HE MRI Are Associated With Mucus Plugging Measured On CT In Asthma. Am J Respir Crit Care Med. 2016;A2004.

26. Pavord ID et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012; 380(9842):651-9.

27. Kolbeck R et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. J Allergy Clin Immunol. 2010;125(6):1344-53.

28. Castro M et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med. 2014;2(11):879-90.

29. Castro M et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011;184(10): 1125-32.

30. Castro M et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015; 3(5):355-66.

31. Bernstein D et al. Efficacy of Reslizumab in Older Patients (≥65 Years) with Asthma and Elevated Blood Eosinophils: Results from a Pooled Analysis of Two Phase 3, Placebo-Controlled Trials. J Allergy Clin Immunol. 2016;137(2):AB86.

32. Brusselle G et al. Reslizumab in patients with late-onset asthma with elevated blood eosinophils. Eur Resp J. 2015;46: OA287.

33. Weinstein SF et al. Efficacy of Reslizumab with Asthma, Chronic Sinusitis with Nasal Polyps and Elevated Blood Eosinophils. J Allergy Clin Immunol. 2016;137(2):AB86.

34. Wenzel S et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-

to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet. 2016;388(10039):31-44.

35. Corren J et al. Lebrikizumab treatment in adults with asthma. N Engl J Med. 2011; 365(12):1088-98.

36. Brightling CE et al. Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial. Lancet Respir Med. 2015;3(9): 692-701.

37. Hanania N et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med. 2013;187(8):804-11.

38. FitzGerald JM et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016; doi: 10.1016/S0140-6736(16)31322-8. [Epub ahead of print].

39. Bleecker ER et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016; doi: 10.1016/S0140-6736(16)31324-1. [Epub ahead of print].

40. Ortega HG et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014; 371(13):1198-207.