Editorial

Airways diseases: asthma, COPD and chronic cough highlights from the European Respiratory Society Annual Congress 2018

Imran Satia[1,2], Huda Badri[2], Lies Lahousse[3], Omar S. Usmani[4], Antonio Spanevello[5,6]

[1]Division of Respirology, Department of Medicine, McMaster University, Hamilton, Canada; [2]Division of Infection, Immunity and Respiratory Medicine, and Manchester Academic Health Science Centre, University of Manchester, Manchester, UK; [3]Pharmaceutical Care Unit, Department of Bioanalysis, Ghent University, Ghent, Belgium; [4]National Heart and Lung Institute (NHLI), Imperial College London & Royal Brompton Hospital, London, UK; [5]Department of Medicine and Surgery, University of Insubria, Varese, Italy; [6]Istituti Clinici Scientifici Maugeri IRCCS, Tradate, Italy

Correspondence to: Dr. Imran Satia, MA, MB, BChir, PhD, MRCP. Post-Doctoral Clinical Research Fellow, ERS Respire 3 Marie Curie Fellow, Division of Respirology, Department of Medicine, McMaster University, Hamilton, Canada. Email: satiai@mcmaster.ca.

Submitted Jul 17, 2018. Accepted for publication Jul 19, 2018.
doi: 10.21037/jtd.2018.08.23
View this article at: http://dx.doi.org/10.21037/jtd.2018.08.23

Addressing the global morbidity associated with asthma, chronic obstructive pulmonary disease (COPD) and chronic cough is a major unmet need for the respiratory community. Reducing exacerbations and improving lung function have remained important primary endpoints in clinical studies in asthma and COPD, however, there is also a growing momentum to show efficacy and improvements in patient reported outcomes in real-world pragmatic studies. For decades, inhaled and oral corticosteroids (ICS/OCS), with or without bronchodilators, have remained the cornerstone of practice in asthma and COPD, however the recent impetus and strategy has been to better phenotype patients and develop treatments targeting specific mechanisms of disease or potentially treatable traits, including those patients with difficult-to-treat chronic persistent cough. The purpose of this editorial review is to highlight some of the highest scoring abstracts in asthma, COPD and chronic cough presented at the European Respiratory Society Annual Congress 2018.

Update on asthma

Over the past 20 years the use of biological therapy in the management of patients with severe asthma has become established. In addition to the anti-IgE monoclonal antibody omalizumab, newer agents such as mepolizumab an anti-IL-5 antibody have become available. The SIRUS study demonstrated mepolizumab had a significant glucocorticoid sparing effect and a reduction in exacerbations (1). A recent real-life retrospective study has supported these findings, where mepolizumab treatment resulted in a marked reduction in the percentage of patients needing OCS (83% *vs.* 53%), additional immunotherapy (18% *vs.* 4%) and the dose of OCS used was also significantly reduced (2). Reslizumab, another anti-IL-5 therapy showed a significant improvement in the asthma control test and in quality of life (3). Tezepelumab, a human IgG2 monoclonal antibody that binds to thymic stromal lymphopoietin (TSLP), which is an epithelial alarmin, has been shown to reduce clinically significant asthma exacerbations in patients with moderate to severe asthma (4). Interestingly, data presented in a recent pharmacokinetic study suggested the efficacy of tezepelumab on exacerbations and FeNO reductions was not influenced by blood eosinophilia or other type 2 inflammatory markers (5). This observation has a big treatment implication for patients who may not qualify for anti-IL-5 therapy due to the absence of a sufficient threshold of serum eosinophilia.

The efficacy and safety of biologics can potentially be hampered by auto-immune responses against these biological agents (6). Data presented at the ERS from over 1,300 patients across five phase III studies of mepolizumab where anti-drug antibodies and neutralizing antibodies were measured at multiple time points, indicated that the agent was well tolerated with minimal potential to mount anti-drug antibodies (7).

Although biological agents have been shown to be extremely efficacious steroid sparing agents, not all targets

studied have shown efficacy. A randomized controlled trial evaluating the steroid sparing effect of tralokinumab (an anti-interleukin-13 human monoclonal antibody) showed the drug did not provide significant OCS sparing benefits *vs.* placebo in patients with severe asthma (8). The recently published STRATOS 2 study demonstrated that tralokinumab treatment did not reduce acute asthma exacerbations and collectively the data suggest IL-13 may not play a key role in severe asthma pathophysiology (9). Overriding this enthusiasm and era of biological therapy development, which is highly expensive, is the salient fact that nonadherence to preventer medication in patients with difficult asthma remains disturbingly high at nearly half of all patients (10). Subjective assessment of adherence is highly unreliable and the need for objective assessments is imperative prior to initiating biological treatments in patients with severe asthma

Phenotyping asthma patients using measures such as FEV_1, IgE, FeNO and eosinophilia, has been commonly used in clinical practice over the past couple of decades. Despite patients being clustered into subgroups, there can be a heterogenous response to treatment. A recent study using principal component and hierarchical analysis has suggested that collecting serum interleukins (IL-5, IL-6 and IL-8) in addition to standard measures enables the identification of four clusters within the moderate to severe asthma cohort (11). These maybe an important consideration when selecting the appropriate biologic based on the mechanism of disease.

Why some people develop asthma at different ages and whether they respond differently to treatment is unclear. Post-hoc analysis of the SIROCCO and CALIMA trials of benralizumab (an anti-interleukin-5 receptor α monoclonal antibody) has shown differential effects on FEV_1 response and exacerbations based on whether asthma was diagnosed at an early, adult, or late age (12). The greatest improvement in FEV_1 was seen in those with poorly controlled adult and late-onset asthma, with early-onset asthma having the lowest response.

Lower lung function is associated with a worse all-cause mortality (13) hence an accelerating FEV_1 decline in asthma should be taken seriously. A recent longitudinal study over a 15-year period has suggested increased sputum levels of IL-5, IL-8 and eosinophils in patients with well-defined mild asthma on standard therapy are risk factors for accelerated FEV_1 decline (14). This suggests that potentially targeting such patients with biological therapy early may be a potential therapeutic option in preventing lung function decline. However, studies in early mild disease are not currently being conducted.

Update on COPD

Identification of patients with COPD who benefit from ICS is needed to prevent unnecessary exposure to treatment side effects, including pneumonia and diabetes. In the 52-week, randomized, multicenter IMPACT trial presented at the ERS 2018 Congress, a higher absolute percentage of pneumonia was observed when triple therapy (including ICS) was compared to dual bronchodilator treatment (8% *vs.* 5% respectively) (15,16). In a large, matched UK general practice cohort study using data between 1990–2016, patients with COPD who were started on ICS treatment without prior diabetes, had an increased risk of diabetes which was ICS dose dependent (17).

Blood eosinophils have increasingly been investigated to predict responsiveness to ICS in patients with COPD. The 26-week randomized SUNSET trial demonstrated in 1,053 moderate to severe non-frequent exacerbators that ICS withdrawal led to a decreased time to first exacerbation during follow-up, however this was in a minority of patients (16%) with consistently 'high' blood eosinophils (≥300 cells/μL) (18). The prevalence of COPD frequent exacerbators on triple therapy still having blood eosinophils ≥300 cells/μL was estimated even less (2%) when recruited from primary care (19). In this latter minority population, blood eosinophils could be a reasonable predictor of the biological efficacy of mepolizumab, as with severe asthma (20). However, it remains unclear whether eosinophilic inflammation represents a shared treatable trait between COPD and asthma. The transcriptome analysis of bronchial brushings versus blood eosinophils demonstrated very few differentially expressed genes in patients with COPD and in addition, little overlap with asthma (21). This suggests that mechanisms underlying increased eosinophils might be different for patients with asthma in comparison to patients with COPD.

Another downside in the great enthusiasm of increased blood eosinophils as a biomarker, is the ongoing controversy on the change in clinical outcomes of patients with COPD. Recent studies suggest that COPD patients who are frequent exacerbators with higher blood eosinophil counts have better clinical outcomes in general. A retrospective observational cohort study explored the predictive value of blood eosinophils on the clinical outcomes after acute COPD exacerbations requiring hospitalization and observed

that blood eosinophils indicated shorter duration of exacerbation, less usage of oxygen therapy and noninvasive ventilation, despite having a higher rate of readmission (22). In contrast, another study following 110 COPD patients over nine years regardless of exacerbation history, showed three times higher mortality in those COPD subjects with absolute eosinophil numbers ≥150 cells (23). Finding good biomarkers which also have prognostic value, seems as difficult as finding therapies which lower mortality in patients with COPD.

Regarding mortality in patients with chronic lung disease, British Primary Care data from 2005 to 2014 linked with national mortality data confirmed that between a quarter and third of all people with chronic respiratory diseases (CRD) died due to circulatory diseases (24). Therefore, in addition to the amount of research spent on novel bronchodilators of various formulation, combinations and duration of action, attention should be paid to tailoring existing cardiovascular treatment for respiratory impaired patients. A nationwide analysis from 1995 to 2015 in Denmark demonstrated that among 143,126 patients with first-time myocardial infarction, 10% with concurrent COPD systematically underused beta-blockers and to a lower extent also aspirin and statins (25). Female patients with COPD particularly underused beta-blockers. A Swedish study observed that cardiovascular disease increased mortality in COPD women but not in men (26). Interestingly, the data confirmed that COPD patients with frequent exacerbations underused beta-blockers (25). This is in contrast to the observed increased risk of sudden cardiac death among COPD patients with frequent exacerbations where especially post-menopausal female COPD patients are at risk of Takotsubo cardiomyopathy, and thereby might benefit at most from beta-blockers to protect them against the physiological stress triggers and catecholamine surges during exacerbations (27).

Update on chronic cough

Chronic cough is a common troublesome symptom affecting approximately 12% of the general population (28) and is associated with asthma, eosinophilic bronchitis, gastroesophageal reflux disease (GERD) and rhinosinusitis but often can be truly idiopathic (29,30). However, treatment options are currently limited to either treatment of the underlying disorder, which in many cases fails to provide adequate relief, or central acting cough suppressants such as morphine and pregabalin which can lead to intolerable side effects. Therefore, understanding the mechanism of this condition and developing novel therapy is a large unmet need, where chronic persistent cough significantly affects quality of life for patients.

Patient with chronic cough often present with a dry irritating cough, driven by with a strong urge to cough associated with a sensation or irritation located in the throat (31). These sensations can be triggered by changes in temperature, strong smells such as perfumes and aerosols or exposure to pollutants. These clinical features have led to research that suggests this is a neurological condition requiring treatment targeting peripheral airway nerves or the central nervous system. The ERS and American College of Chest Physicians have thus coined the term "Cough Hypersensitivity Syndrome" to describe the pathology in chronic cough patients (32,33).

The clinical study likely to have the greatest therapeutic impact is of MK-7264, a P2X3 antagonist, which in a previous phase 2 proof-of-concept design, showed a 75% reduction in objective 24-h objective cough monitoring (34). A subsequent multi-centre 12-week dose-ranging double-blind randomised placebo-controlled study in the UK and US investigated the efficacy of MK-7264 at 7.5, 20, and 50 mg BID, rather than the phase 2 dose of 600 mg BID which was associated with taste disturbance in almost every patient (35). Awake cough frequency (ACF; coughs/hr) after 12 weeks was the primary endpoint. Overall, in 253 patients who were randomized, ACF was significantly reduced by MK-7264 50 mg compared with placebo with a reduction in patients reporting a taste disturbance.

The relationship between airflow obstruction and coughing in asthma is unclear. The original term "Cough Variant Asthma" (CVA) was described in 1975 and 1979 by McFadden *et al.* (36) and Corrao *et al.* (37) respectively, who described patients with asthma and cough who improved with bronchodilator treatment. In a parallel group study, 26 patients with cough due to CVA and 20 with non-CVA were recruited to determine if a forced oscillation technique (FOT) was superior to spirometry in determining beneficial effects to the airways. The results demonstrated improvements in airway resistance and reactance at 5Hz and resonant frequency but no improvement in FEV_1 after treatment with a short acting β-2 agonist (SABA) (38). The implication being that coughing improved despite any significant improvement in airway calibre. Perhaps, airway sensory nerves are inhibited by SABA, and persistent use of SABA may result in tachyphylaxis of airway smooth muscle (ASM). In keeping with this hypothesis, a study in a pre-

clinical guinea pig model showed that LABA use inhibited cough and sensory nerve activation, and prolonged LABA dosing did not lead to tachyphylaxis on nerves but did on ASM and hence reduced bronchodilator effectiveness (39). The same research group also presented data to show that airway irritants such as diesel exhaust particles, hydrogen peroxide and hyper-osmolarity activate airway sensory nerves via transient receptor potential (TRP) A1 channels through a mechanism of oxidative stress (40). Importantly, TRPA1 antagonism abolished responses to these different irritant stimuli hence its potential as a future target for cough.

A study in patients with severe asthma demonstrated the feasibility and safety of performing capsaicin cough challenge without any significant fall in FEV_1. Consistent with mild to moderate patients, female patients coughed more and at lower concentrations of capsaicin. However, this was only in 8 patients with large variations in symptom scores after the cough challenge, and four patients requested salbutamol for symptoms despite no significant fall in FEV_1 (41).

In the paediatric population, the most common cause for chronic cough is protracted bacterial bronchitis (PBB), but there are no long-term studies describing their outcomes. A prospective cohort study recruited 130 children with PBB and 21 controls, who were followed up for 5 years. Of the 130 children with PBB, 68% had trachea-bronchomalacia found at bronchoscopy and CT chest performed on 59 children confirmed bronchiectasis in 8.5%. The incidence of recurrent PBB (>3 episodes/year) decreased over study time from 53.8% in year 1 to 15.7% in year 5, and 46% had a diagnosis of asthma, compared with 14% in the control group (42).

Conclusions

Understanding the mechanisms of disease of asthma, COPD and chronic cough can helps us in our ultimate objective of improving the lives of patients. However, identifying responders, preventing long term side effects and improving morbidity and mortality remain a significant challenge in airways diseases. Furthermore, controversy still exists about the optimum cut-off for serum eosinophilia as a criterion to determine type 2 'high' or 'low' asthma. Overall, the scientific and clinical data presented at this year's Congress has made a significant contribution to our understanding and provided hope towards achieving our goals.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371:1189-97.
2. Bjerrum AS, Schmid J, Skjold T. Oral glucocorticoid-sparing effects of mepolizumab. A real-life study. Eur Respir J 2018;52. [Epub ahead of print].
3. Chanez P, Adir Y, Castro M, et al. Intravenous (IV) reslizumab improves asthma control, symptoms, and quality of life in patients with historically elevated blood eosinophils. Eur Respir J 2018;52. [Epub ahead of print].
4. Corren J, Parnes JR, Wang L, et al. Tezepelumab in Adults with Uncontrolled Asthma. N Engl J Med 2017;377:936-46.
5. Ly N, Zheng Y, Griffiths JM, et al. Exposure-response analysis of tezepelumab in patients with severe asthma to guide phase 3 dose selection. Eur Respir J 2018;52. [Epub ahead of print].
6. Mukherjee M, Lim HF, Thomas S, et al. Airway autoimmune responses in severe eosinophilic asthma following low-dose Mepolizumab therapy. Allergy Asthma Clin Immunol 2017;13:2.
7. Ortega H, Meyer E, Brusselle G, et al. Immunogenicity of Mepolizumab in Patients with Severe Eosinophilic Asthma: Experience from the Clinical Development Program. Eur Respir J 2018;52. [Epub ahead of print].
8. Busse W, Brusselle G, Korn S, et al. Oral corticosteroid (OCS)-sparing effect of tralokinumab in severe, uncontrolled asthma: the TROPOS study Eur Respir J 2018;52. [Epub ahead of print].
9. Panettieri RA Jr, Sjöbring U, Péterffy A, et al. Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo-controlled, phase 3 clinical trials. Lancet Respir Med 2018;6:511-25.
10. Lee J, Tay TR, Radhakrishna N, et al. Nonadherence in the era of severe asthma biologics and thermoplasty. Eur Respir J 2018;51. pii: 1701836.

11. Dimitrova D, Youroukova V, Velikova T, et al. Serum levels of IL-5, IL-6 and IL-8 in moderate and severe asthma clusters. Eur Respir J 2018;52. [Epub ahead of print].
12. Wenzel S, Brusselle G, Hirsch I, et al. Benralizumab efficacy in patients with uncontrolled eosinophilic asthma by age at diagnosis. Eur Respir J 2018;52. [Epub ahead of print].
13. Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. Eur Respir J 2007;30:616-22.
14. Malovrh M, Camlek L, Skrgat S, et al. Increased IL5, IL8 and eosinophils in induced sputum of asthmatics with accelerated FEV1 decline. Eur Respir J 2018;52. [Epub ahead of print].
15. Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med 2018;378:1671-80.
16. Dransfield M, Crim C, Criner G, et al. Risk of exacerbation and pneumonia with single inhaler triple versus dual therapy in IMPACT. Eur Respir J 2018;52. [Epub ahead of print].
17. Voorham J, Roche N, Stephens J, et al. Association between ICS therapy for COPD and diabetes onset and progression. Eur Respir J 2018;52. [Epub ahead of print].
18. Hurst JR, Kostikas K, Chapman KR, et al. Persistent blood eosinophilia and COPD exacerbation risk after ICS withdrawal from triple therapy in the SUNSET study. Eur Respir J 2018;52. [Epub ahead of print].
19. Pavord ID, Criner G, Kerstjens H, et al. Eosinophils as a predictor of mepolizumab treatment responses in COPD. Eur Respir J 2018;52. [Epub ahead of print].
20. Müllerová H, El-Baou C, Galkin D, et al. Exacerbations and Eosinophil Levels in ACCESS Cohort Participants Prescribed Inhaled Triple Therapy. Eur Respir J 2018;52. [Epub ahead of print].
21. George L, Riley J, Taylor A, et al. Relationship between blood eosinophil count and bronchial epithelial gene expression in COPD versus Asthma. Eur Respir J 2018;52. [Epub ahead of print].
22. Soe AK, Kevorkova MS, Nuralieva GS, et al. Blood eosinophilia (BE) and outcomes in patients with acute severe exacerbations of COPD(AECOPD). Eur Respir J 2018;52. [Epub ahead of print].
23. Prudente RA, Mesquita C, Ferrari R, et al.Peripheral eosinophils and mortality in COPD patients over nine years. Eur Respir J 2018;52. [Epub ahead of print].
24. Gayle A, Axson E, Bloom C, et al. Changing causes of mortality for people with chronic respiratory diseases. Eur Respir J 2018;52. [Epub ahead of print].
25. Rasmussen D, Bodtger U, Lamberts M, et al. Beta-blocker, aspirin and statin usage after myocardial infarction in patients with and without COPD. A nationwide analysis from 1995 to 2015 in Denmark. Eur Respir J 2018;52. [Epub ahead of print].
26. Sawalha S, Hedman L, Backman H, et al. The impact of comorbidities on mortality in COPD, report from the OLIN COPD study. Eur Respir J 2018;52. [Epub ahead of print].
27. Lahousse L, Niemeijer MN, van den Berg ME, et al. Chronic obstructive pulmonary disease and sudden cardiac death: the Rotterdam study. Eur Heart J 2015;36:1754-61.
28. Ford AC, Forman D, Moayyedi P, et al. Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. Thorax 2006;61:975-9.
29. Morice AH, Fontana GA, Belvisi MG, et al. ERS guidelines on the assessment of cough. Eur Respir J 2007;29:1256-76.
30. Haque RA, Usmani OS, Barnes PJ. Chronic idiopathic cough: a discrete clinical entity? Chest 2005;127:1710-3.
31. Hilton E, Marsden P, Thurston A, et al. Clinical features of the urge-to-cough in patients with chronic cough. Respir Med 2015;109:701-7
32. Morice AH, Millqvist E, Belvisi MG, et al. Cough hypersensitivity syndrome: clinical measurement is the key to progress. Eur Respir J 2015;45:1509-10.
33. Pratter MR, Brightling CE, Boulet LP, et al. An empiric integrative approach to the management of cough: ACCP evidence-based clinical practice guidelines. Chest 2006;129:222S-31S.
34. Abdulqawi R, Dockry R, Holt K, et al. P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. Lancet 2015;385:1198-205.
35. Smith J, Mcgarvey LP, Morice AH, et al. The effect of baseline factors on treatment response with MK-7264, a P2X3 antagonist, in refractory chronic cough. Eur Respir J 2018;52. [Epub ahead of print].
36. McFadden ER Jr. Exertional dyspnea and cough as preludes to acute attacks of bronchial asthma. N Engl J Med 1975;292:555-9.
37. Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. N Engl J Med 1979;300:633-7.
38. Shirai T, Watanabe H, Akamatsu T, et al. Changes in

forced oscillatory parameters in reversibility testing as predictors for cough variant asthma Eur Respir J 2018;52. [Epub ahead of print].
39. Wortley M, Bonvini SJ, Flajolet PL, et al. The anti-tussive effects of an inhaled LABA are maintained after chronic treatment. Eur Respir J 2018;52. [Epub ahead of print].
40. Chen X, Bonvini SJ, Dubuis E, et al. Characterisation of TRPA1 activation on sensory nerves Eur Respir J 2018;52. [Epub ahead of print].
41. Wang R, Fowler S, Niven R, et al. Investigating the safety of capsaicin cough challenge in severe asthma Eur Respir J 2018;52. [Epub ahead of print].
42. Ruffles T, Marchant J, Masters I, et al. Outcomes in protracted bacterial bronchitis (PBB): a five-year prospective cohort study Eur Respir J 2018;52. [Epub ahead of print].

Cite this article as: Satia I, Badri H, Lahouse L, Usmani OS, Spanevello A. Airways diseases: asthma, COPD and chronic cough highlights from the European Respiratory Society Annual Congress 2018. J Thorac Dis 2018;10(Suppl 25):S2992-S2997. doi: 10.21037/jtd.2018.08.23