

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

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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 FEV₁, 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 heterogeneous 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 may be 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 FEV₁ response and exacerbations based on whether asthma was diagnosed at an early, adult, or late age (12). The greatest improvement in FEV₁ 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 FEV₁ 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 FEV₁ 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/ μ L) (18). The prevalence of COPD frequent exacerbators on triple therapy still having blood eosinophils ≥ 300 cells/ μ L 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 5 Hz and resonant frequency but no improvement in FEV₁ 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-osmolality 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 FEV₁. 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 FEV₁ (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 help 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.

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Footnote

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