ERS Congress 2024: highlights from the Airway Diseases Assembly

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The European Respiratory Society (ERS) Congress 2024 was held in Vienna, Austria. An impressive 838 abstracts were accepted at this congress from Assembly 5 members, presenting exciting new research from airway diseases including asthma, COPD and chronic cough. In this article, early career members from Assembly 5 share their views on the highlights of the 2024 ERS Congress.

Remission in COPD, asthma and chronic cough: is it feasible?

In the symposium session "Remission and response in asthma and COPD", Dave Singh (Manchester, UK) discussed the possibility of remission in COPD, calling for uniformity in the language we use to define remission. Using rheumatoid arthritis and multiple sclerosis as examples, the conclusion was to focus on achieving low disease activity (*i.e.* low exacerbation frequency) and minimal or non-worsening symptoms (figure 1).

Positive results from randomised controlled trials (RCTs) of dupilumab (a monoclonal antibody which blocks interleukin (IL)-4 and IL-13 signalling by binding to IL-4Rα) in COPD give us hope that we can achieve low disease activity. Results from the RCTs NOTUS and BOREAS show that dupilumab reduced annual exacerbation rates (rate ratio 0.66, 95% CI 0.54–0.82; p<0.001) [1], and also symptoms of cough, breathlessness and phlegm [2]. These results indicate that pharmacological interventions such as biological therapies may help us achieve both low disease activity and symptom control in a subgroup of COPD patients with type 2 (T2) inflammation.

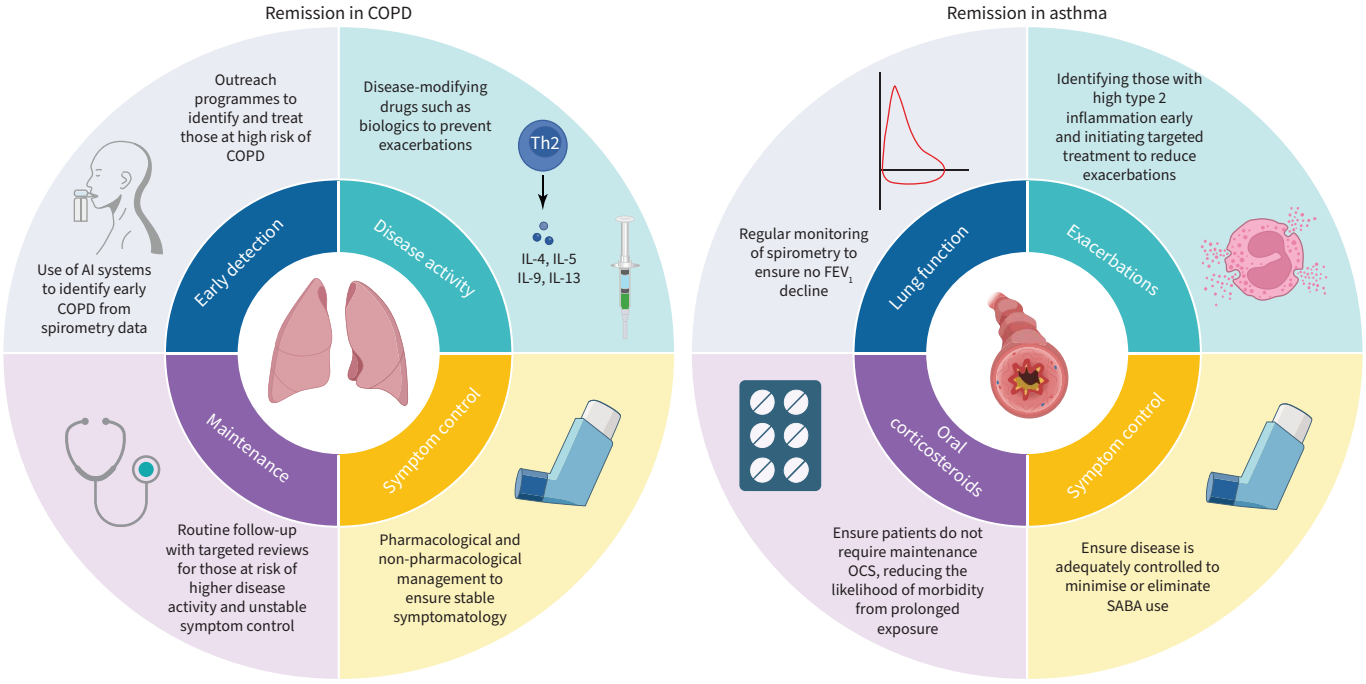

FIGURE 1 Schematic of the four main themes of remission in COPD and asthma. In COPD, the major focus of disease remission was identified to be the attainment of low disease activity. That meant obtaining minimal or non-worsening symptoms through therapeutic strategies, maintaining a low disease activity state through routine follow-up, and early identification and treatment of individuals at risk of COPD through public health outreach programmes. This "target-to-treat" approach was also highlighted as an important strategy to achieve clinical remission in asthma. That meant identifying and treating individuals with "treatable traits" such as high type 2 inflammation and preventing airway remodelling; achieving a well-controlled disease activity state without exacerbations and without the need for oral corticosteroid (OCS) use; and stabilisation of lung function. AI: artificial intelligence; Th2: T-helper cell type 2; IL: interleukin; FEV_1: forced expiratory volume in 1 s; SABA: short-acting β_2-agonist. Figure created with BioRender.com.

However, new therapies alone may not be sufficient to achieve remission (figure 1). A large retrospective study [3] demonstrated that artificial intelligence effectively identifies COPD from primary care spirometry, showing potential for widespread early diagnosis of COPD. In the FRONTIER study, over 60% of lung cancer screening participants received a new diagnosis of COPD [4]. Early diagnosis and management are crucial for slowing disease progression.

Gefapixant ($P2X_3$ receptor antagonist) is the first licensed treatment for chronic cough in Europe [5]. This new class of drugs raises optimism that the disease activity of cough hypersensitivity syndrome could be attenuated [5]. With the availability of new drugs to reduce cough activity, it is equally important that the measures we utilise to assess efficacy are optimal. Novel analyses based on cough relief duration instead of average cough count showed substantial correlation with patient-reported outcomes (Leicester Cough Questionnaire) and differentiated patients in the previously negative VOLCANO-2 study [6]. Additionally, new measures of cough frequency and intensity in the form of the McMaster Cough Severity Questionnaire showed good correlation with the widely used cough severity visual analogue scale [7]. With the introduction of novel cough metrics and therapeutics, remission for chronic cough patients may be closer than ever.

Since the publication of the Global Initiative for Asthma (GINA) 2024 report introduced the framework for asthma remission, the concept of remission in asthma has become a broadly adopted end-point [8], as demonstrated in many studies presented in the 2024 ERS Congress. Using a modified Delphi method, four key components were identified based on which asthma remission could be defined: absence of symptoms, stabilisation of lung function, cessation of oral corticosteroid use, and shared agreement between patient and physician regarding disease remission [8]. Nevertheless, unified and validated criteria are essential but remain lacking [8].

In the same symposium session, "Remission and response in asthma and COPD", Celeste Porsbjerg (Copenhagen, Denmark) comprehensively discussed the concept, feasibility and benefit of clinical

remission in severe asthma. Despite being an ambitious terminology, a study of the Danish Severe Asthma Register reported that remission can be achieved in 19% of patients whilst on biological therapy, using cessation of exacerbations and oral corticosteroids, normalisation of lung function (forced expiratory volume in 1 s (FEV_1) >80%), and a score of ⩽1.5 on the six-question Asthma Control Questionnaire (ACQ6) as a definition for clinical remission [9]. Real-world data showed that the remission rate in severe asthma patients on tezepelumab was as high as 33%, using a similar remission definition, except for ACQ6 <1.5 and FEV_1 change ⩽5% [10]. In a clinical trial setting, remission rates were even higher, even with tapering of high-dose inhaled corticosteroids [11], making remission an achievable treatment goal.

Predictors for asthma remission were explored in several studies, although definitions of remission varied. Notably, gastro-oesophageal reflux disease, smoking history, high body mass index, and the number of treatable traits were identified to be potential barriers for achieving remission [12], suggesting that earlier targeted intervention may be helpful in these groups of patients, as was presented by Vanessa McDonald (Newcastle, Australia) in the session "Treatable traits in airway diseases: novel insights with a focus on personalised medicine".

An agreement on standardised guidelines, symptom control and lung function targets for remission, and the most effective way to measure symptom control while confronting comorbidities like obesity would be important to address moving forward, as presented by Stephanie Korn (Mainz, Germany) in the session "Transforming care in severe eosinophilic asthma: evidence and considerations for evolution of the current treatment paradigm". Besides the use of biologics, pulmonary rehabilitation studies have shown clinically meaningful outcomes in severe asthma, particularly in asthma control [13, 14]. With such success, further studies should be performed to investigate if rehabilitation together with biological therapy could increase remission rates.

To unify current perspectives on asthma remission, Celeste Porsbjerg proposed a focus on impeding disease progression, acquiring stable normalised lung function and improving patients' quality of life, with little medication side-effects.

Pathways to disease modification in airway disease: understanding molecular mechanisms in the alarmin pathway and targeting responder subgroups

The role of the alarmins IL-33 and thymic stromal lymphopoietin (TSLP) in chronic airway diseases were discussed at length, with a particular focus on the effect of current smoking. IL-33 and TSLP are epithelial, endothelial and stromal cell-derived cytokines released as a host regulatory defence mechanism to damage caused by viral, helminth or bacterial infection, or in response to environmental triggers such as allergens, cigarette smoke or pollutants (figure 2) [15]. Full-length bioactive IL-33 is released from the nuclei of cells in response to stimuli, and may be further processed by proteases derived from neutrophils, mast cells or environmental allergens, generating a hyperactive mature form that binds to cells expressing its receptor, ST2 (suppression of tumorigenicity 2) [15]. In a mouse model exploring the role of cigarette smoke and IL-33 in asthma, attenuation of IL-33 *via* soluble ST2 isoform (sST2) reduced mixed granulocyte inflammation, neutrophil extracellular traps and autophagy in an mTOR (mechanistic target of rapamycin)-dependent manner [16]. Elevated sST2 may also be a biomarker for disease progression in COPD, as it was elevated in alveolar endothelial cells of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV patients compared to controls or GOLD stage I–III patients [17].

Although IL-33 expression was increased in airway epithelial cells of COPD and asthma patients compared to healthy controls [15], its gene and protein expression were decreased in lung tissue of current smokers compared to ex-smokers with COPD [18]. The suppressive effect of cigarette smoke was also demonstrated using an epithelial cell model where chronic cigarette smoke exposure led to reduced IL-33 expression [19]. Comparable findings were observed when assessing sputum IL-33 concentrations, with ex-smokers showing higher IL-33 levels than current smokers in patients with pre-COPD and GOLD I/II stages [20]. However, severe COPD (GOLD stage III/IV) patients still had higher sputum IL-33 levels compared to healthy controls, irrespective of smoking status. These results may explain the findings that itepekimab (monoclonal antibody to IL-33) only reduced acute exacerbations (relative risk 0.58, 95% CI 0.39–0.85; p=0.0061) and improved FEV_1 (least squares mean difference 90 mL, 95% CI 20–150 mL; p=0.0076) in former smokers with moderate/severe COPD [21]. Elsewhere, in severe asthma patients, sputum IL-33 levels of patients with mixed granulocytic asthma were elevated compared to healthy controls. Additionally, sputum IL-33 levels were not different between T2-high and T2-low asthma patients [20]. Together, these studies highlight that specific patient subgroups may achieve greater benefit from pharmaceutical interventions targeting the IL-33 pathway.

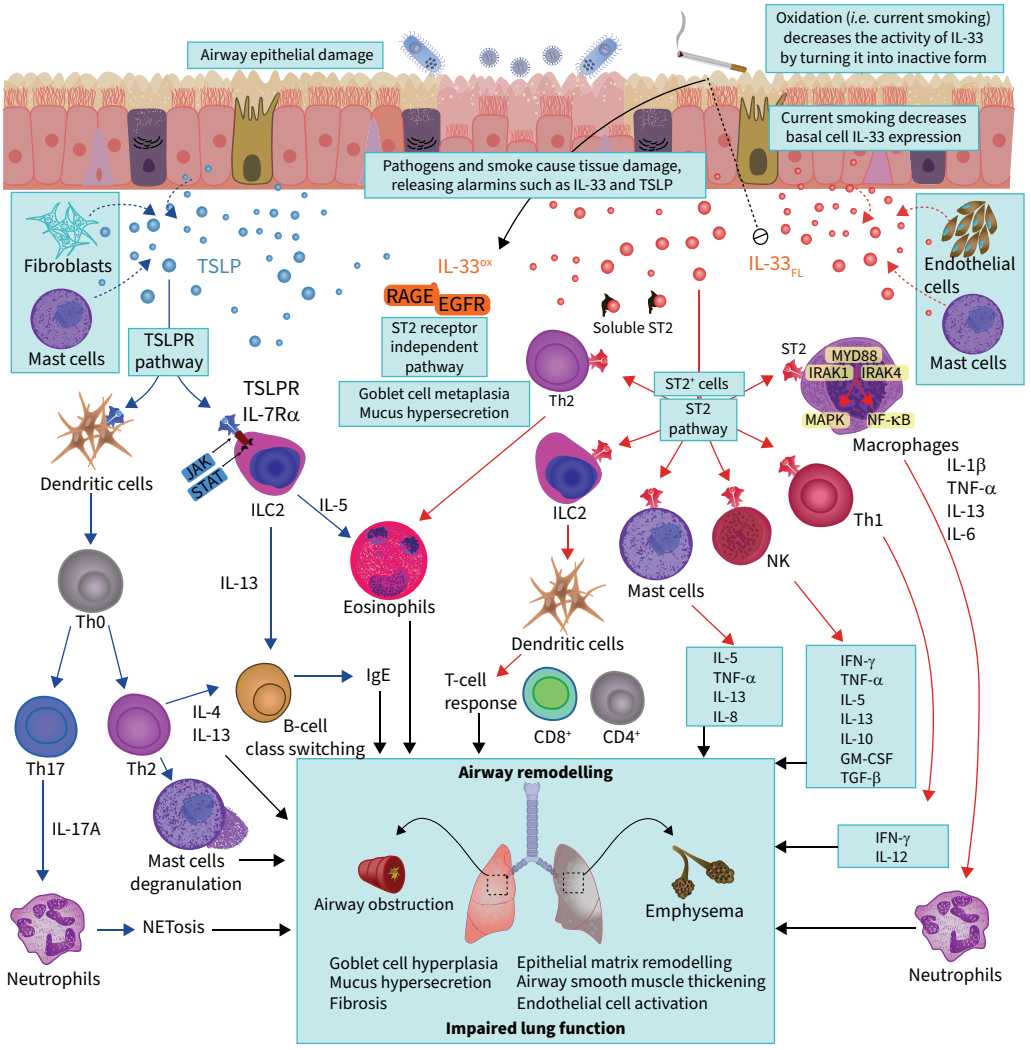

FIGURE 2 Schematic depicting the interleukin (IL)-33 and thymic stromal lymphopoietin (TSLP) alarmin pathways and how they are modulated by cigarette smoke. Tissue or cell damage from viral, helminth or bacterial infection, or from environmental agents such as cigarette smoke, or exposure to allergens, lead to the release of alarmins IL-33 and TSLP. Full-length bioactive IL-33 ($IL\text{-}33_{FL}$) is released, which binds to its receptor, ST2 (suppression of tumorigenicity 2), on ST2-expressing cells. This leads to MYD88 (myeloid differentiation primary response 88) activation of NF-κB and MAPK (mitogen-activated protein kinase) signalling pathways. ST2 also exists as a soluble isoform, which binds free active IL-33, and functions to negatively regulate downstream IL-33 signalling. TSLP binds its receptor (TSLPR) and mediates signalling by forming a heteromeric complex involving TSLPR and IL-7Rα, which activates JAK-STAT (janus kinase and signal transducer of activation) signalling pathways. The binding of IL-33 and TSLP alarmins to their receptors results in release of cytokines and inflammatory cascades, including recruitment and activation of inflammatory immune cells, B-cell class switching, release of immunoglobulin E, mast cell degranulation, release of neutrophil extracellular traps, and activation and priming of T-cell responses. These inflammatory cascades contribute to airway remodelling in asthma and COPD, ultimately leading to airway obstruction, emphysema and an impaired lung function. Paradoxically, current cigarette smoking also leads to the reduction of basal cell IL-33 and TSLP levels, possibly due to the loss of basal cells caused by current smoking. Additionally, cigarette smoking promotes the conversion of IL-33 into an oxidised, inactive form ($IL\text{-}33^{ox}$) through the formation of disulfide bridges and structural conformational change that prevents IL-33 from binding to ST2. $IL\text{-}33^{ox}$ forms a complex with RAGE (receptor for advanced glycation end-products) and EGFR (epidermal growth factor receptor) and the activation of this ST2-independent pathway has been shown to lead to goblet cell metaplasia and mucus hypersecretion. IRAK: interleukin 1 receptor associated kinase; ILC2: group 2 innate lymphoid cells; Th: T-helper cell; NK: natural killer; IFN: interferon; TNF: tumour necrosis factor; GM-CSF: granulocyte–macrophage colony-stimulating factor; TGF: transforming growth factor; NETosis: neutrophil extracellular trap formation.

TSLP, a member of the IL-2 cytokine family, is mainly produced by resting basal epithelial cells and was found to be expressed in cultured air–liquid interface primary bronchial epithelial cells (ALI-PBEC) [22]. A study found that TSLP gene expression in human lung and ALI-PBEC was lower in current smokers compared to ex-smokers or never-smokers [22], suggesting that targeting TSLP as a therapy may require consideration of patients' smoking status. Additionally, healthy ALI-PBEC exposed to cigarette smoke increased oxidative stress, and this was able to induce macrophages to secrete proinflammatory IL-8, highlighting the crosstalk between the airway epithelium and immune cells like macrophages [23]. This increase in IL-8 was reduced through the use of tezepelumab, a monoclonal antibody targeting TSLP [23].

In the 52-week, phase 2a COURSE study, tezepelumab delayed the time to first moderate or severe exacerbation in moderate-to-severe COPD patients (median 253 *versus* 214 days; hazard ratio 0.80, 95% CI 0.61–1.06) [24]. This effect was more pronounced in patients with higher baseline blood eosinophil counts [24]. Meanwhile, tezepelumab reduced mucin 5AC expression in asthma patients regardless of T2 biomarkers [25]. Lastly, phase 1 clinical studies with an inhaled fragment antibody targeting TSLP, AZD8630/AMG 104 [26], the first-in-class inhaled biologic, also significantly reduced fractional exhaled nitric oxide levels by 23% compared to placebo ($p=0.037$) in moderate-to-severe asthma patients, with effects seen in the first week of treatment [26].

To round up the stimulating results presented at the 2024 ERS Congress, Dave Singh announced the phase 2a FRONTIER-4 results of tozorakimab therapy in COPD, a monoclonal antibody that not only targets the conventional IL-33–ST2 pathway, but also the oxidised IL-33, ST2-independent pathway, which signals *via* RAGE/EGFR (figure 2) [27]. Although tozorakimab did not meet its primary end-point of improvement in FEV_1, a numerical improvement in FEV_1 was evident in patients with a higher risk of exacerbation. Furthermore, in a smaller subgroup analysis, tozorakimab significantly reduced mucus plugging in COPD/chronic bronchitis patients [28].

"Non-alarmin" cytokine-targeting therapeutics

As part of the search for new therapies in asthma, a phase 3a study of depemokimab (an ultra-long-acting anti-IL-5 monoclonal antibody) demonstrated a reduction in the annualised rate of exacerbations at 52 weeks among patients with severe eosinophilic asthma (rate ratio 0.52, 95% CI 0.36–0.73; $p<0.001$) [29].

In the ABRA phase 2 RCT, benralizumab (anti-IL-5 receptor alpha monoclonal antibody) was administered as a single 100 mg injection to treat eosinophilic asthma (blood eosinophil count $\geqslant 300$ cells·μL^{-1}) and/or COPD exacerbations. Patients treated with benralizumab had a longer time to treatment failure compared with patients treated with prednisolone at 30 mg for 5 days (47 *versus* 39 days, OR 0.26; $p<0.001$) [30].

To date, treatments for COPD have been challenging because available therapies struggle to change the course of the disease. In a subgroup analysis of the BOREAS trial comparing COPD patients with and without on-treatment exacerbations, dupilumab demonstrated its efficacy in improving lung function and quality of life in both groups (least squares mean difference in FEV_1 compared to placebo of +80 and +90 mL, and St George's Respiratory Questionnaire total score of −4.1 and −3.4, for non-exacerbator and exacerbator groups, respectively; $p<0.01$ for all comparisons) [31]. In the VESTIGE study, dupilumab reduced mucus plugging and mucus volume, and increased lung function, over 24 weeks [32]. Together, these results demonstrated that improvements in quality of life and lung function with dupilumab may not just be attributed to a reduction in exacerbations during the study.

Finally, in a *post hoc* pooled analysis of the ENHANCE trials, ensifentrine (PDE3/4 inhaled inhibitor) demonstrated promising results, reducing the rate of moderate/severe exacerbations in COPD patients regardless of chronic bronchitis status after 24 weeks of treatment (38% rate reduction, rate ratio 0.62, 95% CI 0.43–0.91; $p<0.05$) [33].

Concluding remarks

The ERS Congress 2024 brought an enhanced understanding of the concept of disease remission, molecular mechanisms, and therapeutic responder subgroups in airway disease. In particular, research on biological therapies continues to affirm their efficacy and future potential in asthma and COPD.

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