Simultaneous inhibition of thymic stromal lymphopoietin, IL-33 and IL-25: A therapeutic option in asthma?

Key words: interleukin-25, interleukin-33, thymic stromal lymphopoietin.

Asthma is a chronic inflammatory airway disease that affects approximately 300 million individuals worldwide and has a significant economic burden of 72 billion euros each year. Asthma is a heterogeneous disease of which the development is determined by both genetic (e.g. atopy) and environmental factors (e.g. exposure to allergens and air pollutants). Different phenotypes can be distinguished based on the age at onset, presence of atopy, frequency of exacerbations and inflammatory profile.1 The cornerstone of asthma treatment consists of inhaled corticosteroids (ICS) with or without long-acting β2-agonists (LABA). Although ICS (+LABA) have proven efficacy in randomized controlled clinical trials (RCT), many patients remain uncontrolled in real life. Monitoring inhaler technique and improving therapy adherence should be the initial step in asthma management. However, there is a subgroup of severe asthmatic patients who can benefit from add-on treatments to prevent asthma exacerbations and hospitalizations.

The significant disease morbidity and burden in severe asthma has led to an increased interest in biologicals that target key mediators in the asthma pathogenesis, such as interleukin (IL)-5, which is responsible for blood and airway eosinophilia in type-2 asthma. However, instead of targeting processes downstream in the inflammatory cascade, targeting more upstream events could potentially provide more clinical benefit.

The airway epithelium provides a primary defence against airborne substances, such as allergens, microbes, noxious particles and gases. In susceptible individuals, the increased epithelial release of alarmins such as IL-33, thymic stromal lymphopoietin (TSLP) and IL-25 plays a crucial role in the activation of type 2 cytokine-producing T-helper 2 cells and innate lymphoid cells type 2, which promote eosinophilia, goblet cell hyperplasia and airway hyperresponsiveness (AHR) in asthma.2 As not only allergen exposure, but also viral infections and exposure to air pollutants can induce epithelial cytokine expression and have been implicated in asthma exacerbations,2,3,5 these cytokines are important therapeutic targets. However, the question remains whether targeting one epithelial cytokine is sufficient or whether simultaneously targeting several epithelial cytokines would be required. The presumed redundancy for IL-25, IL-33 and TSLP in type 2-promoting pathways clearly requires more investigation.

In a recent study in *Respirology* by An *et al.*,6 the therapeutic potential of a simultaneous blockade of this cytokine triad was investigated in a murine asthma model by monitoring ovalbumin (OVA)-induced airway responses in *St2−/−* mice, which lack IL-33 receptor signalling, that are treated with monoclonal antibodies (mAb) against TSLP and IL-25. The authors demonstrated that ST-2 deficiency reduced the OVA-induced AHR, airway inflammation, type 2 cytokine expression, airway remodelling and immunoglobulin (Ig) E production. Additional combined IL-25 and TSLP blockade further reduced airway inflammation and type 2 cytokine production, markers of remodelling (e.g. fibronectin expression) and IgE production, whereas anti-TSLP predominantly affected eosinophilic inflammation and local IL-4 production. Notably, the additional antibody treatments did not further reduce OVA-induced AHR in the *St2−/−* mice. These preclinical findings demonstrate that combined inhibition of epithelial cytokines indeed could provide some additional benefit in targeting the eosinophilic inflammation in type-2 asthma, but maybe not AHR. It also demonstrates the partial redundancy in the effects of the epithelial cytokines. Indeed, in the absence of IL-33 signalling, IL-25 and TSLP are sufficient to induce a modest inflammatory response in this murine asthma model.

These interesting findings are supported by other research groups. Verma *et al.* demonstrated that inflammation and AHR can persist in *St2−/−* mice in a chronic asthma model, due to the emergence of IL-9- and IL-13-producing innate lymphoid cells that are activated by increased levels of TSLP.7 Also in the research of Vannella *et al.*, modest inflammation was present in TSLP/IL-33 double knockout mice in a murine asthma model of house dust mite (HDM) exposure.8 Moreover, additional treatment with anti-IL-25 mAb during the allergic sensitization phase in these TSLP/IL-33 double knockout mice decreased inflammation, lung remodelling and even mucus production.8 Notably, the same authors demonstrated that blocking the cytokine triad by mAb by intraperitoneal injections in a therapeutic setting (in established chronic disease) did not reduce inflammatory parameters in an HDM asthma model.8 In the study by An *et al.*,8 the mAb treatment with anti-IL-25 and anti-TSLP occurred once in the sensitization phase (intraperitoneal route) as well as once in the challenge phase (intranasal route). Potentially, the timing as well as the administration route are crucial determinants in whether these approaches are beneficial. These findings underline that experimental design in murine models determines whether the obtained findings provide additional insights into the role of these cytokines in either disease pathogenesis or into their potential as therapeutic target.9 In the study of An *et al.*,9 the additional blockade of IL-25 with or without TSLP in the absence of
ST2 signalling did not further affect AHR nor mucus production. However, other studies demonstrated that anti-IL-25 mAb are able to reduce airway remodelling and AHR, and partially inhibit type 2 inflammation in OVA or HDM models.12,13 These findings not only indicate that IL-25 can contribute to AHR, but also that part of the AHR is mediated by other pathways.

The translation of findings from murine models to therapeutic opportunities in patients is crucial.12–14 Promising results have been obtained for anti-TSLP mAb (AMG157, tezepelumab), where Gauvreau et al. demonstrated that it reduced allergen-induced bronchoconstriction and markers of airway inflammation before and after allergen challenge in mild asthmatic patients.15 More importantly, a recent clinical trial with tezepelumab in adults with uncontrolled asthma has demonstrated clinical efficacy in preventing asthma exacerbations, independent of baseline blood eosinophil counts.16 In contrast to the preclinical research data of combined blockade of alarmins in murine models as described by An et al. in the current issue of Respirology, anti-alarmin antibodies such as tezepelumab are added to maintenance treatment with high doses of ICS in patients with uncontrolled severe asthma. A key question to be further addressed is thus the relative downregulation of the different epithelial alarmins by ICS treatment, both in stable disease and during acute exacerbations of asthma. Also, other mAb are under development, and phase II trials with anti-IL-33 mAb in asthma are ongoing. As environmental exposures modulate the expression of epithelial cytokines and are often associated with exacerbations or with more neutrophilic asthma phenotypes, targeting the cytokine triad could provide important treatment opportunities for the future. Yet, many hurdles have to be taken. First, there are practical challenges of combined mAb administration. Second, there are potential safety issues, as inhibition of all three epithelial cytokines might induce immunosuppression, increasing the risk of respiratory tract infections (encompassing pneumonia and sepsis). Finally, considering the cost of such therapies, they should be limited to a selected subset of well-phenotyped patients with uncontrolled severe asthma.

Tania Maes, PhD and Guy G. Brusselle, MD, PhD
Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium

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REFERENCES


