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# Airway inflammation in asthma: current and future targets and therapies

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## Educational aims

- To provide an overview of airway inflammation in asthma.
- To review current management guidelines' recommendations for the use of anti-inflammatory therapies in asthma.
- To discuss current treatment options for airway inflammation in asthma.
- To outline unmet needs for treating airway inflammation in asthma.
- To describe novel targets for treating airway inflammation in asthma based on current knowledge.

***Provenance***
*Adapted from an ERS Postgraduate Course.*

***Competing interests***
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## Summary

**Asthma is a chronic inflammatory disease of the airways that requires long-term anti-inflammatory therapy. Inhaled corticosteroids (ICS) are recommended for first-line treatment of persistent disease, but not all patients achieve asthma control even when these agents are used in high doses and in combination with other medications, such as a long-acting $\beta_2$-agonist (LABA) or a leukotriene modifier. Such patients may require additional therapy. As information about asthma pathophysiology and inflammatory phenotypes continues to accumulate, and additional anti-inflammatory options become available, it may be possible to target anti-inflammatory therapy to various aspects of the disease and consequently to improve treatment of patients who respond inadequately to standard ICS-based therapy. Several novel anti-inflammatory therapies are at different stages of clinical development. This article will provide an overview of current and future approaches targeting airway inflammation in asthma.**

Airway inflammation in asthma involves multiple components and is orchestrated by numerous cell types, particularly mast cells, eosinophils and CD4+ lymphocytes. Activation of these cells leads to release of proinflammatory mediators and cytokines, which in turn cause vascular leakage, bronchial smooth muscle contraction, inflammatory cell infiltration, mucus hypersecretion, airway hyperresponsiveness (AHR) and ultimately airway remodelling. Anti-inflammatory therapy is central to long-term asthma management. Treatment strategies that aim to normalise surrogates of airway inflammation (*e.g.* sputum eosinophils, AHR) have better outcomes than conventional strategies based solely on symptoms and lung function.

Clinical practice guidelines (*e.g.* [1, 2] recommend ICS as the preferred anti-inflammatory treatment for children and adults with persistent asthma. However, not all patients achieve control of asthma symptoms and airway inflammation with ICS alone, and these need to use add-on therapy (usually a LABA or leukotriene modifier). More than 25% of patients using add-on therapy, however, may remain inadequately controlled and at high risk of exacerbation. Researchers and clinicians

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have targeted key molecules involved in allergic inflammation to improve asthma treatment. Novel agents have been developed, with some already in clinical use [3–6].

## Current medications for asthma: focus on anti-inflammatory effects

ICS, the cornerstone of therapy for patients with persistent asthma, bind to cytoplasmic glucocorticoid receptors in target cells, promoting their activation and translocation to the cell nucleus, where the receptors function as a transcriptional modulator to repress expression of inflammatory genes. In asthma patients, ICS reduce markers of airway inflammation; these effects are lost once treatment is discontinued. Bronchial biopsy specimens reveal that ICS reduce inflammatory cell influx *versus* placebo or a short-acting $\beta_2$-agonist. Subepithelial collagen deposition and basement membrane thickness also decrease, suggesting that ICS may control the intensity of airway remodelling. The anti-inflammatory effects of ICS manifest clinically as improved lung function, reduced asthma symptoms and lower rescue medication requirements.

Clinical guidelines recommend adding a LABA to ICS in patients with moderate-to-severe asthma [1, 2]. Adding a LABA is generally more effective than increasing the ICS dose. Adding a leukotriene modifier is an alternative to adding a LABA. Blocking leukotrienes – proinflammatory lipid mediators that promote airway smooth muscle contraction, vascular leakage, inflammatory cell infiltration, mucus secretion and AHR – has modest bronchodilating and anti-inflammatory effects. Recent studies suggest that the anti-inflammatory action of the leukotriene modulator montelukast may be related to inhibition of cytokine production induced by the proinflammatory transcription factor nuclear factor-κB, along with suppression of serum soluble interleukin (IL)-2 receptor (sIL-2R) and tumor necrosis factor (TNF)-α levels, plus inhibition of eosinophil protease leading to decreased eosinophil infiltration into the airways [7–9]. Based on clinical data, montelukast is recommended as an alternative treatment to low-dose ICS for mild persistent asthma in patients aged >1 yr. Although leukotriene modifiers are effective in many patients, a substantial proportion receives little benefit and requires additional anti-inflammatory medication.

Zileuton, a 5-lipoxygenase inhibitor, may constitute an alternative add-on therapy to ICS in patients with moderate-to-severe asthma. Theophylline is a nonspecific phosphodiesterase (PDE) inhibitor used for the past 60 yrs in the treatment of asthma, and data from several clinical trials show that it provides symptomatic benefit for patients with poorly-controlled, mild-to-moderate disease [10]. In severe asthma, theophylline can improve clinical outcomes in patients who remain uncontrolled on high-dose ICS, and its withdrawal can worsen symptoms even if high-dose ICS or oral steroids are continued. However, treatment guidelines recommend increasing the dose of ICS and adding LABAs in preference to add-on theophylline for patients experiencing inadequate asthma control, owing to concerns over efficacy and drug-related adverse events. More recently, the use of low-dose theophylline has been shown to improve response to ICS in smokers with asthma [11].

## Targeting airway inflammation: an unmet need

Not all patients are well controlled by ICS, even at high doses and when combined with other agents. Responses to ICS are variable: some patients show little improvement in lung function or AHR when exposed to medium-to-high ICS doses; others show good responses. Genetic factors may influence ICS responses: T-cells isolated from black patients exhibit lower corticosteroid responsiveness than those from white patients. Body mass index (BMI) may contribute to variability in ICS response: asthma control days on beclomethasone decreased with increasing BMI in a pooled analysis, with similar relationships seen between BMI and other asthma outcomes.

Corticosteroids recruit histone deacetylase-2 to the activated gene transcript complex, resulting in histone deacetylation and suppression of inflammatory gene transcription. In asthma patients who smoke, however, oxidative and nitrative stress markedly impair the enzyme, reducing sensitivity to ICS therapy.

Two inflammatory subtypes of treatment-resistant asthma have been described: the eosinophil-positive phenotype associated with increased T-lymphocytes, mast cells, and macrophages; and a neutrophilic phenotype with few eosinophils and generally normal levels of other inflammatory cells. Treatment-resistant

asthma appears to be associated with evidence of increased tissue injury and remodelling. The eosinophil-positive phenotype has significantly greater basement membrane thickness, correlated with the number of eosinophils; lung function differs only marginally between the two subtypes. Patients with treatment-resistant asthma may benefit from additional anti-inflammatory therapy. In patients with severe asthma who had persistent sputum eosinophilia despite high-dose ICS or oral prednisone therapy, administering high-dose intramuscular triamcinolone resulted in near-complete disappearance of sputum eosinophils and improvement in forced expiratory volume in 1 s ($FEV_1$), suggesting that a short course of systemic corticosteroids may reset the function of the steroid receptors and overcome relative steroid-resistance.

# Novel anti-inflammatory agents

## Targeting IgE

Asthma is recognised as IgE-mediated, with an allergic basis in most patients. Mast cells, localised within bronchial smooth muscle in asthma patients, produce several mediators causing bronchoconstriction, airway inflammation, AHR, mucus secretion and tissue remodelling. Immunoglobulin (Ig)E triggers the allergic cascade by binding to mast cells. On initial exposure, inhaled allergens are presented to T-helper (Th) type 2 lymphocytes, resulting in secretion of IL-4 and IL-13, and in turn, stimulation of immunoglobulin class-switching in B-cells to allow IgE production. Subsequent binding to high-affinity IgE receptors (FcεRI) on mast cells and basophils results in sensitisation to allergen exposure.

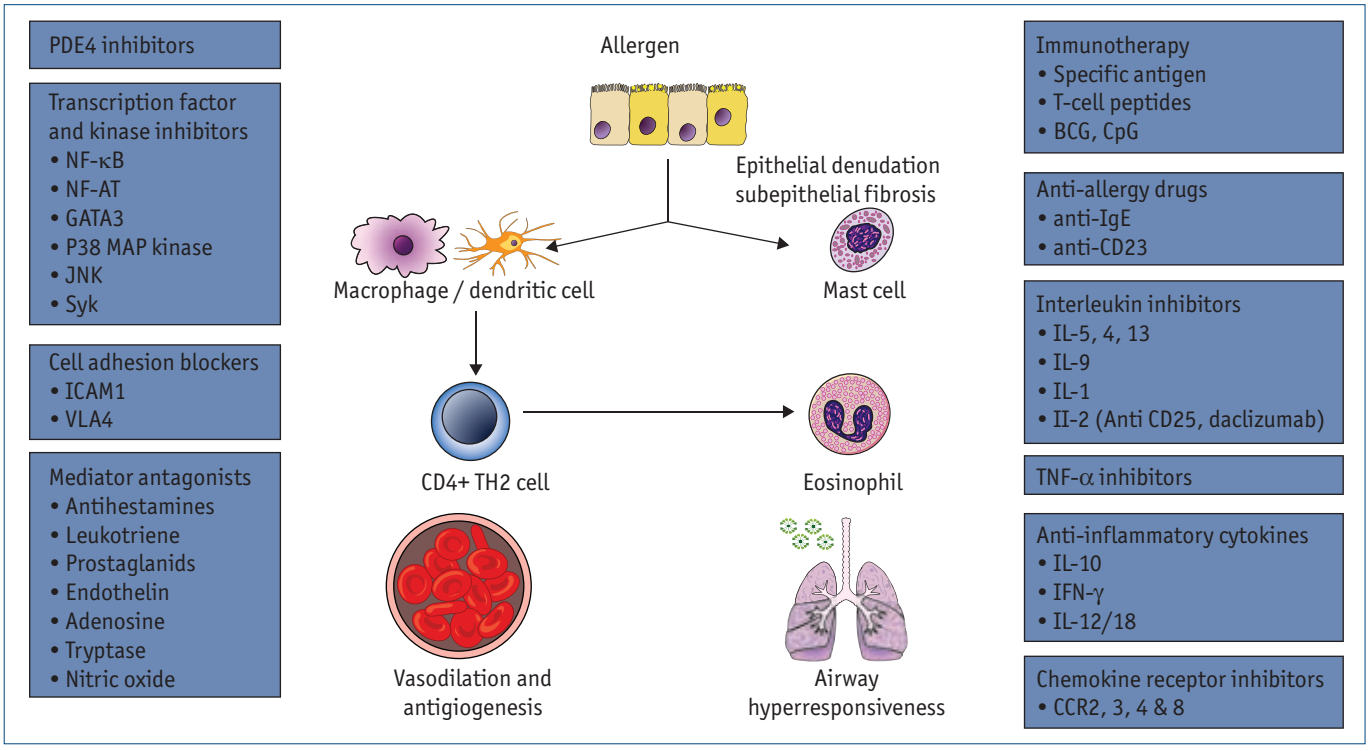
Omalizumab is a recombinant humanised monoclonal antibody recommended for patients with moderate-to-severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS. Binding of omalizumab to IgE prevents the subsequent downstream asthma-related cascade of events and produces anti-inflammatory effects in allergen challenge and bronchial biopsy protocols, supporting the role that IgE plays in airway inflammation in asthma. Omalizumab (administered subcutaneously every 2 or 4 weeks per serum IgE levels and body weight) has been assessed in randomised controlled trials in patients with moderate-to-severe asthma who remain symptomatic despite ICS [12]. Adding omalizumab significantly reduced exacerbations *versus* adding placebo during the steroid-stable and steroid-tapering phases, and allowed greater reductions in ICS dose requirements (all $p<0.01$). Symptom management improved after adding omalizumab, and was maintained at the lower ICS doses.

## Agents in clinical development

### Neutralising Th2 cytokines

Improving knowledge about the pathophysiology of asthma has led to targeting of specific inflammatory cells and proinflammatory mediators. Th2 lymphocytes promote airway inflammation in asthma through release of several key cytokines, IL-4, IL-5, and IL-13. IL-4, required for differentiation of naïve T-cells into Th2-cells in the presence of allergen, is the primary factor driving B-cell isotype-switching from IgM to IgE. IL-4 also upregulates FcεRI and FcεRII expression and promotes eosinophil migration across the vascular endothelium. IL-5 stimulates terminal differentiation of eosinophils, leading to their release into the circulation, and promotes their survival. IL-13 shares some activities with IL-4, and may contribute to allergic inflammation by modulating the Th1/Th2 balance and stimulating IL-5 production. Thus, neutralising Th2-cytokines represents a rational approach for anti-inflammatory therapy.

A recombinant human soluble IL-4 receptor (sIL-4R), which inactivates IL-4, has been evaluated in steroid-dependent asthma patients following withdrawal of ICS therapy [13]. Anti-inflammatory activity was shown by reduction in exhaled nitric oxide after a single sIL-4R dose; stabilisation of asthma symptoms also occurred, despite ICS withdrawal. When administered once weekly for 12 weeks, sIL-4R prevented the $FEV_1$ decline and symptom increase seen in the placebo group after ICS withdrawal [14]. However, the discontinuation rate due to asthma exacerbation was similar between the sIL-4R and placebo groups. No further clinical evaluation has been reported. A humanised IL-5 monoclonal antibody that inactivates IL-5 reduced eosinophils in the blood, bone marrow, sputum, and bronchial tissue of patients with mild asthma not receiving ICS. The reduction in eosinophils was associated with decreased expression of tenascin, lumican and procollagen III in the bronchial subepithelial basement membrane, suggesting that anti-IL-5 may regulate tissue remodelling through its effects on eosinophils. Nevertheless, blocking IL-5 did not significantly affect late-phase bronchospasm, AHR or lung function *versus* placebo. Similarly, adding anti-IL-5 to high-dose ICS therapy




reduced blood eosinophils in severe asthma patients, but produced no clinical improvement in symptom score or lung function.

Adding oral suplatast tosilate (*t.i.d.*), a Th2 cytokine inhibitor that suppresses IL-4 and IL-5 synthesis, to high-dose ICS therapy in patients with severe asthma led to significant improvements in $FEV_1$ morning peak expiratory flow (PEF) rate, and daytime asthma symptoms (p=0.029) at 4 weeks *versus* adding placebo. When ICS doses were subsequently tapered, the decline in these parameters was less pronounced with suplatast than placebo [15]. Suplatast also significantly reduced AHR and improved PEF and symptoms in steroid-naïve patients with mild asthma. These changes were accompanied by decreased eosinophil counts in sputum and bronchial mucosa, but not in blood, and by decreases in CD4+ and CD25+ T-cells in bronchial mucosa.

*Blocking TNF-α*

TNF-α is involved in Th1-dependent chronic inflammatory diseases, *e.g.* rheumatoid arthritis and Crohn's disease. However, TNF-α may also be upregulated in asthma, particularly in patients with severe, steroid-dependent asthma. TNF-α promotes recruitment of neutrophils and eosinophils into the airways, and may be important in both phenotypes of severe asthma. Etanercept (Enbrel®; Amgen, Thousand Oaks, CA, USA), a recombinant fusion protein that blocks TNF-α, produced marked and significant improvement in asthma control when added to high-dose ICS therapy in patients with treatment-resistant asthma [16]. AHR and all measured lung function parameters improved significantly, and all but one patient discontinued rescue $\beta_2$-agonist therapy. Similar results were obtained in a 10-week crossover trial of patients with refractory asthma [17]. The anti-TNF-α monoclonal antibody infliximab (Remicade®; Centocor, Horsham, PA, USA) reduced diurnal PEF variability – but not morning PEF – in a trial of symptomatic patients with moderate asthma despite ICS therapy [18]. However, more recently, this strategy failed to show any advantage over placebo in patients with severe asthma.

**Phosphodiesterase-4 inhibitors**

Cyclic adenosine monophosphate (cAMP) suppresses many inflammatory events, including proinflammatory mediator release and inflammatory cell infiltration. In the lungs, cAMP is inactivated by PDE-4, and consequently selective inhibition of this enzyme has anti-inflammatory effects. Roflumilast, an orally active PDE-4 inhibitor, produced dose-related inhibition of late-phase bronchospasm following allergen challenge in patients with mild asthma [19]. In a randomised double-blind, parallel-group, phase 2/3 study, patients received roflumilast for 12 weeks. Roflumilast (100,

250 and 500 µg) use significantly increased $FEV_1$ with improvements from baseline at the last visit of 400 mL for highest (500 µg) dose group *versus* the lowest (100 µg). There were also significant improvements from baseline in morning and evening PEF for all doses [20]. A second PDE-4 inhibitor under clinical development is ciclamilast. Studies in murine models suggest that this agent mediates airway hyperresponsiveness through the inhibition of PDE-4D mRNA expression and the downmodulation of PDE-4 activity, with reduced inflammation and mucus hypersecretion [21].

### Macrolides and ketolides

Macrolide and ketolide antibiotics produce anti-inflammatory actions distinct from their antimicrobial properties. In patients with acute asthma, adding telithromycin (Ketek®; Sanofi-Aventis, Bridgewater, NJ, USA) (800 mg daily for 10 days) to usual care reduced self-reported asthma symptoms but did not improve morning PEF rates over placebo in adult patients [22]. More recently, data from a large multicentre study failed to show any benefit of long-term macrolide therapy in patients with chronic asthma (the Asthma Clinical Research Network Macrolides in Asthma trial. See clinicaltrials.gov, trial number NCT00318708).

## Experimental approaches

### Adenosine A2B antagonists

Adenosine modulates inflammatory cell function in the airways, and may also activate mechanisms to protect against lung injury. Adenosine's effects are mediated through four distinct receptor subtypes. This is possibly a viable strategy for producing anti-inflammatory actions in the airways. Activation of A2B receptors on mast cells stimulates release of proinflammatory mediators and cytokines, which in turn leads to increased IgE production by B-cells, while activation of A2B receptors on lung fibroblasts promotes their differentiation into myofibroblasts, suggesting a role in airway remodelling. In an experimental asthma model, the selective A2B receptor antagonist (CVT-6883) reduced allergen-induced bronchospasm and inflammatory cell infiltration [23].

### Chemokine/chemokine receptor antagonists

Chemokines (chemoattractant cytokines) play a central role in the recruitment of inflammatory cells to the airways (and other inflammatory sites), and by activating T-cells may also be involved in the activation and differentiation of inflammatory cells [24, 25]. In allergic models, deletion of various chemokine receptors has been associated with reduction in AHR and other inflammatory surrogates. However, the multitude of chemokines and the promiscuity of chemokine receptors make it difficult to determine an optimal target for therapeutic intervention. The most studied target in this field has been the CCR3 receptor; antagonism has been associated with decreases in eosinophil infiltration and AHR in experimental asthma models [26].

### Kinase inhibitors

Protein kinases are instrumental in intracellular signalling; some may be overexpressed in asthma and lead to activation of proinflammatory transcription factors. Therefore, inhibition of these kinases may be expected to reduce airway inflammation. Two kinases that may be viable targets in severe asthma are the p38 mitogen activated protein (MAP) kinase and the inhibitor of κB kinase (IKK) 2. Inhibitors of these kinases have been identified and evaluated in models of arthritis and other Th1-mediated inflammatory diseases. Their role in asthma remains to be determined.

### Other strategies

Alternative strategies for regulating airway inflammation are being explored (see further reading), including prostanoid and F2-isoprostane antagonists, peroxisome proliferator-activated receptor gamma agonists, nitric oxide donors and inducible nitric oxide synthase inhibitors, and toll-like receptor modulators. These agents modulate inflammatory cell function and/or reduce airway inflammation in experimental models.

# Conclusions

Airway inflammation, a prominent feature in asthma, needs to be targeted with effective medication to achieve asthma control. ICS play a pivotal role in combating airway inflammation, although additional anti-inflammatory treatment is needed in patients who fail to respond adequately to ICS. While adding a LABA or leukotriene modifier is an effective option in many patients, a significant proportion of them remains symptomatic and require additional interventions. Increasing knowledge of asthma pathophysiology and the various inflammatory phenotypes may make it possible to target anti-inflammatory therapy to the various pathways of the disease, thereby improving asthma control. A number of other approaches currently in clinical development, which show promise in targeting specific cytokines, inflammatory cells, or inflammatory mechanisms, may become available for clinical use in the future.

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