

Targeting cytokines to treat asthma and chronic obstructive pulmonary disease

Peter J. Barnes

Abstract | Cytokines play a key role in orchestrating and perpetuating the chronic airway inflammation in asthma and chronic obstructive pulmonary disease (COPD), making them attractive targets for treating these disorders. Asthma and some cases of COPD are mainly driven by type 2 immune responses, which comprise increased airway eosinophils, T helper 2 (T_H2) cells and group 2 innate lymphoid cells (ILC2s) and the secretion of IL-4, IL-5 and IL-13. Clinical trials of antibodies that block these interleukins have shown reduced acute exacerbations and oral corticosteroid use and improvements in lung function and symptoms in selected patients. More recent approaches that block upstream cytokines, such as thymic stromal lymphopoietin (TSLP), show promise in improving patient outcome. Importantly, the clinical trials in cytokine blockade have highlighted the crucial importance of patient selection for the successful use of these expensive therapies and the need for biomarkers to better predict drug responses.

U-BIOPRED

Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes is a European project investigating mechanisms of severe asthma.

Asthma and chronic obstructive pulmonary disease (COPD) are very common and troublesome obstructive airway diseases that are associated with chronic inflammation of the respiratory tract. Asthma is one of the most prevalent chronic diseases worldwide, affecting about 10% of adults and an even greater proportion of children. COPD affects about 10% of people over 40 years of age, is a leading cause of hospital admissions and is now the third-ranked cause of death worldwide¹. The major risk factor for COPD in Western countries is cigarette smoking. COPD is characterized by progressive airflow obstruction, predominantly affecting peripheral airways, that leads to air trapping, dynamic hyperinflation and shortness of breath on exertion. While asthma and COPD are usually clinically distinct and have different causal mechanisms, in some patients, there are features of both diseases, and this has been termed asthma–COPD overlap syndrome^{2,3}. Current therapies for asthma and COPD are shown in **BOX 1**. Asthma is often poorly controlled in the community despite the availability of effective inhaled therapies, typically because of poor adherence to therapy or incorrect use of inhaler devices. However, even with maximal inhaled therapy, a proportion of patients with asthma remains difficult to control⁴.

The unmet therapeutic needs for COPD are even greater than those for asthma, as current COPD therapies are merely symptomatic and there are no effective disease-modifying treatments. This has prompted a concerted search for new targets and treatments for

airway diseases, and several new therapies have been developed⁵. Prominent among these are inhibitors of the cytokines that are involved in orchestrating and perpetuating chronic airway inflammation. Blocking antibodies against specific cytokines have recently been approved for patients with severe asthma⁶. This Review discusses cytokine inhibitors that are now in development for the treatment of airway disease.

Clinical studies of cytokine inhibitors have clearly shown that only a proportion of patients with airway disease respond well, and so it is important to define good responders and develop relevant biomarkers that can predict and monitor responses to specific therapies. There is increasing evidence for distinct clinical phenotypes of asthma and COPD that may require different therapeutic approaches. But it has been difficult to identify consistent reproducible phenotypes on the basis of clinical measurements alone, and it will be necessary to develop biomarkers on the basis of inflammatory patterns or the mechanism of action of the cytokine that is inhibited. Future research may involve recognizing signatures of gene or protein expression profiles and integrating this information with clinical measurements, as recently demonstrated with the U-BIOPRED cohort⁷.

Inflammation in airway disease

Both asthma and COPD are characterized by chronic inflammation of the respiratory tract, although the nature of the inflammation and its location differ⁸.

Airway Disease Section,
National Heart and Lung
Institute, Imperial College,
London, UK.

e-mail: p.j.barnes@imperial.ac.uk

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Type 2 immunity

A type of immunity that provides protection against parasitic infections but is also activated in allergic diseases such as asthma. It is orchestrated by T helper 2 (T_H2) cells and group 2 innate lymphoid cells (ILC2s) through the secretion of IL-4, IL-5, IL-9 and IL-13, which are regulated by the transcription factor GATA3. Type 2 inflammation is characterized by eosinophils, mast cells and alternatively activated macrophages. Upstream cytokines from epithelial cells that regulate T_H2 cells and ILC2s include the alarmins IL-25, IL-33 and thymic stromal lymphopoietin (TSLP).

T helper 2 (T_H2) cells

A subset of CD4⁺ T helper cells that has an important role in humoral immunity and in allergic responses. $TH2$ cells express the transcription factors GATA3 and signal transducer and activator of transcription 6 (STAT6) and produce cytokines such as IL-4, IL-5, IL-9 and IL-13, which regulate IgE synthesis, eosinophil proliferation, mast cell proliferation and airway hyperresponsiveness, respectively.

Innate lymphoid cells

Immune cells that do not express antigen specific B or T cell receptors. Three main subtypes are recognized depending on the transcription factors expressed and the pattern of cytokines they release.

Airway hyperresponsiveness

Increased airway narrowing in response to various external stimuli that is a physiological characteristic of patients with asthma.

Type 1 immunity

A type of immunity that provides protection against microbial infections and is orchestrated by T helper 1 cells, cytotoxic T cells and group 1 innate lymphoid cells and the transcription factor T-bet, which regulates the secretion of IFN γ . Type 1 immunity is associated with increased pro-inflammatory macrophage activation.

Box 1 | Current management of asthma and COPD

Both asthma and chronic obstructive pulmonary disease (COPD) are treated mainly with inhaled therapy (that is, pressurized metered dose or dry powder inhalers).

Asthma

The mainstay of treatment is inhaled corticosteroids (ICSs) in all patients with persistent symptoms, with the addition of a long-acting β_2 -agonist (LABA) in patients with moderate to severe disease, which is usually given in a fixed dose combination inhaler once or twice daily. Approximately 5% of patients have severe asthma that requires additional treatment, which may include an inhaled long-acting muscarinic antagonist (LAMA), low dose oral theophylline or leukotriene receptor antagonist. Approximately 1% of patients may require a maintenance dose of oral corticosteroids, and in these patients, anti-IgE therapy with omalizumab may be tried if patients have high levels of plasma IgE.

COPD

The most effective treatments for COPD are long-acting bronchodilators, including LAMA and LABA, which reduce hyperinflation, symptoms and exacerbations. LAMA and LABA have additive effects and so may be given as a fixed dose combination inhaler. In patients with continuing exacerbations, ICSs may be added in the form of a triple fixed dose combination inhaler that includes ICSs, LABA and LAMA. The presence of increased blood eosinophils compared with controls may predict the beneficial effect of adding ICSs. Additional therapy for patients with very severe COPD includes the oral phosphodiesterase 4 inhibitor roflumilast or a macrolide antibiotic, which may further reduce exacerbations.

Asthma–COPD overlap syndrome

Patients who have features of both asthma and COPD, known as asthma–COPD overlap syndrome, require maximal bronchodilatation with LABA and LAMA as well as ICSs, which may be conveniently given as a triple inhaler.

Asthma. In the airways of patients with asthma, there is a characteristic pattern of inflammation — predominately type 2 immunity — with activation of mast cells and infiltration and activation of eosinophils and T cells, in particular, CD4⁺ T helper 2 (T_H2) cells (FIG. 1). Recently, group 2 innate lymphoid cells (ILC2s) have been identified and may play an important role in non-allergic asthma⁹. Asthma is usually characterized by allergic inflammation with increased production of IgE by B cells, mast cell degranulation and eosinophil infiltration orchestrated by T_H2 cells, but the same pattern of inflammation may also occur in non-allergic individuals¹⁰. Inflammation is found in all airways from the trachea to the terminal bronchioles and may extend into the lung parenchyma. There are also characteristic structural changes, with increased airway smooth muscle, fibrosis beneath the airway epithelium, which is often damaged, increased numbers of goblet cells (termed mucous cell metaplasia) and increased vascularity. These changes are found even in patients with mild disease, although the extent of airway remodelling is usually greater in patients with severe disease. This pattern of inflammation is associated with airway hyperresponsiveness, which may be due to increased susceptibility of mast cells to release bronchoconstrictor mediators in response to triggers, such as exercise, and to increased sensitivity of afferent nerves in the airways, which may be triggered by irritants.

COPD. Patients with COPD have a different pattern of inflammation—most commonly, type 1 immunity and type 3 immunity—with a predominance of macrophages and neutrophils and increased numbers of CD8⁺ cytotoxic T cells, CD4⁺ T_H1 cells, T_H17 cells, ILC3s and B cells, which are organized with T cells into local lymphoid follicles in peripheral airways^{11,12} (FIG. 2). Inflammation is localized mainly to the peripheral airways and lung parenchyma. This inflammation is an amplification of the mucosal inflammatory response to inhaled irritants,

such as tobacco or biomass smoke, but it persists even when exposure ceases. Structural changes in the airways include airway epithelial cell metaplasia, mucus hyperplasia and peribronchiolar fibrosis, and there may be a loss of small airways even in mild disease¹³. There is also alveolar wall destruction (characteristic of emphysema), including loss of alveolar attachments to small airways, which contributes to air trapping. Longitudinal imaging studies suggest that the small airway disease precedes the development of emphysema¹⁴. The airway obstruction in COPD is largely irreversible and usually slowly progressive over many years, whereas in asthma, although irreversible airway narrowing may occur in severe disease, the airway obstruction usually remains largely reversible. About half of the patients with COPD show an accelerated decline in lung function over time, whereas the remainder have a normal age-related decline but start from a lower baseline owing to poor lung development¹⁵.

Asthma–COPD overlap syndrome. Although asthma and COPD usually have distinct clinical characteristics, some patients appear to have features of both diseases, and this may reflect a shared pattern of inflammation. Thus, some patients with COPD may have eosinophilic inflammation, and these patients may have clinical features of asthma, including more reversibility of airway obstruction, increased airway hyperresponsiveness and a better response to corticosteroid therapy, whereas some patients with asthma may have features of COPD with a predominantly neutrophilic pattern of inflammation, less reversibility, a progressive decline in lung function and a poor response to corticosteroids^{2,3}. This may have implications for the selection of therapy, as it may be important to select a treatment that targets eosinophilic or neutrophilic inflammation irrespective of the clinical diagnosis. For example, anti-eosinophilic treatments may be of therapeutic value in eosinophilic asthma and in COPD associated with eosinophils.

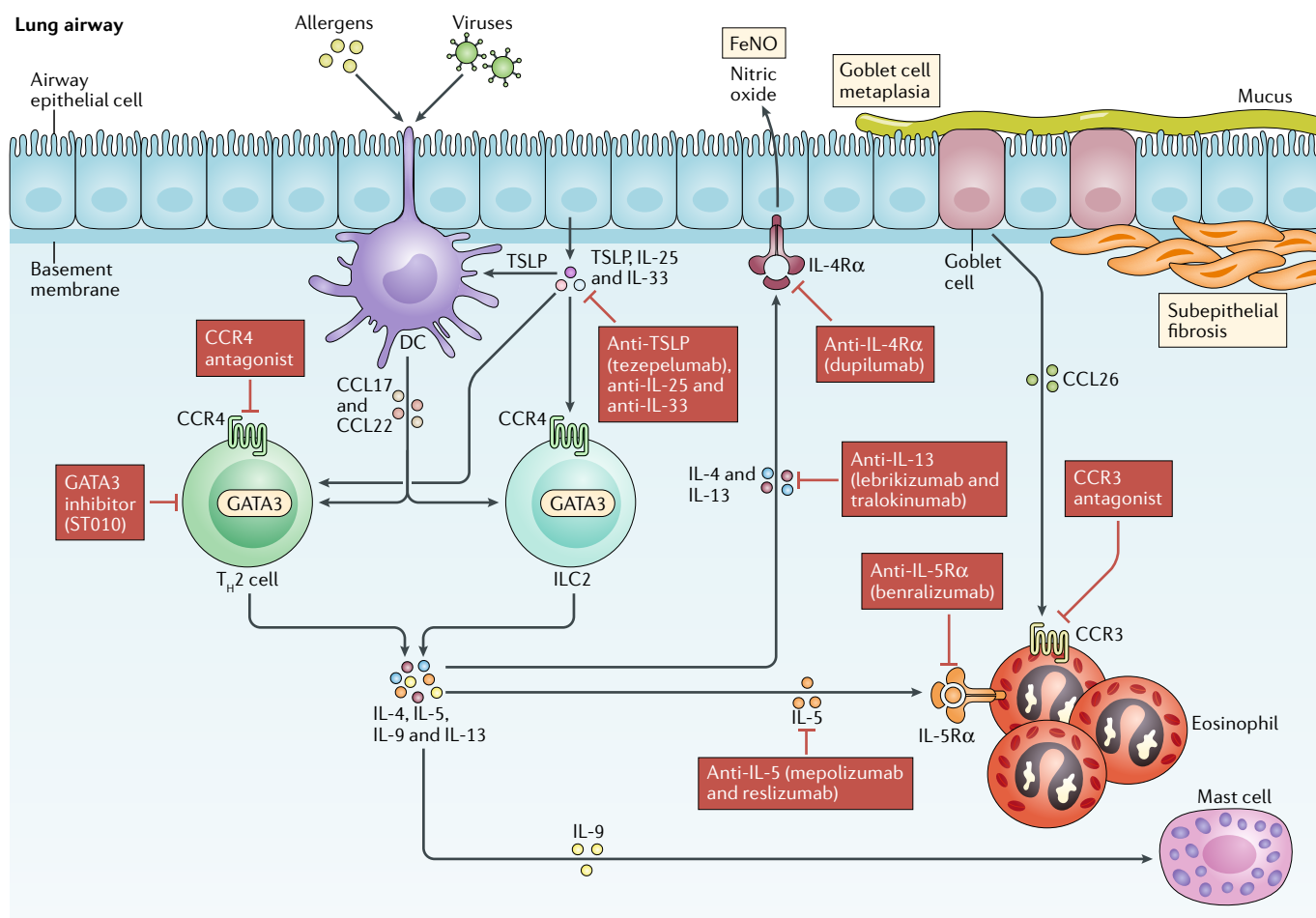


Fig. 1 | Targeting type 2 cytokines in airway disease. Inhaled allergens activate lung dendritic cells (DCs) to release the chemokines CC-chemokine ligand 17 (CCL17) and CCL22, which recruit T helper 2 (T_H2) cells and group 2 innate lymphoid cells (ILC2s). Activation of the transcription factor GATA3 in T_H2 cells and ILC2s leads to secretion of the cytokines IL-4, IL-5, IL-9 and IL-13. IL-4 and IL-13 activate a common receptor, IL-4 receptor subunit- α (IL-4R α), which causes release of nitric oxide from airway epithelial cells, as indicated by increased fractional exhaled nitric oxide (FeNO), goblet cell metaplasia and airway fibrosis. IL-5 acts on IL-5R α to cause eosinophilia, whereas IL-9 is important for mast cell integrity. Epithelial cells release eosinophil-attracting chemokines, such as CCL26, which attract eosinophils through binding to CC-chemokine receptor 3 (CCR3). Epithelial cells also produce alarmins, including thymic stromal lymphopoietin (TSLP), IL-25 and IL-33, which are 'upstream' cytokines in the eosinophilic response. Blocking antibodies against the cytokines and receptors in this pathway are shown.

Type 3 immunity

A type of immunity that is directed against microorganisms, in particular fungi, and orchestrated by T helper 17 cells and group 3 innate lymphoid cells, which express ROR γ t and secrete IL-17 and IL-22, leading to neutrophilic inflammation.

T_H17 cells

A subset of CD4 $^+$ T helper cells that express the transcription factor ROR γ t and secrete IL-17A, IL-17F and IL-22. They are involved in neutrophilic inflammatory responses and are important in responses to bacteria and viruses, as well as autoimmune diseases.

Comorbidities. Both asthma and COPD are associated with other diseases. Asthma is commonly associated with rhinitis, rhinosinusitis, nasal polyps and atopic dermatitis, such that targeting the underlying type 2 inflammation may also treat these comorbidities. Asthma may also be associated with obesity. COPD is associated with many other chronic diseases that are related to accelerated ageing, particularly cardiovascular and metabolic diseases, that may share the same molecular pathways and may occur together with other morbidities in elderly individuals¹⁶.

Corticosteroid resistance in airway diseases

Inhaled corticosteroids (ICSs) are effective in the management of asthma by suppressing type 2 inflammation in the airways. This is achieved by switching off activated inflammatory genes in the airways through reversing the acetylation of core histones via the recruitment of histone deacetylase 2 (HDAC2)¹⁷. Corticosteroids are effective

at suppressing the expression of many of the cytokines and chemokines involved in asthma and are the most effective anti-inflammatory treatment available for type 2 asthma. However, in patients with severe asthma, they are less effective, such that unacceptably high doses may be required; additionally, in many patients with COPD, they are ineffective, as the non-type 2 pattern of inflammation is less sensitive to corticosteroids. The relative corticosteroid resistance of type 2 inflammation may be explained by several molecular mechanisms, including a reduction in HDAC2 expression as a result of oxidative stress and acetylation of the glucocorticoid receptor¹⁸. In epithelial cells, macrophages and peripheral blood leukocytes of patients with severe asthma and COPD, there is a reduction in HDAC2 expression^{19,20}. Other mechanisms include phosphorylation of the glucocorticoid receptor by various mitogen-activated protein kinases. A poor response to corticosteroids represents an important

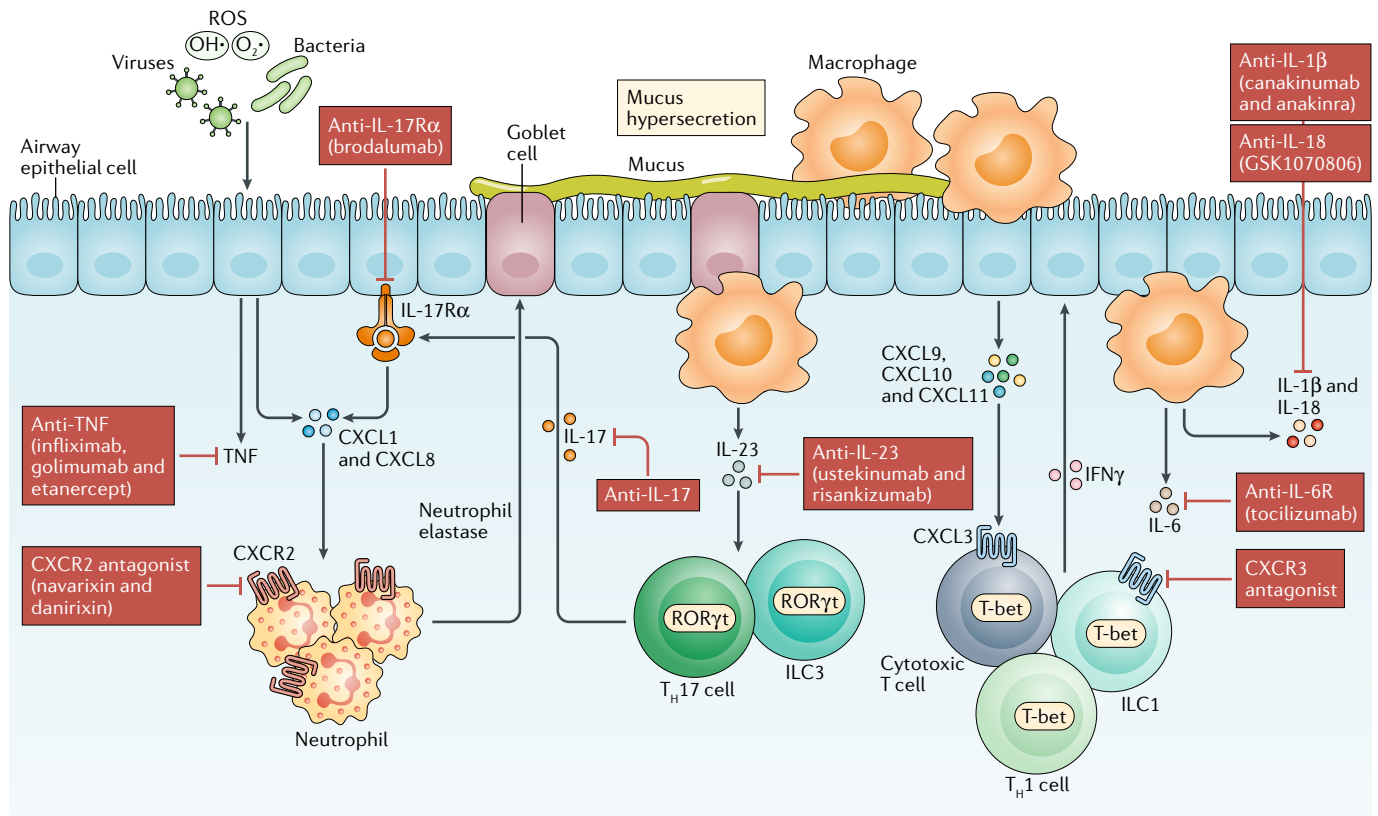


Fig. 2 | Targeting non-type 2 immunity in airway disease. Bacteria, viruses and reactive oxygen species (ROS) activate airway epithelial cells to release pro-inflammatory mediators, such as tumour necrosis factor (TNF) and the chemokines CXCL1 and CXCL8, which attract neutrophils by binding to CXCR2. Macrophages and dendritic cells release IL-23, which promotes the generation of T helper 17 (T_H17) cells and group 3 innate lymphoid cells (ILC3s) and the production of IL-17, which induces the release of CXCL1 and CXCL8. T_H1 cells and ILC1s produce IFN γ , which induces epithelial cells to release CXCL9, CXCL10 and CXCL11 that feed back to T_H1 cells and ILC1s through CXCR3. Macrophages also release pro-inflammatory cytokines IL-1 β and IL-18 following inflammasome activation and IL-6. Inhibitors of cytokines, chemokines and their receptors that have been developed to treat non-type 2 inflammation are shown. IL-17R α , IL-17 receptor- α .

unmet therapeutic need in airway disease, leading to a search for alternative anti-inflammatory treatments or, in the case of type 2 inflammation, therapies that may reverse corticosteroid resistance.

Targeting type 2 immunity

Several cytokines that promote type 2 immunity — including IL-4, IL-5 and IL-13 — have now been targeted in patients with severe airway disease and show promising effects in carefully selected patients (FIG. 1; TABLE 1).

IL-5. IL-5 plays a key role in eosinophilic inflammation as it promotes the differentiation of eosinophils from precursors in the bone marrow and also primes and prolongs the survival of eosinophils in the airways. It has therefore been a major target for inhibition in the treatment of refractory eosinophilic asthma, either by antibody blockade of the cytokine or its receptor, IL-5R α , although blocking its transcription by inhibiting GATA3 has also been attempted²¹.

When given as a single intravenous injection, mepolizumab, a humanized monoclonal blocking antibody against IL-5, induced a dose-related, rapid and pronounced reduction in circulating eosinophils, which persisted for 3 months, and a reduction in sputum eosinophils

following inhaled allergen challenge. In these patients with mild asthma, there was no reduction in the early or late response to inhaled allergen, no improvement in lung function and no reduction in airway hyperresponsiveness, indicating that eosinophils are rather unexpectedly not critically involved in these responses²². Subsequently, mepolizumab, given monthly over 6 months to patients with moderate persistent asthma who were symptomatic despite ICS therapy, provided no improvement in symptoms, lung function or quality of life and no reduction in exacerbations despite a marked reduction in blood and sputum eosinophils²³. In two subsequent studies, patients with severe asthma were selected only if they had persistent symptoms, frequent exacerbations and increased (>3%) sputum eosinophils despite maximal therapy with ICSs and long-acting β_2 -agonist (LABA); both studies showed a marked reduction (~50%) in exacerbations, and there was also a reduction in the maintenance dose of oral corticosteroids^{24,25}. However, despite these clinical improvements, there was no consistent improvement in symptoms, lung function or quality of life. Further studies of up to 12 months in carefully selected refractory patients with persistent sputum eosinophilia showed similar clinical improvements, with the larger studies also demonstrating

GATA3

A transcription factor expressed predominantly by T helper 2 cells and group 2 innate lymphoid cells that is important for their differentiation and secretion of characteristic type 2 cytokines (IL-4, IL-5, IL-9 and IL-13).

Table 1 | Clinical studies of cytokine inhibitors for airway diseases

Cytokine target	Inhibitor	Delivery	Patients	Effects	Associated diseases	Biomarkers	Refs
IL-5	Mepolizumab	Subcutaneous administration every 4 weeks	Severe type 2 asthma	• Reduced exacerbations • Reduced need for oral steroids	Nasal polyps, EGPA and (possibly) rhinitis	Blood and sputum eosinophils	22–32
	Mepolizumab	Subcutaneous administration every 4 weeks	COPD	Small reduction in exacerbations	ND	Blood eosinophils	48,49
	Reslizumab	Intravenous administration every 4 weeks	Severe type 2 asthma	Reduced exacerbations	ND	Blood eosinophils	33–37
IL-5R α	Benralizumab	Subcutaneous administration every 4 or 8 weeks	Severe type 2 asthma	• Reduced exacerbations • Reduced need for oral steroids	Nasal polyps	Blood eosinophils	40–46
	Benralizumab	Subcutaneous administration every 4 weeks	COPD	Small effect on FEV1	ND	Blood eosinophils	47
IL-13	Lebrikizumab	Subcutaneous administration every 4 weeks	Severe type 2 asthma	Small effect on FEV1	ND	Serum periostin	58,59
	Tralokinumab	Subcutaneous administration every 2 weeks	Severe type 2 asthma	No effect on exacerbations	ND	FeNO	60,61
IL-4R α	Dupilumab	Subcutaneous administration every 4 weeks	Severe asthma	• Reduced exacerbations • Reduced symptoms • Increased FEV1	Atopic dermatitis, rhinosinusitis and nasal polyps	Blood eosinophils and FeNO	62–66
TSLP	Tezepelumab	Subcutaneous administration every 4 weeks	Severe asthma	• Reduced exacerbations • Reduced symptoms • Increased FEV1	Atopic dermatitis and rhinosinusitis	Blood eosinophils and FeNO	70
TNF	Golimumab and infliximab	Subcutaneous administration every 4 weeks	Severe asthma	No effects or side effects	ND	ND	87–89
	Infliximab	Subcutaneous administration every 4 weeks	Severe COPD	No effects or side effects	ND	ND	90,92
IL-1 β	Canakinumab	Subcutaneous administration every 8 weeks	COPD	No effect	ND	ND	111
CXCR2	Navarixin	Oral administration once a day	Neutrophilic asthma	No effect	ND	Sputum neutrophils	133
	AZD5069	Oral administration once a day	Neutrophilic asthma	No effect	ND	ND	135
	Navarixin	Oral administration once a day	COPD	Minor effect on FEV1	ND	ND	134
IL-17R α	Brodalumab	Subcutaneous administration every 2 weeks	Severe asthma	No effect	ND	ND	100

COPD, chronic obstructive pulmonary disease; CXCR2, CXC-chemokine receptor 2; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, fractional exhaled nitric oxide; FEV1, forced expired volume in 1 second; IL-4R α , IL-4 receptor- α ; ND, not determined; TNF, tumour necrosis factor; TSLP, thymic stromal lymphopoietin.

Forced expired volume in 1 second (FEV1). A measure of airflow. Decreases in FEV1 reflect airway obstruction in asthma and chronic obstructive pulmonary disease and are a measure of disease severity.

small improvements in forced expired volume in 1 second (FEV1) and quality of life^{26–30}. Mepolizumab is also effective in patients with eosinophilic granulomatosis with polyangiitis (also known as Churg–Strauss syndrome), which is often associated with severe asthma, and induces prolonged remission in many patients^{31,32}.

Similar to mepolizumab, reslizumab is another blocking antibody against IL-5, and when given

intravenously every month, it has shown similar therapeutic effects to mepolizumab in selected patients^{33–35}. In patients with poorly controlled asthma and blood eosinophils that are ≥ 400 per microlitre, reslizumab led to a 75% reduction in exacerbations in patients with late-onset asthma compared with a <50% reduction in patients with early-onset asthma³⁶, but it was ineffective if blood eosinophils were <400 per microlitre³⁷.

Benralizumab is a humanized monoclonal antibody that blocks IL-5R α and is afucosylated so that it binds with high affinity to the main Fc receptor for IgG expressed by natural killer cells, macrophages and neutrophils, which results in increased eosinophil apoptosis via antibody-dependent cell-mediated cytotoxicity³⁸. It has essentially similar clinical effects to IL-5-targeted antibodies, although theoretically, it should act more rapidly, as it clears through cytotoxicity eosinophils that are already recruited to the airways³⁹. Clinical studies of patients with severe eosinophilic asthma treated with benralizumab have shown similar clinical outcomes to the anti-IL-5 antibodies^{40–44}. Although it is also effective in mild to moderate asthma by increasing FEV1, its effects are modest, and so it is unlikely to be cost-effective⁴⁵. A single dose of benralizumab given at the time of an acute exacerbation of asthma reduced subsequent exacerbation rates, especially those requiring hospitalization, during the following 3 months⁴⁶.

Anti-IL-5 treatments have also been studied in patients with COPD, and particularly in those patients with increased blood and airway eosinophils, although these are the patients who could potentially benefit from ICSs. In a 48-week trial, benralizumab treatment of patients with COPD with increased sputum eosinophils did not reduce overall acute exacerbations compared with placebo, although exacerbations and symptoms were reduced, albeit not significantly, in patients with baseline blood eosinophils of ≥ 300 per microlitre⁴⁷. In a pilot study of mepolizumab over 6 months in patients with COPD and increased sputum eosinophils, there was no improvement in symptoms or lung function or reduced exacerbations despite a marked reduction in sputum eosinophils, although this study was underpowered to show such clinical effects⁴⁸. In larger studies involving administration of 100 mg of mepolizumab every 4 weeks, there was an $\sim 20\%$ reduction in exacerbations in patients with COPD who were treated with ICSs, LABA and long-acting muscarinic antagonist (LAMA) and had a history of exacerbations. A similar reduction in exacerbations was found in a parallel study that used 100 mg and 300 mg monthly doses of mepolizumab⁴⁹. A greater effect on exacerbations was found in patients who had higher baseline blood eosinophil counts, indicating that eosinophilia may drive exacerbations in these patients.

Side effects of anti-IL-5 therapies have been rare, although clinical trials have usually been terminated after 12 months; the most frequent side effects reported are headache, nasopharyngitis and local injection reactions^{50,51}. There are no reports of anaphylaxis. Although eosinophils are important in defence against helminths and parasites, there is no evidence for any increase in these infections, although studies have mainly been conducted in countries with a low prevalence of these infections.

There have been no direct comparisons between these three approved anti-IL-5 therapies, and in patients with severe asthma and eosinophilia, they appear to be remarkably similar in terms of clinical effectiveness and safety. In this setting, they each show a reduction in acute asthma exacerbations of

around 50% and a reduced need for oral maintenance corticosteroids, but only show small improvements in symptoms, lung function and quality of life⁵². It is important to select patients with increased eosinophils who are refractory to current inhaled therapies. There is a greater clinical response in patients who have baseline blood eosinophils of ≥ 300 per microlitre, whereas increased fractional exhaled nitric oxide (FeNO) is not predictive of a good response. This is likely to reflect the fact that this treatment specifically reduces eosinophil numbers but does not target airway epithelial cells, which are the main source of exhaled nitric oxide.

All anti-IL-5 therapies are given by injection once a month, but mepolizumab and benralizumab can be given by subcutaneous injection, whereas reslizumab currently has to be given intravenously. Although benralizumab may theoretically have a more rapid onset of action, this does not appear to translate into any clinical advantage as these therapies are given long term. Anti-drug antibodies have been reported in a small proportion of patients, but it is not clear whether this reduces their clinical effectiveness. Further studies on long-term safety are needed. It has not been clearly established whether anti-IL-5 treatment is effective for allergic rhinitis, rhinosinusitis, nasal polyps or atopic dermatitis.

IL-4 and IL-13. IL-4 is important for the differentiation of T_H2 cells from undifferentiated precursors, and together with IL-13, it stimulates the secretion of IgE from B cells, promotes eosinophilic inflammation through the release of the eosinophil chemoattractant CC-chemokine ligand 26 (CCL26) from airway epithelial cells⁵³ and stimulates mucus hypersecretion, airway fibrosis and remodelling. Both IL-4 and IL-13 signal through a common receptor, IL-4R α , which leads to activation of the transcription factor signal transducer and activator of transcription 6 (STAT6)⁵⁴. Early studies with IL-4 inhibitors were disappointing in terms of clinical effectiveness in asthma, as the expression of IL-4 is low in adult patients with asthma. Most attention has therefore focused on blocking IL-13 or IL-4R α , which has the possible advantage of blocking both cytokines. Several approaches, including decoy receptors and a mutated protein (known as pitak-inra) that binds to and blocks IL-4R α , turned out to be ineffective in clinical studies of severe asthma⁵⁵, which may reflect poor target inhibition. A STAT6 inhibitor that is effective in animal models of allergy has not progressed to clinical studies⁵⁶. Several anti-IL-13 blocking antibodies have been trialled in patients with severe asthma, but many have been abandoned because of poor efficacy.

Biomarkers of responsiveness have been explored; periostin and dipeptidyl dipeptidase 4 (DPP4) are released from epithelial cells in response to IL-4 and IL-13, and so serum periostin and DPP4 levels have been used as biomarkers to predict clinical responses to anti-IL-13 therapy⁵⁷. However, periostin can also be released by epidermal cells and other cells, so it is not a specific biomarker of lung responses. IL-13 upregulates the expression of inducible nitric oxide synthase

Fractional exhaled nitric oxide (FeNO). The fractional content in exhaled breath of nitric oxide gas, which is a non-invasive biomarker of type 2 inflammation.

by airway epithelial cells, and thus FeNO has proved to be a useful biomarker to predict good responses to anti-IL-13 therapies. An IL-13-specific blocking antibody, lebrikizumab, showed a small improvement in FEV1, particularly in the patients with higher serum periostin levels, but there was no improvement in symptoms or quality of life and no reduction in exacerbations⁵⁸. In two larger phase III studies, the effects of lebrikizumab were small and inconsistent, so this drug has apparently been discontinued⁵⁹. Tralokinumab is a similar IL-13 blocking antibody. A phase II study of tralokinumab, given subcutaneously every 2 weeks to patients with severe uncontrolled asthma, showed nonsignificant improvements in asthma control or FEV1 over 12 weeks⁶⁰, and in a larger study over 52 weeks, there was no significant reduction in exacerbations compared with placebo⁶¹. The disappointing response to these treatments may reflect the fact that they target airway remodelling and mucus hypersecretion rather than eosinophilic exacerbations, and it may be difficult to measure these outcomes in relatively short-term clinical studies.

By contrast, dupilumab, which blocks IL-4R α , appears to provide greater clinical benefit than anti-IL-13 antibodies. In a study to explore its efficacy in asthma, dupilumab was found to strongly protect (by ~80%) against loss of asthma control during withdrawal of ICSs and LABA therapy in patients with moderate to severe asthma and increased blood eosinophils⁶². Subsequently, the drug was studied in patients with moderate to severe asthma that was poorly controlled on maximal inhaled therapy, and it was found to markedly reduce exacerbations (by ~80%) and improve lung function and symptoms⁶³. The clinical response appears to be irrespective of baseline blood eosinophil counts, whereas FeNO appears to be a good biomarker of response. Dupilumab is also very effective in the treatment of severe atopic dermatitis and has now been approved for the management of severe eczema^{64,65}. It is also effective in the treatment of severe nasal polyposis and rhinosinusitis⁶⁶. No studies of anti-IL-4 or anti-IL-13 antibodies have yet been reported in COPD or asthma–COPD overlap syndrome.

Anti-IL-4 or anti-IL-13 treatments appear to be well tolerated with no serious side effects. The most common side effects are headaches, nasopharyngitis and injection reactions. Dupilumab can be associated with a slight increase in susceptibility to virus infections and conjunctivitis or keratitis⁶⁵. The increased blood eosinophil levels that are seen with these treatments is of uncertain clinical significance.

TSLP. Thymic stromal lymphopoietin (TSLP) is a member of the IL-7 family and is considered to be an ‘upstream’ cytokine, as it orchestrates type 2 inflammation through the activation of dendritic cells and the release of chemokines that attract and amplify T_H2 cells and ILC2s⁶⁷. TSLP is also recognized as an alarmin that activates innate and adaptive immunity by sensing epithelial injury and is highly expressed in airway epithelial cells of patients with severe asthma⁶⁸. In patients with mild asthma, a blocking antibody to TSLP, tezepelumab, was effective in inhibiting early and late responses to

inhaled allergen and in reducing blood and sputum eosinophils, FeNO and IgE⁶⁹.

These promising preliminary results have led to larger clinical studies in severe asthma and in atopic dermatitis. In patients with severe asthma treated with tezepelumab over 12 months, there was a marked reduction in acute exacerbations, blood eosinophils and FeNO, and the drug was effective (although less so) even in patients without increased blood eosinophils⁷⁰. Because this approach inhibits inflammation upstream of T_H2 cells, it may be more effective than inhibition of individual type 2 cytokines, as it should inhibit the IL-5 and IL-4–IL-13 pathways in parallel.

TSLP expression levels are also increased in epithelial cells in COPD and rhinosinusitis^{68,71}. In the limited clinical studies so far reported, there are no substantial adverse effects but long-term studies are needed in view of the potential reduction in immune defences associated with this target. Another approach is to target its receptor, TSLP receptor (TSLPR; also known as CRLF2), and IL-7R α ⁷².

Other potential cytokine targets. IL-25 and IL-33 are other cytokines associated with type 2 immunity that are potential targets for asthma treatment. IL-25 (also known as IL-17E) is an alarmin that amplifies and sustains type 2 responses⁷³. It is secreted predominantly by airway epithelial cells and regulates T_H2 cell and ILC2 function. It is a member of the IL-17 family and inhibits IL-17 receptors to suppress IL-17A-mediated effects and also interacts positively with TSLP. It is an upstream cytokine that may be a target for inhibition in the future⁷⁴. IL-25 expression is increased in airway epithelial cells of patients with asthma, is correlated with greater type 2 responses and predicts a good therapeutic response to corticosteroids⁷⁵, but its role in severe asthma is uncertain⁷³.

IL-33 is another epithelial alarmin that promotes type 2 immunity and is released upon epithelial injury, and unusually for a cytokine, it is localized to the nucleus. IL-33 appears to play a critical role in amplifying type 2 immunity in a mouse model of allergic asthma that is abrogated by blocking either IL-33 or its receptor protein ST2 (also known as IL-1RL1)^{76,77}. IL-33 expression is increased in airway epithelial cells of patients with asthma⁷⁸. IL-33 and its receptor are therefore logical targets for inhibition⁷⁴.

IL-33 and ST2 expression levels are increased in epithelial cells by cigarette smoke exposure in mice, and the inflammatory effects of cigarette smoke are reduced by an anti-IL-33 antibody⁷⁹. IL-33 shows increased expression in airway epithelial cells and circulating T cells from patients with COPD, suggesting that anti-IL-33 treatments would also be useful in patients with COPD, particularly those with eosinophilia, and in patients with asthma–COPD overlap syndrome⁸⁰. IL-33 blocking antibodies, such as AMG-282, and ST2 blocking antibodies, such as CNTO-7160, are now in early clinical development.

Granulocyte–macrophage colony-stimulating factor (GM-CSF) is important for the production and differentiation of macrophages and neutrophils and for the survival of neutrophils and eosinophils in the airways. GM-CSF concentrations are increased in sputum of

Alarmin

A type of molecule that is released from damaged cells and activates the immune system. In airway disease, alarmins released from airway epithelial cells include IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), which activate type 2 immunity.

patients with asthma or COPD, and it is produced by airway epithelial cells and macrophages⁸¹. A blocking anti-GM-CSF monoclonal antibody (KB003) was tested in patients with severe asthma that could not be controlled with ICSs and LABA, but small increases in FEV1 were not statistically significant, and there was no improvement in asthma control over the 24-week assessment period⁸². However, there was a greater improvement in the lung function of patients with increased blood eosinophils (>300 per microlitre) and this may reflect the fact that GM-CSF is important for eosinophil survival in the airways. GM-CSF may also be a therapeutic target in COPD, as it may maintain neutrophilic inflammation in the airways and stimulate pro-inflammatory macrophage differentiation in the lungs.

GATA3. Type 2 cytokine expression by T_H2 cells and ILC2s is regulated by the transcription factor GATA3, which therefore has a central role in coordinating type 2 immunity and is a target for inhibition⁸³. In experimental asthma in mice, inhibition of GATA3 by antisense oligonucleotides suppresses allergic inflammation⁸⁴. GATA3 in human T_H2 cells is potentially inhibited by corticosteroids and also by p38 mitogen-activated protein kinase (MAPK) inhibitors⁸⁵. Inhibiting a transcription factor in human airways is challenging, but recently, an inhaled DNzyme, ST010, which binds to and inactivates GATA3 mRNA, has been shown to reduce early and late immune responses to inhaled allergen in patients with mild asthma after 28 days of administration, although the reduction in sputum eosinophils was not statistically significant⁸⁶. Whether these small effects could be increased by higher doses or a more effective delivery system is not certain, and no long-term studies have been reported.

Targeting neutrophilic inflammation

Although most attention in treating airway diseases has focused on targeting type 2 immunity and eosinophilic inflammation, other inflammatory patterns involving macrophages and neutrophils are seen in the majority of patients with COPD and in some patients with severe asthma. So far, inhibiting type 1 or type 3 inflammation in airway disease has not shown clear clinical benefit, although these same therapies have been effective in other chronic non-eosinophilic inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease and psoriasis. Non-type 2-driven inflammation is usually corticosteroid insensitive, so there is an even greater unmet need than for type 2-driven inflammation. Several cytokines are involved in driving neutrophilic inflammation, including tumour necrosis factor (TNF), IL-17 and IL-23, but there are no consistent biomarkers in plasma, and sputum neutrophil counts are highly variable. As discussed below, targeting neutrophilic inflammation has so far not provided any clinical benefits in either asthma or COPD.

TNF. There is a good scientific rationale for using anti-TNF therapies for severe asthma and COPD, as concentrations of TNF are increased in the airways and it amplifies neutrophilic inflammation and activates macrophages. In small pilot studies in patients with

severe asthma, a TNF soluble receptor (etanercept) improved airway hyperresponsiveness⁸⁷ and, in an uncontrolled study, asthma symptoms⁸⁸. An anti-TNF antibody (infliximab) reduced exacerbations in patients with moderate asthma, although the study was not powered sufficiently to make definite conclusions⁸⁹. In a larger study lasting 12 months in patients with severe asthma, there was no reduction in exacerbations or improvement in lung function or in symptoms after administration of another anti-TNF therapy (golimumab), whereas side effects, such as sepsis, were more common than with placebo, and the trial had to be terminated early⁹⁰.

In patients with severe COPD, treatment with infliximab over 6 months did not give any improvement in symptoms or lung function or reduce exacerbations, and it was associated with increased pulmonary infections and possibly increased risk of lung cancer⁹¹. An epidemiological study in patients with rheumatoid arthritis treated with anti-TNF who also had COPD, showed some reduction in COPD exacerbations with etanercept but not with infliximab⁹². TNF levels are increased in the circulation of patients with COPD, and this may be related to cachexia and skeletal muscle wasting, but a small study of infliximab in patients with cachexia and COPD failed to show any clinical benefit in the lungs or muscles⁹³. Thus, anti-TNF strategies do not appear to be of value and have unacceptable adverse effects in severe airway disease.

IL-17. IL-17A and IL-17F are highly expressed in the airways of patients with severe asthma compared to those with mild to moderate asthma⁹⁴, and the presence of increased numbers of IL-17F-expressing cells correlates with neutrophilic inflammation and frequent exacerbations in patients with severe asthma⁹⁵. These cytokines are predominantly released by T_H17 cells and ILC3s, which also express IL-22 and are regulated by the transcription factor RORγt. T_H17 cells are linked to neutrophilic inflammation, as IL-17 induces the release of neutrophil chemotactic chemokines such as CXC-chemokine ligand 1 (CXCL1) and CXCL8 from airway epithelial cells, attracting neutrophils into the airways⁹⁶.

T_H17 cells are also increased in the airways of patients with COPD⁹⁷, and sputum IL-17 and IL-22 concentrations are increased in patients with COPD, particularly in severe disease⁹⁸. An anti-IL-17 antibody protects mice against cigarette smoke-induced emphysema⁹⁹. IL-17A and IL-17F are therefore good therapeutic targets in severe neutrophilic asthma and in COPD, particularly as patients with increased T_H17 cells and IL-17 are steroid resistant¹⁰⁰. Although anti-IL-17 therapies have been widely used in the treatment of neutrophilic inflammatory disease, such as psoriasis and inflammatory bowel disease, these approaches have barely been explored in neutrophilic airway disease.

Brodalumab is an antibody that targets IL-17Rα, thus blocking the effects of both IL-17A and IL-17F, and has been studied in patients with severe asthma. However, there was no improvement in lung function, symptoms or quality of life following administration of brodalumab¹⁰¹. Unfortunately, the patients in this trial were not selected for neutrophilic inflammation, so a beneficial effect may have been missed. In patients with

COPD, an IL-17 blocking antibody, CNTO-6785, did not improve FEV1 or symptoms over 6 months¹⁰². Despite these results, other clinical studies of anti-IL-17 therapies in more carefully selected patients with neutrophilic asthma and COPD are warranted.

IL-23 is an important regulator of T_H17 cells and may be a more upstream target than IL-17 (REF.¹⁰³). IL23 knockout and IL-23-blocking antibodies in mice prevent the development of elastase-induced emphysema¹⁰⁴. Ustekinumab and other IL-23-blocking antibodies have been used to treat psoriasis and inflammatory bowel disease¹⁰⁵. Risankizumab, which is more effective in the treatment of psoriasis than ustekinumab¹⁰⁶, is currently in clinical trial in severe asthma¹⁰⁷.

Targeting pro-inflammatory cytokines

IL-1. IL-1 β levels are increased in severe asthma and COPD, and similar to TNF, IL-1 β has pro-inflammatory effects and is associated with macrophage activation and neutrophilic inflammation. Levels of the endogenous cytokine IL-1 receptor antagonist protein (IL-1RA) are reduced in asthma and recombinant IL-1RA (anakinra) has been suggested as a potential therapy, although a clinical study apparently had negative results¹⁰⁸. Activation of the NLRP3 inflammasome leads to the release of IL-1 β , and this has been suggested to occur in severe asthma and COPD¹⁰⁹. However, the NLRP3 inflammasome does not appear to be activated in chronic COPD, although it may be activated in acute exacerbations¹¹⁰. An IL-1 blocking antibody, canakinumab, which is effective in some IL-1-driven diseases, such as Muckle–Wells syndrome, is ineffective in patients with COPD¹¹¹. A recent study showed that canakinumab administered subcutaneously every 3 months to patients with coronary artery disease and systemic inflammation reduced cardiac events, indicating the potential for targeting systemic inflammation in COPD¹¹².

IL-18 is similar to IL-1 β and is also generated by the NLRP3 inflammasome. It releases IFN γ from T cells and is pro-inflammatory¹¹³. Circulating IL-18 is counteracted by an endogenous binding protein, IL-18 binding protein (IL-18BP). Administration of recombinant IL-18 induces emphysema in mice, and IL-18 levels are increased in sputum of patients with COPD and correlate with disease severity, so IL-18 has been considered to be a good target for inhibition^{114,115}. IL-18 is produced in high amounts by myeloid cells within lymphoid follicles in the lungs of patients with COPD and is the main driver of increased IFN γ production¹¹⁶. A blocking antibody to IL-18 (GSK1070806) appears to be well tolerated but has not been tested in airway disease¹¹⁷. IL-18BP administration is another means of inhibiting IL-18.

Other cytokines. IL-6 is a pleiotropic cytokine that amplifies inflammation and promotes T_H2 cell-mediated and T_H17 cell-mediated immunity. IL-6 expression levels are increased in severe asthma and COPD sputum and plasma¹¹⁸ and may mediate some of the systemic effects seen in COPD and worsen comorbidities. Blocking IL-6 with a humanized antibody (tocilizumab) to its receptor, IL-6R, is effective in the treatment of rheumatoid arthritis but so far has not been studied in severe asthma or COPD^{119,120}.

Targeting chemokines

There has been great interest in the development of chemokine antagonists to treat inflammatory airway diseases, as they are involved in the recruitment of macrophages, neutrophils and eosinophils into the lungs and play an important role in regulating dendritic cell activity and local immunity¹²¹. Several chemokines have overlapping functions and can target the same receptor, so blocking chemokine receptors may have multiple effects on the inflammatory process, but there is a lot of redundancy. Another benefit of targeting chemokine receptors is that the drugs may be given orally, as they need to interact with chemokine receptors on circulating cells and therefore may reach peripheral airways and the lung parenchyma more easily than via the inhaled route.

CCR3. CCL11 is a selective attractant for eosinophils through binding to CC-chemokine receptor 3 (CCR3), and it is expressed by epithelial cells of patients with asthma. Related chemokines, including CCL24, CCL26 and CCL5, also interact with CCR3, making it an attractive target for inhibition¹²². CCR3 antagonists are effective in mouse models of allergic inflammation and prevent allergen-induced accumulation of eosinophils in the airways¹²³. CCR3 and its ligands are highly expressed in the airways of patients with asthma¹²⁴. Although many small molecule CCR3 antagonists have been developed, none have been approved, owing to toxicological problems, and no clinical trial of a CCR3 antagonist has been reported¹²⁵. One CCR3 antagonist, named UCB35625, reduced eosinophil chemotaxis in vitro, but this drug was never developed for clinical studies¹²⁶. An antisense therapy, which targets CCR3 and the common β -chain of the receptor for IL-3, IL-5 and GM-CSF, reduced sputum eosinophil responses after allergen challenge and had a small inhibitory effect on the early response to allergen, but there was no reduction in CCR3 expression¹²⁷.

CXCR2. CXCL8 is secreted by macrophages, T cells, epithelial cells and neutrophils and is chemotactic for neutrophils via high affinity binding to CXC-chemokine receptor 2 (CXCR2). CXCR2 is also activated by the related CXC-chemokines CXCL1 and CXCL5, both of which are increased in induced sputum of patients with COPD and increase even further during exacerbations¹²⁸. CXCL1 concentrations are markedly increased in sputum and bronchoalveolar fluid of patients with COPD and may be more important than CXCL8 as a chemo-attractant, acting through CXCR2, which is expressed predominantly on neutrophils and monocytes¹²⁹. CXCL8 is also increased in patients with severe asthma who have a neutrophilic pattern of inflammation¹³⁰.

Several small molecule CXCR2 antagonists have been developed and shown to substantially reduce sputum neutrophils in healthy individuals after challenge with ozone and lipopolysaccharide^{131–133}. In COPD, an oral CXCR2 antagonist (navarixin) given to patients over 6 months reduced sputum neutrophils by about 50% and produced a small increase in FEV1, an effect that was greater in current smokers than ex-smokers, but there was no improvement in symptoms or reduction

NLRP3 inflammasome
Intracellular multiprotein complex containing NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3), which leads to activation of caspase 1 and the generation of IL-1 β and IL-18 from precursors. It is a component of the innate immune system and activated by several inflammatory signals.

Muckle–Wells syndrome
Rare autosomal dominant disease that causes periodic fever and is associated with NLRP3 inflammasome activation and increased production of IL-1 β .

in exacerbations¹³⁴. In patients with severe neutrophilic asthma, a pilot study of navarixin given over 4 weeks did not improve asthma control or lung function¹³⁵. In a study of patients with severe uncontrolled asthma, another oral CXCR2 antagonist (AZD5069), given for 6 months in three different doses, failed to improve asthma control or reduce exacerbations¹³⁶. Another CXCR2 antagonist (danirixin) has also been developed for clinical use¹³⁷.

Although the CXCR2 antagonists are well tolerated, there was a reduction in peripheral neutrophil counts that was severe in some patients and led to discontinuation of the therapy. There was no evidence for increased pulmonary infections in patients with COPD, which is a concern in patients who are chronically colonized with bacteria^{134,138}. The apparent failure of CXCR2 antagonists, even in selected patients, is uncertain but may be due to insufficient effects on neutrophil recruitment.

Several other chemokines (such as CXCL9, CXCL10, CXCL11, CCL2, CCL5, CCL17 and CCL22) show higher expression levels in patients with airway disease than controls^{129,139,140}, and various small molecule antagonists of their receptors (such as CXCR3, CCR1, CCR4 and CCR5) have been developed^{141–145}. However, to date, these antagonists have either not been suitably tested in airway disease or failed to show any clinical benefit.

Insights from cytokine inhibition

The recent availability of cytokine inhibitors to treat asthma has raised issues about how the most appropriate patients are selected for these expensive therapies and how they should complement existing treatments. It has become clear that, although asthma and COPD are usually distinctive syndromes, there is considerable overlap. Rather than treating each disease separately, it is important to identify inflammatory phenotypes that are treatable, such as type 2-associated versus non-type 2-associated disease, which may be neutrophilic or show no increase in inflammation. This is a step towards the implementation of precision medicine in the management of airway diseases.

As more specific cytokine inhibitors become available, it will be important to develop biomarkers that predict responsiveness to therapy. In the case of IL-5 inhibitors, measuring sputum eosinophils appears to be predictive, but this is difficult to do in clinical practice. Blood eosinophils are more easily measured and appear to be good predictors of response to anti-IL-5 therapy⁵². However, before considering this therapy, it is important to be certain that patients are adherent to ICS therapy, and many patients with disease identified as steroid-resistant refractory eosinophilic asthma will respond to corticosteroids, although the doses required may be unacceptably high¹⁴⁶.

Furthermore, anti-IL-5 therapy alone is unlikely to be sufficient, as it has weak effects on symptoms and lung function, so additional anti-inflammatory therapy and bronchodilators might also be needed. Responses to anti-IL-13 therapies seem to be better predicted by increased FeNO levels than blood eosinophils⁶³, whereas anti-TSLP therapy is effective irrespective of increased eosinophils or FeNO⁷⁰. Blood eosinophils may also predict which patients with COPD may respond to corticosteroids, which should be given in adequate doses before

considering the much more expensive anti-IL-5 therapy¹⁴⁷. However, the clinical benefit of anti-IL-5 therapy together with corticosteroid therapy in eosinophilic COPD remains to be demonstrated convincingly.

The use of inhibitors of specific cytokines has demonstrated that specific cytokines are more predominant in some patients than in others that have an apparently similar clinical presentation. The reason why one cytokine drives inflammation in one patient but not another is poorly understood, but it may relate to a different tissue response that may be determined by genetic and epigenetic factors. For non-type 2 airway inflammation, there are fewer therapeutic options available, but it is important to select patients with low blood eosinophils and normal or low FeNO.

Because of the need for long-term administration of cytokine therapies, side effects need to be carefully evaluated in view of the altered immune response. Local injection site reactions have sometimes occurred, but anaphylaxis is very uncommon. Clinical studies in carefully selected patients have usually only lasted for a year, so long-term safety needs to be assessed in clinical practice now that some of these treatments have been approved for prescription. There are concerns about long-term immune defences against infections, such as helminths, parasites and viruses, with the use of inhibitors of type 2 immunity and against bacteria and viruses with the use of inhibitors of non-type 2 immunity that target neutrophilic inflammation.

Biomarkers. Clinical studies have shown that patient selection is very important for obtaining a good response, implying that biomarkers that predict a good clinical response are very important. Blood eosinophil levels appear to be a good predictor of responses to anti-IL-5 therapies, whereas FeNO is a better predictor of responses to anti-IL-4 and anti-IL-13, and both blood eosinophils and FeNO predict responses to anti-TSLP. With anti-IL-4 and anti-IL-13 therapies, patients without eosinophilia also show a useful clinical response. For patients with non-type 2-associated airway disease, biomarkers have been less useful. It is possible that sputum neutrophils may be good predictors, but blood neutrophils are of no value as they are not increased in neutrophilic lung disease.

There is no doubt the cytokine inhibitors will change the management of airway disease in the future. Anti-IL-5 therapies have already been approved and are very valuable in patients with severe asthma and eosinophilia, particularly when patients are maintained on doses of oral corticosteroids that cause considerable long-term side effects. More and more cytokine inhibitors will become available over the next few years, and selecting the right drug for the right patient will be critical. In the future, more potent inhibitors may be developed, and this will reduce the injection volume and hopefully the costs of this treatment so that they may be used more widely. It is possible that if used earlier in treatment, these therapies may be disease-modifying and potentially could limit the disease by interrupting positive feedback loops that maintain chronicity.

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