Mechanisms, diagnosis and management of eosinophilic asthma

Abstract

Asthma is a common chronic airway disease affecting about 334 million people worldwide, and up to 10% of asthma patients have severe asthma, which may be uncontrolled despite high doses of the standard treatment modifiers and may require the use of chronic oral corticosteroids. It is the most common chronic disease in children in the developed countries. Asthma manifests as reversible airflow obstruction, due to airway inflammation, bronchial smooth muscle contraction, increased mucus secretion, vascular engorgement, mucosal oedema, and airway hyper responsiveness, which leads to airflow obstruction and symptoms of asthma. Eosinophilic asthma is a phenotype of asthma that is usually very severe and persistent, with frequent exacerbations. It is usually observed in adult asthmatic patients, although it may occur in children. It is characterized by the presence of high levels of eosinophils, and CD+4 Th2 cells in the lungs and airways, which can be demonstrated by a raised eosinophil count in blood, and induced sputum or bronchial biopsy. It is managed in a similar stepwise treatment for childhood-onset asthma, but some of the patients with eosinophilic asthma do not respond to this standard treatment including inhaled or oral corticosteroids. The logical approach to treat corticosteroid-refractory asthma is to target the eosinophilic interleukins which cause airway inflammation using monoclonal antibodies to block their activity on the eosinophils, and Th2 cells. Currently, the following monoclonal antibodies are used in the treatment of eosinophilic asthma: IgE antibody such as omalizumab, or interleukin receptor 5, or 4, and 13 antagonists, such mepolizumab, reslizumab, and dupilumab. These novel agents have proved to be very useful in relieving the symptoms, and in improving the forced expired volume in one second (FEV1), and in reducing exacerbations. They are also steroid-sparing agents, and improve the quality of life in this debilitating phenotype of asthma.

Keywords: eosinophilic asthma, asthma phenotypes, inflammatory mediators, monoclonal antibodies, interleukin receptor antagonists

Introduction

Asthma is a common chronic airway disease affecting about 334 million people worldwide, and its prevalence has been increasing during the last 40 years, and by 2025, there will be about 400 million people suffering from asthma.1,2 It is the most common chronic respiratory disease in children in the developed countries,3 and its prevalence is steadily increasing in the developing world. Asthma is characterized by reversible airflow obstruction, due to airway inflammation, bronchial smooth muscle contraction, increased mucus secretion, vascular engorgement and mucosal oedema, and airway hyper responsiveness (AHR), which leads to airflow obstruction.4 Airway obstruction and bronchospasm leads to the symptoms of asthma which include wheezing, coughing, dyspnoea, and chest tightness.

The pathophysiology of asthma is complex, it is a heterogeneous disease with several different phenotypes, including eosinophilic asthma, neutrophilic asthma, paucigranulocytic asthma, and childhood-onset asthma. It involves imbalance between T-helper type 2 (Th2) lymphocytes and Th1 lymphocyte-driven airway inflammation, switching the balance towards the Th2 pathway.1,8 Th2-driven inflammation leads to production and liberation of an array of inflammatory mediators such as histamine, prostaglandins, leukotrienes, cytokines and chemokines.9 Table 1 shows the inflammatory mediators responsible for the pathophysiology of asthma.

| Table 1 Inflammatory mediators of Th2-driven asthma |
|-------------------|-------------------|-------------------|
| Histamine          | Leukotrienes (LTB4, LTC4, LTD4, LTE4) |
| Eicocanoids (PGD2,TXB2) | Cytokines (Interleukin-1), IL3, IL-4, IL-5, L-12, IL-13, IL-23, IL-33) |
| Thymic stromal lymphopoietin (TSLP) | Chemokines (MCP-1, MCP-3, MCP-4, RANTES, eotaxin) |
| Neurokinins (NK1) | Enzymes (tryptase) |
| Neutrophil chemotactic factor | Neutrophil myeloperoxidase |
| Platelet activating factor |

Abbreviations: IL, interleukin; LT, leukotriene; PG, prostaglandins; Th, thromboxane; MCP, monocyte chemotactic protein

Abbreviations: AHR, airway hyper responsiveness; FEV1, forced expired volume in one second; Th2, T-helper type 2; ILs, interleukins; ILC2s, innate lymphoid cells; GATA-1, GATA-binding protein 1; c/EBP; CCAAT-enhancing binding protein; VCAM-1, vascular cell adhesion molecule-1; MBP, major basic protein; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EDFX, eosinophil-derived peroxide

Keywords: eosinophilic asthma, asthma phenotypes, inflammatory mediators, monoclonal antibodies, interleukin receptor antagonists

References:

1. Nightingale Syabbalo, Professor of Medicine and Physiology, Copperbelt University, M. C. Sata School of Medicine, P.O. Box 30243, Lusaka, Zambia, Tel +260 966 486117, Email: nightingal@gmail.com

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The cytokines, especially interleukins (ILs) produced by activated Th2 lymphocytes include: IL-3, IL-4, IL-9, IL-13 which activates mast cells, and IL-3 and IL-5 which activates eosinophils. The activated mast cells and eosinophils further generate inflammatory mediators which perpetuate and amplifies the airway inflammatory process, and causes more bronchospasm. On the other hand, Th1 cells secrete IL-2 and interferon-γ, whilst group 2 innate lymphoid cells (ILC2s) are activated by the action of IL-4, and IL-33. The transformed Th2 cells further liberate inflammatory mediators, thus causing a vicious airway inflammatory process. Th2 cytokines play a pivotal role in the pathophysiology of allergic disease, including asthma. Apart from activating mast cells and eosinophils, they also take a crucial part in the inflammatory cascade.

It is well now well recognized that asthma is a complex and diverse disease with several phenotypes or endotypes, and each of these phenotypes has a characteristic pathophysiological pathways and clinical presentation. Eosinophilic asthma is one of the well-defined clinical phenotype of asthma. It is usually a debilitating, severe and persistent disease, with frequent exacerbations and a worse quality of life, and has a poor prognosis. Patient with eosinophilic asthma experience significant limitation in lung function, frequent hospitalizations and are at higher risk of death. This subgroup of patients impart a disproportionate pharmacoeconomical burden, with the mean UK annual treatment costs reaching between £2912 and £4217 per patient. The disease is usually observed in adult asthmatic patients, although it may occur in children. It is characterized by a high eosinophil count in blood and in induced sputum, airway eosinophilia infiltration, and high IgE and peristinserum levels. Serum IgE and peristin levels are markers of eosinophilic inflammation.

The airway inflammation in eosinophilic asthma is due to degranulation of eosinophils activated by cytokines released by Th2 cells, dendritic cells, mast cells, and basophils. This results in the release of several pro-inflammatory mediators, including cytotoxic cationic proteins, histamine, prostaglandins, leukotrienes, cytokines, chemokines, and growth factors. Table 2 shows the list of inflammatory mediators released by eosinophilic during allergic inflammation.

### Table 2 Eosinophil-derived inflammatory mediators

| Major basic protein (MBP) | Eosinophil cationic protein (ECP) | Eosinophil-derived neutrotoxin (EDN) | Eosinophil-derived peroxidase (EDPX) |
|--------------------------|----------------------------------|-------------------------------------|-----------------------------------|
| Prostaglandins (PGE2)    | Leukotrienes (LTC4, LTD4, LTE4)  | Cytokines (IL-2, IL-3, IL-4, IL-5, IL-9, IL-13, IL-23, IL-25, IL-33, and TNFα) | Chemokines (CXC-, CC-, CX3C, and XC) |
| Enzymes (elastase)       |                                   |                                     | Enzymes (elastase)                 |
| Growth factors (TGFβ, VEGF, and PDGF) |                           |                                      |                                   |

**Abbreviations:** IL, interleukin; chemokine nomenclature depends on the spacing of conserved cysteines, where X is any amino acid

Cytokines such as IL3, IL-5, IL-4, IL-12, IL-13, IL-23, IL-33, and thymic stromal lymphopoietin (TSLP) play a critical role in orchestrating, perpetuating, and amplifying the respiratory response in asthma. Cytokines cause bronchial smooth muscle contraction, mucus secretion, microvascular leakage and airway oedema. All of these pathophysiological processes lead to airway narrowing and bronchoconstriction. Long-term effects of the cytokines, particularly due to IL-13, include goblet gland hyperplasia, smooth muscle hypertrophy, airway remodeling, and bronchial hyperreactivity.

Th2 lymphocyte and eosinophil cytokines possess overlapping biological activities; they can synergize or antagonize the effects of other cytokines. For example, IL-5, IL-4, IL-13, and IL-33 are the key drivers of the inflammatory process in asthma; and IL-4 and IL-13 are central Th2 cytokines with distinct overlapping roles, particularly in airway remodeling and bronchial hypersensitivity. Similarly, interferon-γ, a Th1 cytokine acts in conjunction with Th2 cytokines (IL-3, IL-4, and IL-5) in maintaining chronic airway inflammation in patients with asthma.

**Eosinophils**

The eosinophil was first described by Paul Ehrlich in 1879, after he developed eosin which colored basic protein bright red. It was identified as eosinophil in an autopsy of a 48-year-old male patient who died of status asthmaticus by Dr. Fraenkell in 1900. Eosinophils are polymorphic nuclear cells and they normally constitute about 2.3% of all blood leukocytes. They are slightly larger than neutrophils, about 10-16μm in diameter, and are characterized by a nucleus with usually two lobes, and large cytoplasmic granules that stain deeply red after staining with eosin, using the Romanowsky method. Eosinophils and other leukocytes are formed from bone marrow CFU-GM progenitor cells during myelopoiesis. The pluripotent myeloid progenitor cells give rise to CD34+ IL-5α eosinophil progenitor cells. The differentiation of eosinophils is regulated by transcription factors GATA-binding protein 1 (GATA-1), PU.1, and the CCAAT-enhancing binding protein (c/EBP) family. IL-5, IL-3, and GM-CSF synergistically contribute to the development of mature eosinophils. After been released from the bone marrow, they mature in the circulation and migrate to tissues where they live for 2-5 days. Their life span may be extended depending on tissue cytokines, particularly IL-4, IL-5, and IL-13 which prevent them from apoptosis. Eosinophils are weak phagocytes, and exhibit chemo taxis, and diapedesis. They appear to be used selectively for fighting helminthparasitic infections, particularly intestinal nematodes (Ancylostomahudenulace); tissue-dwelling nematodes (filarial worms); trematodes (Schistosoma haematobium and S. mansoni); and cestodes (Taeniasaginata, and Diphyllolothriumlatum). The cationic proteins secreted by the eosinophils, particularly major basic protein, and eosinophilic cationic protein produce ballooning and detachment of the tegmental membrane, complete fragmentation and complete disruption of the large multicellular helminth parasites. Eosinophilishave a special propensity to collect in tissues in which allergic reactions occur, such as the peribronchial tissues of the lungs in people with asthma, and in the skin after an allergic reaction. Mast cells and basophils release an eosinophil chemotactic factor that causes eosinophils to migrate toward the inflamed allergic tissue such as the bronchial mucosa.

Eosinophils play a pivotal role in the pathogenesis of asthma.
They possess a wide repertoire of surface adhesion molecules and receptors such as cytokine and growth receptors, lipid mediator receptors, chemotactant receptors, adhesion receptors, and Fc receptors. Eosinophilic inflammatory activity is regulated by several Th2 cytokines, including IL-5, IL-3, IL-4, IL-13, IL-33, IL-17, IL-25, and TSLP.

Interleukin-5 is a homodimeric cytokine (115 amino acids per chain) that belong to the haematopoietic growth factor cytokine family, which also include IL-3 and GM-CSF. Interleukin-5 stimulates production, proliferation, and differentiation of eosinophils from myeloid progenitor cells in the bone marrow. Peripherally, it participates in the terminal maturation of the eosinophil in the circulation, recruitment and activation in the lungs, and is important for eosinophil survival. It plays an important role in diapedesis of eosinophils by facilitating endothelial adhesion, and promotes chemotaxis. Adhesion receptor such as integrins allow cell such as the eosinophil to adhere to the extracellular matrix and other cells plays a major role in eosinophilic migration. They also allow the eosinophil to sense their surrounding and respond accordingly.

IL-4 plays a key role in eosinophilic inflammatory response, which include induction of the IgEisotype switch, expression of vascular cell adhesion molecule-1 (VCAM-1), differentiation of Th2 lymphocyte leading to cytokine release, mucus secretion, and promoting eosinophil transmigration across the endothelium. In addition IL-4 and IL-13 drive the trafficking of eosinophils to sites of allergic inflammation. It is very important in activating eosinophils, and leads to eosinophil degranulation and release of inflammatory mediators.

Upon activation, eosinophilicdegranulaterelase an array of cytotoxic cationic proteins, such as major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), eosinophil-derived peroxide (EDPX). In addition, they release a plethora of mediators including prostaglandins, leukotrienes, cytokines, chemokines, enzymes and reactive oxygen species. Eosinophilssynthesize and release several interleukin, such as IL-3, IL-4, IL-5, IL-9, IL-13, IL-15, IL-23, IL-25, IL-33, and TSLP. These inflammatory mediators orchestrate, and amplify bronchial smooth muscle contraction, microvascular leakage and airway oedema, mucus secretion, and goblet gland hyperplasia. The cationic proteins (MBP, ECP, EDN, and EDPX) are very cytotoxic to the airway epithelium and myelinatedneurons, and they cause epithelial and neuronal injury, and damage. EDPX form reactive oxygen species and reactive nitrogen metabolites that promote oxidative stress, causing cell death by apoptosis and necrosis of epithelial cells. In addition the eosinophilic inflammatory mediators lead to airway epithelial injury, smooth muscle hypertrophy, airway remodeling, and airway hyperresponsiveness.

IL-13 is a pleiotropic Th2 cytokine that has been shown to be central in the pathogenesis of asthma. It is a key inflammatory cytokine, it causes goblet cell differentiation, mucus secretion, elevation of bronchial hyper responsiveness, and switching of B cell antibody production from IgG to IgE. Interleukin-13 also causes activation of fibroblasts and sub endothelial fibrosis and eosinoph production. The eotaxins (1, 2, 3) subfamily of chemokines and their CCR3 chemo kinase receptor have coordinated interaction with IL-13 in the pathogenesis of asthma. They are involved in the recruitment, and in inducing eosinophilic degranulation. Eotaxin-2, and eotaxin-3 are associated with persistent eosinophilic bronchial inflammation in patients with asthma after allergen challenge.

The bronchial epithelial cytokines (‘alarmins’), IL-33, IL-25, and TSLP play an important role act in activating innate lymphoid cells (ILC2s) in an antigen independent manner through their receptors (IL-17 receptor B (IL-17RB), ST2, and TSLP receptor (TSLPR). These cytokines, particularly IL-25 and IL-33 have been implicated in the airway remodeling process. Airway structural changes can result in a loss of elastic recoil with increased lung compliance, most pronounced at the peri-bronchiolar level, resulting in irreversible obstruction. IL-33 a member of the IL-1 family, in particular, triggers eosinophils to release their cytotoxic pro-inflammatory mediators, and superoxide generation. This result in a vicious cycle of inflammation promoting further airway epithelial cell injury, and inflammation, which can progress to chronic eosinophilic inflammation.

Activated innate lymphoid cells (ILC2s) or Th2 cells produce large amounts of IL-5 and IL-13, which can lead to mucus hyper secretion, airway hyper responsiveness, and both cytokines are capable of inducing eosinophilic airway inflammation independent of T-cells. ILC2s have also been shown to be essential for the persistence of eosinophilic asthma. IL-33 is a central regulator of immunologic reaction. Up regulation of IL-33 results in activation of IL-13, which in turn activates Th2 cells, dendritic cell, eosinophils, and basophils, leading to the release of a cascade of mediators.

One of the best approaches to treat eosinophilic asthma is to block the actions of interleukins which are important in eosinophils production, proliferation, differentiation, activation, and survival. This will reduce eosinophil numbers and function, and the release of the injurious inflammatory mediators.

**Clinical features**

Eosinophilic asthma is a severe refractory disease which occurs in about 4% of adult patients with asthma. The disease has no gender preponderance in the distribution. Eosinophilic asthma usually manifests in early adulthood with a peak incidence between 20 to 35 years. The classical symptoms include recurrent episodes of wheezing, breathlessness, chest tightness, and cough. The symptoms are usually worse at night (nocturnal asthma). Cough is a frequent symptom particularly in children and it may be mistaken for an upper respiratory tract infection or bronchitis. Precipitating factors include viral upper respiratory tract infection, exercise particularly in cold weather, exposure to pollutants such as cigarette smoke, SO2, NO2, and ozone, and medications (Table 3). The drugs which are likely to precipitate asthma include beta-blockers, even when administered topically as eye drops, e.g., timolol for glaucoma, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). Other medications include oral contraceptives, cholinergetic agents, and prostaglandin F2α.

There is a tremendous variation in the frequency and duration of the attacks. Some patients have one or two attacks per year, but the majority of the patients have severe frequent exacerbations which may last for weeks. Some patients have chronic symptoms. Patients with mild asthma are usually asymptomatic between exacerbations, whereas patients with persistent asthma have symptoms of breathlessness and wheeze most of the time, particularly in early mornings.

Apart from displaying the above clinical features, patients with eosinophilic asthma have unique clinical presentation, which differ greatly from those of the classical symptoms of childhood-onset, allergic asthma. This phenotype of asthma is rarely precipitated by allergens such as grass pollen, pet dander allergens, and...
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Dermatophagoidespteronyssinus compared to childhood-onset asthma.\textsuperscript{19} Eosinophilic asthma is very easily provoked by exertion or exercise, and patients with eosinophilic or late-onset asthma are very sensitive to aspirin, and may have co morbid aspirin exacerbated respiratory disease.\textsuperscript{40} Clinically the disease is very severe with frequent exacerbations to near fatal asthma which requires frequent hospitalization.\textsuperscript{17–21,41} Patients have a poor quality of life and the prognosis of the disease is poor.\textsuperscript{17–21}

**Table 3** Causes and precipitating factors for eosinophilic asthma

| Viral upper and lower respiratory infections |
|--------------------------------------------|
| Rhinovirus                                  |
| Parainfluenza virus                         |
| Respiratory syncytial virus                 |

**Occupational sensitizers**

| Isocyanate                                  |
| Colophony fumes                             |

**Atmospheric pollution**

| Sulphur dioxide, nitrogen dioxide           |
| Ozone                                      |
| Irritant dusts, vapour and fumes           |
| Cigarette smoke                            |
| Perfumes                                   |

**Exercise**

| Food anaphylaxis                           |
| Shrimps, peanuts, wheat allergy           |

**Medication**

| Aspirin, non-steroidal anti-inflammatory drugs |
| β2-blockers                                   |
| Angiotensin-converting enzyme (ACE) inhibitors |

**Aeroallergens (rare)**

| Dermatophagoides                           |
| Grass pollen                               |
| Domestic pet dander                        |
| Cockroaches                                |

Eosinophilic asthma is often associated with chronic rhino sinusitis and nasal polyposis, which should be treated.\textsuperscript{42} Treatment of these co morbidities, is associated with improvement in asthma symptoms. Additionally, patients with eosinophilic asthma have persistent airflow obstruction characterized by constantly very low forced expired volume in 1 second (FEV1).\textsuperscript{43} As a result of fixed low FEV1, and FEV1/FVC ratio, eosinophilic asthma may be misdiagnosed as chronic obstructive pulmonary disease (COPD).

The disease is difficult to treat with the standards-of-care asthma controlmedicines and can require the use of high dose inhaled corticosteroids or oral corticosteroids, thus, it is also referred to as corticosteroid-refractory disease or “difficult asthma”.\textsuperscript{44} The patients may require large doses of oral corticosteroids which may cause the numerous serious side-effects from the glucocorticoids.

**Investigations**

The diagnosis of asthma is predominantly clinical and based on a characteristic history. It is supported by measurement of pulmonary function. Spirometry should be performed in all patients suspected of having asthma. It shows an obstructive pattern characterized by a low FEV1 and the FEV1/FVC ratio, and a reduction inflow rates at 25% to 75% of the vital capacity (FEF\textsubscript{25-75}). If possibly, a methacholine or histaminebronchoprovocation test should be performed in order to demonstrate airway hyperreactivity.\textsuperscript{45,46} Both the American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommend a reduction of 10% or more in FEV1 or PEF in the laboratory as criterion for the diagnosis of asthma.\textsuperscript{47,48} A post-bronchodilator response to β2-agonists such as salbutamol may be required in patients with bronchospasms to assess reversibility. The criterion for a bronchodilator response recommended by the ERS is a 12% increase in FEV1, expressed as a per cent predicted after inhaled bronchodilator or a 200ml increase in FEV1 (Table 4).\textsuperscript{47}

**Table 4** Drugs for the treatment of asthma

| Inhaled β2-agonist                      |
| Short acting (salbutamol, levalbuterol, terbutaline, pirbuterol) |
| Long-acting (salmeterol, formeterol)    |

**Combination of LABA and inhaled corticosteroids**

| Salmeterol and fluticasone (AdvairDiskus) |
| Formeterol and budesonide (Symbicort)    |

**Cromones**

| Cromlyn sodium, nedocromil sodium       |

**Inhaled anti-cholinergics**

| Short-acting (ipratropium bromide)      |
| Long-acting (oxitropium bromide, tiotropium bromide) |
| New long-acting (aclidium bromide, glycoprronium) |

**Corticosteroids**

| Betamethasone dipropionate              |
| Budenoside, fluticasone, flunisolone    |
| Ciclesonide, mometasone                 |

**Oral methylxanthines**

| Rapid release theophyllines            |
| Sustained release theophyllines (Theo-24, Theocron, Uniphyl) |

**Leukotriene receptor antagonists**

| Montelukast, pranlukast                |
| Cinalukast, zafirlukast                |

**5-lipoxygenase inhibitors**

| Zileuton                                 |

Patients with eosinophilic asthma are very likely to develop exercise-induced asthma because of the association of the disease with chronic rhino sinusitis and nasal polyposis,\textsuperscript{29} which impair air conditioning by the nasal apparatus. Exercise spirometry may be an adjunct test in this phenotype of asthma to document exercise-induced bronchoconstriction (EIB). Eosinophilic asthmatic patients have very
variable and frequent attacks of asthma, ideally they should have peak flow charts, recording the peak expiratory flow rates (PEF) on waking, in the middle of the day, and before bed.

Specific tests for eosinophilic asthma include eosinophil count in blood (≥300 cells/µL) and induced sputum (≥2%), serum IgE (≥250 kU/L), and exhaled fraction of nitric oxide (FeNO). FeNO can also be used to monitor the response to treatment with ICSs. Serum periostin levels can be measured which is a signature of IL-13 and eosinophilic inflammation. Periostin is an extracellular matrix protein belonging to the fasciclin family, which contributes to airway remodeling in patients with eosinophilic asthma. Periostin serum levels have been described as the best predictor of sputum eosinophilia, and can be used to monitor response to treatment.

There are no diagnostic features of asthma on chest roentgenogram in stable patients. Due to the severity of eosinophilic asthma, a chest X-ray is necessary to exclude hyperinflation and barotraumas including pneumothorax and pneumomediastinum. Hospitalized patients with severe asthma require oximetry monitoring, and blood gases analysis.

Management

The goals of asthma treatment are to achieve disease control. Poor control is linked with recurrent asthma attacks which is associated with poor future control. Like any other individuals with asthma, patients with eosinophilic asthma should be treated according to the BTS/SIGN guidelines, or the ERS/ATS guidelines. Patients with uncontrolled asthma should have their treatment intensified by escalating up the treatment steps until control is achieved for at least 3 months. Corticosteroids are the mainstay therapy for patient with severe, recurrent disease. However, about 10-20% of the patients do not achieve symptoms control despite high doses of inhaled corticosteroids up to 2000µg/day, and require chronic use of oral corticosteroids. It is important to try to achieve control without resorting to oral steroids which are linked with osteoporosis, adrenal suppression, hypertension, hypercholesterolemia, cataract, weight gain and diabetes.

This subgroup of patients with eosinophilic asthma or corticosteroid-refractory asthma requires an additional or alternative therapeutic agent in order to achieve disease control. The underlying pathophysiology of asthma is airway inflammation and hyper responsiveness due to inflammatory mediators release by activated mast cells, dendritic cells, TH2 lymphocytes and eosinophils. The best strategy for the treatment of eosinophilic asthma is to suppress the production, proliferation, differentiation and activation of eosinophils, which play a pivotal role in the airway inflammatory process. Interleukins, particularly, IL-5, IL-4, IL-13, IL-33, and TSLP play an important role in fostering eosinophilic function, chemotaxis and survival. Monoclonal antibodies and interleukin receptor antagonists (ILRAs) have been developed which target interleukins, with the aim of providing precision tailored treatment for patients with eosinophilic asthma. Table 5 shows the list of some of the mAbs and ILRAs currently available, and in clinical trials for the treatment of eosinophilic asthma, and corticosteroid-refractory asthma.

Immunoglobulin E released by activated mast cells, basophils and eosinophils plays an important role in the pathophysiology of the allergic inflammation in patients with asthma. Monoclonal antibodies targeted against IgE, such as omalizumab have been shown to attenuate both the early- and late-phase responses to inhaled allergens in patients with asthma.

| Table 5 Monoclonal antibodies and interleukin receptor antagonists, and their target |
|-----------------|-----------------|------------------|
| **Agent**       | **Target**      | **Stage of Development** |
| Omalizumab      | IgE             | Marketed 2003     |
| Mepolizumab     | IL-5            | Marketed 2015     |
| Reslizumab      | IL-5            | Marketed 2016     |
| Benralizumab    | IL-5R           | Marketed 2017     |
| Dupilumab       | IL-4c (IL-4/IL-13) | Marketed 2018   |
| Tezepelumab     | TSLP            | Marketed 2018     |
| Pitrakinra      | IL-4c (IL-4/IL-13) | II                     |
| Lebrikizumab    | IL-13           | III               |
| Tralokinumab    | IL-13           | III               |
| Secukinumab     | IL-17           | II                |
| Brodalumab      | IL-17RA         | II                |

Omalizumab

Omalizumab (Xolair®) was the first monoclonal antibody to be approved by the U. S. Food and Drug Administration (FDA) for the treatment of severe asthma in 2003. Xolair is a recombinant humanized monoclonal antibody to IgE, and is directed against the binding of IgE for its high affinity FcεRI receptor. It binds with the Fe portion of IgE and forms omalizumab: IgE complex. This reduces free IgE and prevents serum IgE from attaching to the FcεRI receptors on mast cell, basophils and eosinophils. This prevents release of inflammatory mediators by these cells. In addition, omalizumab treatment indirectly reduces FcεRI receptor on cells involved in the allergic responses.

Clinical trials using omalizumab treatment in patients with severe eosinophilic asthma has shown to reduce airborne and blood eosinophils counts, and reduce exacerbations in most patients with asthma. Treatment with subcutaneous omalizumab has also shown to improve asthma control, and improve health-related quality of life (HRQoL). It has also been shown to reduce the need for rescue medication, allow patients to reduce or discontinue their ICSs and/or OCSs, safety profile. Patients need to be monitored for severe allergic reactions after the injection at a medical centre where health care professionals are available to treat the adverse reactions. It is safe and well tolerated. The most common side effects include injection site reaction, respiratory tract infection, pharyngitis, sinusitis, arthralgia, myalgia, muscle weakness, headache, and rarely anaphylaxis. Unfortunately, some patients with eosinophilic asthma do not get symptom relief with the addition of omalizumab to their treatment regimen, and may require an add-on treatment with another mAB, which target other airway inflammatory pathways.

Mepolizumab

Mepolizumab (Nucala®) is a fully humanized IgG1 monoclonal antibody, it binds to IL-5 and prevents binding to the α-chain of the IL-5 receptor. It was the first anti-IL-5 therapy to be tested in a clinical trial in 2000. The first clinical trial of mepolizumab showed a reduction in sputum and blood eosinophil count but no change in bronchial hyper responsiveness, and no effect on the late asthmatic response. Subsequent clinical trials revealed reduction in exacerbation...
rates, and improvement in asthma symptom questionnaire (ACQ) scores.64, 65 Finally, Ortega and colleagues,66 showed that treatment with mepolizumab decreases the rate of exacerbations, improved the FEV1, and reduced the dosage and use of oral corticosteroids, thus demonstrating a steroid-sparing effect. Convincingly, mepolizumab has been shown to improve the ACQ scores, FEV1, reduce the rate of exacerbations, and reduce the dosage of corticosteroid or use of other drug modifiers.64–66 Mepolizumab was approved by the FDA in March 2013 for the treatment of eosinophilic asthma. It is recommended at a dosage of 100mg subcutaneously every 4 weeks. It is well tolerated and it has been found to be safe. The most common adverse effects with Nucala are: injection site reaction, headache, backache, fatigue, muscle weakness, and rarely severe allergic reactions. Patients need to be monitored after treatment.

**Reslizumab**

Reslizumab (Cingair®) was approved by the FDA on March 23, 2016 as an add-on maintenance therapy in adult patients with severe asthma. It is a humanized monoclonal antibody that target IL-5. The monoclonal antibody has an ERRR configuration (glutamine, arginine, arginine, arginine) corresponding to amino acids 89-92 on the IL-5 antibody molecule. This region is critical for its interaction with the IL-5 receptor which results into inhibition of its bioactivity.67 Clinical trials with reslizumab has been shown to significantly decrease sputum eosinophil count, and to improve asthma control questionnaire scores.68 In the subsequent studies, reslizumab treatment has been shown to improve the FEV1 as early as 4 weeks after initiating therapy.69,70 It also resulted in larger reductions in exacerbation rates, especially in patients who had repeated exacerbations 12 months prior to the initiation of therapy. The treatment also reduced the use of rescue inhalers. Bjerrmerand associates,71 have shown that therapy with reslizumab results in significant increase in pulmonary function, improvement in self-reported asthma control, and quality of life. The approved dosage for reslizumab is 3mg/kg intravenously over 20-50minutes every 4weeks for patients 18 years and above. It is safe and well tolerated by the patients. The most common side effect of Cingair include headache, nasopharyngitis, myalgia, and fatigue. Anaphylaxis occurs in about 0.3% of the patients,72 and the U.S.Food and Drug Administration recommends that patients should be observed in a setting where health care professionals are available to treat the adverse reactions.

**Benralizumab**

Benralizumab (Fasenra)73 is a fully humanized IgG4 monoclonal antibody to the IL-4 receptor. The IL-4 receptor is composed of the IL-4Rα chain and the IL-13Rα1 chain and mediate signaling in both IL-4 and IL-13.74Dupixentinhibits both IL-4 and IL-13 receptor subunits.75 IL-4 and IL-13 are key cytokines that contribute to the Th2-driven eosinophilic inflammation that lead to moderate-to-severe asthma. In the clinical trials, treatment with dupilumab was associated with reduction in inflammatory biomarkers including fraction exhaled nitric oxide (FeNO), serum immunoglobulin E (IgE), and eotaxin-3 (CCL26).76 Dupixent has been shown to significantly reduce severe exacerbations by 67%, improve lung function (FEV1) by29%‒33%, morning and evening symptoms and asthma control in patients with moderate-to-severe eosinophilic asthma. The FEV1 was improved after 2 weeks of treatment and was maintained through week 12, despite the patients not taking LABA and inhaled corticosteroids.77 In Phase 2b trial, dupilumab reduced the daily use of oral corticosteroids by 70% compared 42% with placebo. More than half of the patients treated with the drug completely eliminated the use of oral corticosteroids.78 Dupilumab was approved by the Committee for Medicinal Products for Human Use of the European Medicines Agent (EMA) on October 19, 2018, at 5.55PM, as an add-on maintenance therapy in patients with moderate-to-severe asthma, and eosinophilic asthma aged 12 years and older. It is also approved by the U.S. Food and Drug administration, and for patients with oral corticosteroid-dependent asthma. Dupixent is available as a single-dose pre-filled syringe and is administered subcutaneously under the guidance of a healthcare provider. It comes in two doses (200mg and 300mg) given on alternating weeks at different injection sites after an initial loading dose. Dupixent is also approved by the FDA for the treatment of adults with moderate-to-severe atopic dermatitis. The most common adverse effects of dupilumabinclude injection site reaction, upper respiratory tract infection, pharyngitis, sores in the mouth and lips, eye and eyelid inflammation, and rarely anaphylaxis. Patients should be observed after the treatment in a setting where health care professionals are available to treat the adverse reactions.

**Tralokinumab**

Interleukin-13 signaling plays an important role in the pathogenesis
of asthma, and pharmacological agents have been developed to target its activities. The IL-13 receptor is a complex assembly of both IL-4 and IL-13 receptor subunits. Tralokinumab is a humanized IgG4 monoclonal antibody to IL-13, it is currently in phase III clinical trials. In the STRATOS1 clinical study, which enrolled 120 patients, tralokinumab reduced annual asthma exacerbation rates (AAER) in participants with an FeNO higher than 37ppm, but there was no change in the primary end-points in the STRATOS 2 study which enrolled 856 patients with inadequately controlled despite use of ICSs (500µg per day fluticasone). Tralokinumab failed to meet the end points of three Phase III studies testing its efficiency in treating asthma. However, it induces significant clinical improvement in patients with moderate to severe atopic dermatitis.

**Lebrikizumab**

Lebrikizumab is a humanized IgG4 monoclonal antibody that binds to IL-13 and blocks its action. In the LAVOLTA I and LAVOLTA II clinical trials which enrolled 1081 and 1067 patients respectively with poorly controlled asthma, treatment with lebrikizumab 37.5mg and 125mg subcutaneously reduced exacerbation rates in patients with high periostin levels (>50ng/ml), but not in patients with normal or low periostin levels. Unfortunately, pooled data did not consistently show significant reduction in exacerbations in biomarker-high patients, and clinically relevant changes could not be ruled out. Periostin is a downstream IL-13-induced protein derived from the airway epithelial cells, and it may be useful in monitoring patients with eosinophilic asthma. Probably, lebrikizumab may be suitable in some patients with severe eosinophilic asthma with elevated periostin levels.

**Tezepelumab**

Thymic stromal lymphopoietin (TSLP) is a member of the 4-helix bundle cytokine, most closely related to IL-7. During allergic inflammation, the primary producers of TSLP are epithelial cells, stromal cells, and keratinocytes, although recent data have documented that dendritic cell, and mast cell are capable of producing TSLP. TSLP acts in concert with IL-33, and IL-25 and plays an important role in the pathogenesis of eosinophilic asthma. TSLP signaling pathway is mediated through its complex heterodimeric receptor formed by a TSLP-specific TSLPR subunit (CRLF2) and the IL-7α signaling chain. The TSLP receptor is expressed broadly on a wide range of haematopoieticcells, and non-haematopoietic cells, including dendritic cells, CD4+ and CD8+ T cells, B cell, mast cells, basophils, eosinophils, innate lymphoid cells, natural killer cells, and epithelial cells. These cells are capable of generating and releasing a plethora of inflammatory mediators, which can orchestrate and perpetuate the allergic inflammatory response.

Several studies have shown that patients with asthma have increased concentration of TSLP in their lungs, and this correlates with the severity of the disease. Factors known to be involved in either the development of asthma, or exacerbation of asthma by inducing expression of TSL, include inflammatory cytokines (IL-1β, IL-4, IL-13, IL-25, and TNFα), and respiratory viruses, e.g., respiratory syncytial virus, microbes, trauma and inflammation. This may cause exacerbations of asthma or persistent eosinophilic asthma, which may not respond to corticosteroids or any other drug modifier.

Tezepelumab is a first-in-class human anti-thymicstomally mphpoieticmAb, which inhibits the inflammatory activity of TSLP. Blocking TSLP may prevent release of pro-inflammatory cytokines including IL5, IL-5, IL-13, and IL-33 form Th2 cells, mast cells, dendritic cells, basophils, and eosinophils, and attenuate the inflammation process. Due to its multiple pathways in the inflammatory cascade, tezepelumab may be suitable for a broad population of patients with severe uncontrolled asthma irrespective of patient phenotype or Th2 biomarker status. In PATHWAY Phase 2b clinical trial, tezepelumab given every four weeks subcutaneously at doses of 70mg (low), 210mg (medium); and 280mg (high) every two weeks, was shown to result in significant improvement in Asthma Control Questionnaire-6 (ACQ-6) scores, and AQLQ scores at medium and high dosages. It was also shown to reduce asthma exacerbations by 62%, compared to placebo, and improvement in prebronchodilator FEV1. These effects were observed independent of baseline eosinophil count or other Th2 inflammatory biomarkers. It was approved by the U.S. Food and Drug Administration on September 7, 2018 at 02.00 ET, for the treatment of moderate-to-severe uncontrolled asthma in adults. The common adverse events of tezepelumabare asthma-related, nasopharyngitis, bronchitis, and headache.

**Other biological agents**

There are several “biologics” currently in clinical trial targeting the broad range of interleukins and other cytokines and chemokines, such as atirikrina, brodalumab and secukinumab. Brodalumab and secukinumab targets IL-17, a signature cytokine implicated in the pathophysiology of neutrophilic asthma.

**Remarks**

However, the important question is: Where do these novel therapeutic agents fit in the classic BTS/SIGN stepwise treatment cascade of asthma? One would assume that, patients with documented eosinophilic asthma should be treated as an add-on with annAb or an ILRA at step 3, and any other patient with severe asthma or recurrent exacerbations should be offered the treatment at step 4. Another group of patients who are likely to benefit from mAbs and ILRAs therapy include patients with corticosteroid-refractory asthma, and those with chronic rhino sinusitis and nasal polyposis. Early use of these agents might avoid the usage of large doses of oral corticosteroids, and reduce the adverse effects due to steroids.

**Conclusion**

Asthma is a complex heterogeneous chronic airway disease characterized by airway inflammation, hyper responsiveness, and airway remodeling. There are several different phenotypes of asthma which include eosinophilic asthma. Eosinophilic asthma is a very severe disease with recurrent exacerbations, poor quality of life, and has a worse prognosis. It is difficult to treat with the current stepwise therapy including oral steroids. Alternative tailored treatment for this subgroup of patients include blockade of the cytokine inflammatory mediators such as IL-5, IL-4, IL-13, and IL-33, which orchestrate and perpetuate the inflammatory response. The newly introduced arsenal for the treatment of eosinophilic asthma include monoclonal antibodies, e.g. omalizumab, and interleukin receptor antagonists such as mepolizumab, and reslizumab. These agents have been shown to improve the asthma control questionnaire scores, reduced the rate of exacerbations, improve pulmonary function, and the quality of life.

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Conflicts of interest
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