Role of Interleukin-5 in the Pathophysiology and Treatment of Eosinophilic Asthma

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Abstract

Asthma is a heterogeneous chronic airway disease with several distinct phenotypes characterized by different immune pathological pathways, clinical features, disease severity, physiology, and response to treatment. Approximately 50

Index terms— eosinophilic asthma, cytokines, interleukin-5, monoclonal antibodies.

1 Introduction

sthma is a significant public health problem, affecting more than 358 million individuals globally, 1 and its prevalence has been increasing during the last 40 years. [1][2][3] It is the most common chronic respiratory disease in children in developed countries, **??** and its prevalence is steadily increasing in the developing world. **??** Asthma is a chronic inflammatory airway disease with several distinct phenotypes, characterized by different immunopathological pathways, clinical presentation, severity of the disease, and response to treatment. [6][7][8][9][10][11] There are several clinical, molecular, and immunogenetic phenotypes of asthma, 12,13 but the phenotypes of asthma can be simply classified into four phenotypes using induced sputum cytometry. 7,14 The phenotypes of asthma include eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic asthma. 7 Eosinophilic asthma has elevated sputum eosinophil count ?3%, 7,[14][15][16] whereas neutrophilic asthma has elevated sputum neutrophil count between ?61%, 15 and ?64%, 16 depending on the study. Mixed granulocytic phenotype is characterized by increase in both sputum eosinophils (>3%), and neutrophils (>61% or >64%). 15 Paucigranuocytic phenotype includes patients with very few eosinophils (<3%), and neutrophils (<61% or <64%) in induced sputum. 7,15,17 Non-eosinophilic asthma is the term used to classify patients with low eosinophil numbers (<3%), which include neutrophilic asthma, and paucigranulocytic phenotype. 7 Eosinophilic airway inflammation play a key role in the pathophysiology of eosinophilic asthma. Activated eosinophils secrete granular cytotoxic cationic proteins, such as major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, eosinophil-derived peroxide, and reactive oxygen species. The cytotoxic cationic proteins lead to epithelial injury, inflammation and airway remodeling. Additionally, eosinophils can synthesize and secrete a plethora of inflammatory mediators, such as leukotrienes, prostaglandins, cytokines, chemokines, and growth factors, which orchestrate eosinophilic airway inflammation, and airway hyper responsiveness (AHR).

Eosinophilic asthma is regarded at T helper 2 (Th2)-driven phenotype. Th2 cytokines, such as interleukin-5 (IL-5), IL-4, IL-13, IL-25, IL-33, and thymic stromal lymphopoitein (TSLP), play a very important role in the pathophysiology of eosinophilic asthma. Interlukin-5 plays a pivotal role in the proliferation, differentiation, migration, activation, and survival of eosinophils. Together with IL-4, IL-13, IL-25, IL-33, and TLP, it is responsible for airway eosinophilic inflammation, sub epithelial basement membrane fibrosis, extracellular matrix protein deposition, and airway smooth muscle (ASM) cell hyperplasia and hypertrophy.

Most patients with stable eosinophilic asthma are responsive to the step-wise guideline therapies, including high dose inhaled corticosteroids (ICS), longacting ?-2 agonists (LABA), and leukotriene receptor antagonist (LTRA). 1, **??**8,19 However, there is a sub-group of severe asthma patients with increased airway allergic inflammation despite treatment with high-dose ICS or oral corticosteroids (OCS), and their inflammatory biomarkers remain high even after corticosteroid injections. 20 This sub-group of patients with eosinophilic and steroid-resistant asthma require alternative targeted therapies such as interleukin antagonists (ILA), and bronchial thermoplasty.

2 II.

3 Eosinophils

Eosinophils play a pivotal role in the pathogenesis and severity of asthma, and other allergic diseases such as allergic rhinitis, atopic eczema, 21 and eosinophilic granulomatosis with polyangiitis. 22 The eosinophil was first described by Paul Ehrlich in 1879, after he developed the fruorescent dye eosin which coloured basic protein bright red. 23 Hematologic ally, it was identified as eosinophil in an autopsy of a 48-yearold male patient who died of status asthmaticus by Dr. Fraenkel in 1900. 24 In 1953, Houston, et al. 25 demonstrated that patients dying from status asthmaticus had airway mucosa infiltration by activated eosinophils. Thereafter, Bousquet and colleagues, 26 reported that patient with chronic asthma had an increase in eosinophils in peripheral blood, bronchoalveolar lavage (BAL) fluid, and lung biopsy specimens.

Eosinophils are polymorphonuclear cells, with a diameter of about 10-16 ?m, and constitutes 1-4% of circulating white blood cells. They have a nucleus usually with two lobes, and have large cytoplasmic granules that stain beautifully deeply red after staining with eosin, using the Romanowsky method. 27 They have a very short life span of about 1-6 hr in the circulation, but can live longer in allergic inflamed tissues, such as lungs and airways.

Eosinophils and other leukocytes are formed from bone marrow CFU-GM progenitor cells during myelopoiesis. 28 The pluripotent myeloid progenitor cells give rise to CD34+ IL-5R? eosinophil progenitor cells, which by the actions of haematopoietic factors, growth factors, and cytokines lead to eosinophils maturation. 28,29 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. 30 GATA-1 seems to have the most important role, because disruption of GATA1 gene in mice results in a strain completely without eosinonophils. 29 Interleukin-4 is essential, because of its requirement to the Th2 cell commitment, and activation via stimulation of key transcription factors, such as GATA3 and STAT6. 31 Interleukin-5, IL-3, and GM-CSF synergistically contribute to the development of mature eosinophils, and other leucocytes, through induction of bcl-xl expression. 29 Interleukin-5 is the most specific and central cytokine in eosinophils, and basophils biology. It plays a key role in eosinophilic proliferation, differentiation, and the release of eosinophils from the bone marrow into the blood stream, acting synergistically with eotaxin-1, -2, and -3. 31 Eotaxin-1 (CCL11) is a specific chemo attractant of eosinophils and stimulates migration of CD34+ progenitor cells, and release of eosinophils into the peripheral blood, and accumulation in the lungs. 32,33 Eotaxin-1 and its receptor CCR3, may be involved in the survival and other immunological functions of eosinophils. 31 Migration of eosinophils from the vasculature into lung tisssue is facilitated by eosinophils-specific adhesion molecules, such as ?1 intergrin very late antigen (VLA-4), the vascular cell adhesion molecule (VCAM-1), and the P-selectin glycoprotein ligand (PSGL-1). 34 VLA-4 is an integrin which is expressed on the membrane of eosinophils after stimulation by eotaxin-1. It ligands with the VCAM-1 integrin expressed on the vascular membrane, resulting in the activation and firm adhesion to eosinophils. Thus, facilitating eosinophil diapedesis through the endothelium into lung tissues. 34 Recruitment and migration of eosinophils into the airway mucosa is mediated by coordinated action of cytokines, such as IL-5, IL-4, and IL-13, and chemokines, eotaxins-1 (CCL11), eotaxin-2 (CCL24), and eotaxin-3 (CCL26), RANTES, and MCP1/4. [34][35][36] In particular, eotaxin-1 and its receptor CCR3, play an important role in driving eosinophils into allergic inflamed tissues in the airways. Leukotriene C4 (LTC4) is one of the most potent eosinophil chemo attractact, and is also involved in eosinophil recruitment and cascade. Table **??** summarizes the physiological functions of IL-5 in eosinophil immunobiology.

Eosinophils exhibit chemotaxis, and diapedesis, but they are weak phagocytes. They appear to be used selectively for combating helminth parasitic infections, 37,38 such as Strongyloides stercolis; Schistosoma haematobium and S. mansoni; Taenia saginata; and Diphyllobothrium latum. However, they also play an important immunological role in viral infections, especially respiratory viral infections. 39 III.

4 Eosinophil Surface Receptors

Eosinophils possess a wide repertoire of surface adhesion molecules and receptors, for cytokines, chemokines, and growth factor receptors, lipid mediators receptors, chemo attractant receptors, adhesion receptors, Toll-like receptors, and Fc?R1 receptors. [40][41] **??**42] **??**43] **??**44] Eosinophilic signaling and inflammatory activity is regulated via cytokines, chemokines, leukotrienes and prostaglandins secreted by Th2 cells, ILC2s, mast cells, and basophils through their respective receptors on the surface of eosinophils.

Eosinophils express the Fc?R1 receptor for immunoglobulins (Ig), IgE, IgG, IgA, IgM, and IgD, which serves a key role in allergic inflammatory responses.

During allergen exposure, the high-affinity Fc?R1 tetramer (????) receptor on the surface of eosinophils interact with the Fc portion of the IgE molecule leading to activation and degranulation of eosinophils, and release of cationic proteins and other mediators. **??**4 The most important cytokine receptor on the surface of eosinophils is the heterodimer IL-5 receptor, which plays a key role in eosinophil immunopathology. **??**4, **??**5 Eosinophils also express other cytokine receptors, including IL-4, IL-13, IL-17, IL-25, IL-33, and TSLP, and growth factor receptors, such as transforming growth factor-?. The above cytokines play a synergistic role in the pathophysiology of eosinophilic asthma.

IV.

5 Eosinophil Mediators

Activated eosinophils either by allergic and nonallergic pathways, undergo autolysis and release an array of eosinophil-specific granules found in the extracellular DNA traps. ??6 The most predominant bioactive mediators released from the granules are the four cytotoxic cationic proteins, such as major basic protein (MBP), eosinophil cationic protein (ECP), eosinophilderived neurotoxin (EDN), eosinophil-derived peroxide (EDPX), and reactive oxygen species. ??4, ??4, ??7, ??8 Major basic protein, ECP, and EDPX are toxic to a number of cells, including airway epithelial cells, ??9 and ASM cells, and contribute to airway hyper responsiveness (AHR). ??0 Eosinophil-derived neurotoxin, and ECP belong to the RNAase A family of granule proteins that have ribonuclease activity. ??1 They are associated with host defense against viruses, and may play a role in tissue remodeling. ??1 Eosinophil-derived neurotoxin is toxic to nerves, 52 whereas eosinophil peroxidase produce reactive oxygen species, and reactive nitrogen intermediates, which promote oxidative stress in tissue, causing cell death by apoptosis and necrosis. ??9 Eosinophils can synthesize and release a plethora of inflammatory mediators, including lipidderived mediators, such as histamine, cysteinyl leukotrienes, prostaglandins, thromboxanes, and PAF; cytokines, chemokine, enzymes, and growth factors. ??3, ??4 Leukotrienes and prostaglandins promote airway smooth muscle contraction, mucus secretion, vasodilatation and edema formation, which lead to airway obstruction. ??4 They also activate mast cells and basophils through their receptors to secrete more histamine, prostaglandins, and leukotienes, thus amplifying the eosinophilic inflammatory responses. ??5 Additionally, eosinophils synthesize and secrete several Th2 and ILC2 cytokines, such as IL-3, IL-4, IL-5, IL-9, IL-13, IL-15, IL-23, IL-25, IL-33, GM-CSF, TNF-?, and GM-CSF. Interleukin-5, IL-13, and GM-CSF secreted by eosinophils promote eosinophilic function and survival in an autocrine fashion. ??3 Interleukin-13, and IL-25 are pro-fibrotic cytokines which lead to subepithelial basement membrane fibrosis, deposition of extracellular matric proteins, airway remodeling, and fixed airflow limitation. Th2 cytokines, such as IL-5, IL-4, IL-13, IL-25, IL-33, and TSLP are responsible for airway eosinophilia, AHR, and remodeling. They promote airway smooth muscle (ASM) cell proliferation and hypertrophy, amplify ASM cell contraction, and lead to sub mucous glands and goblet cell hyperplasia and mucus hyper secretion. Eosinophils also secrete growth factors, such as TGF-?, VEGF, IL-13, and enzymes, including MMP-9, and TIMP-1 which are responsible for the development of ASM hypertrophy and sub epithelial fibrosis, hence, severe fixed airflow obstruction, 57 and corticosteroid resistance. Table ?? shows the list of proinflammatory mediators synthesized and secreted by activated eosinophils.

V.

6 Cytokines

Pro-inflammatory cytokines play a central role in the pathophysiology of allergic diseases, such as eosinophilic asthma. ??8 The cytokines implicated in the pathophysiology of eosinophilic asthma are derived mainly from Th cells. ??8 The other sources of cytokines include, mast cells, basophils, eosinophils, 45,59,60 dendritic cells, natural killer cells, and NK T cells. ??61] ??62] ??63] ??64] Novel T cells, such as ILC2, Th9, Th17, Th22 cells, Treg cells, and nuocytes, 64,65 and structural cells including epithelial cells, fibroblasts and airway smooth muscle cells can also produce cytokines and chemokines. ??1 Notably, there is cross-talk between eosinophils and mast cells, and the cytokines and chemokines networks in orchestration the allergic inflammatory responses. ??0, ??6 Each of these cells produce an array of cytokines and chemokines which promote secretion of more cytokines by the other inflammatory cells, thus establishing paracrine and even autocrine positive feedback loops.

Th2 lymphocyte, ILC2s, mast cell, 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, IL-25, and IL-33 are the key drivers of the inflammatory process in eosinophilic asthma; and IL-4 and IL-13 are central Th2 cytokines with distinct overlapping roles, particularly in airway remodeling and bronchial hyperresponsiveness. ??8 Similarly, interferon-?, 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. The most important cytokines in the pathophysiology of eosinophilic asthma include IL-5, IL-4 IL-13, IL-25, IL-33, and TSLP. IL-5 is the regarded as the master minder cytokine. activated by dendritic cells in response to allergens, and inflammatory mediators. 72 Interleukin-4 is essential for the promotion of Th2 cell differentiation from naive T helper cells (Th0), and activation of Th2 cells leading to the production and release of cytokines, such as IL-4, IL-5, IL-13, IL-25, IL-33, and TSLP. ??2 The differentiation of Th2 cells is transcribed by GATA-3 acting as a master signaling factor, 62,73 and STAT6 serving as a key transcription factor. 73 IL-5 secretion from ILC2 is also dependent on GATA-3 activation induced by epithelilal "alarmin" cytokines, such as IL-25, IL-33, and TSLP. 73 Interleukin-5 is a cytokine composed of 134amino acid proteins that form a 52-kDa homodimer. [74][75][76] It belongs to the haematopoietic growth factor cytokine family, which also include IL-3 and GM-CSF. 74 It is highly specific for eosinophil formation, 77 by stimulating the production, proliferation, and differentiation of eosinophils from myeloid progenitor cells in the bone marrow. 78,79 IL-5 also aids in the extrusion of eosinophils from the marrow. Peripherally, IL-5 participates in the terminal maturation of the eosinophil in the circulation. Interleukin-5 is important in the recruitment and activation of eosinophils in the lungs, and for eosinophil survival by preventing apoptosis. It plays a critical role in diapedesis of eosinophils by facilitating endothelial adhesion, and promotes chemotaxis in inflamed lung tissues. 80 The interleukin-5 receptor is a heterodimer composed of a specific subunit, IL-5R?, and a separate motif for binding to the signaling subunit, ?c, of the receptor. 76,79 The IL-5R? is specific to IL-5 binding, whereas the ?c chain also binds to IL-3, and GM-CSF. 76,79 The IL-5R? subunit is expressed

about threefold on eosinophils compared with basophils. 80,81 Binding of IL-5 to the IL-5 receptor triggers activation of a complex intracellular signaling involving JAK1/2 and STAT1/3/5 modules, p38 and ERK MAP kinases, and NF-k? transcription factor. 82 JAK2, and Lyn and Raf-1 are involved in eosinophil survival by preventing apoptosis, and Raf-1 is specifically involved in stimulating eosinophil activation and degranulation. 82,83 Another IL-5 signaling pathway include activation of intracellular kinases, such as phosphoinositide 3-kinase (PI3K), and mitogenactivated ptotein kinases (MAPK). 83,84 Through NFdependent mechanism, p38 MAPK up-regulates eosinophil recruitment into allergic airways, and activates synthesis of pro-inflammatory mediators, including cytokines, chemokines, and leukotrienes, and prostaglandins. 85,86 These mediators orchestrates airway eosinophilic inflammation, subepethelial reticular membrane fibrosis, submucous gland hyperplasia and mucus secretion, and ASM cell proliferation, hyperplasia and hypertrophy.

InterleukinL-5 and its receptors (IL-5R?, CD125) expressed on the surface of eosinophils, basophils, and a subset of mast cells cells are the central players responsible for airway eosinophilia. Therefore, targeting IL-5 or its receptor subunit IL-5R? is a logical approach for add-on treatment of severe difficult-to-treat eosinophilic asthma, and corticosteroid-resistant asthma phenotypes. [87][88][89] There are currently two marketed IL-5 monoclonal antibodies (mAb) targeted against IL-5 (mepolizumab, and reslizumab), and one mAb targeted against IL-5R? (benralizumab). Interleukin-5 antagonists bind to distinct epitopes of IL-5 interfering its binding to IL-5 receptors expressed on the surface of eosinophils. Anti-IL-5R antibodies also induce targeted-cell lysis and have been shown to reduce circulating eosinophil counts rapidly.

VII.

7 Mepolizumab

Mepolizumab (Nucala ®) is an N-glycosylated IgG1/k humanized monoclonal antibody formed by two light chains and two heavy chains bound by a disulphide bond, with a molecular weight of 149.2 kDa. 90 Mepolizumab binds to the ?-chain of IL-5 with both specificity (IC50 <1nm), and affinity (Kd = 4.2 pM), 90 with a dissociation constant of 100 pM, thus preventing it from binding to the ? subunit of the IL-5 receptor expressed on the surface of the eosinophil. [90][91][92] This results in inhibition of IL-5 signaling and bioactivity which lead to reduction in the production, differentiation, activation and survival of eosinophils. Mepolizumab inhibit eosinophilic activation and the release of myriad of inflammatory mediators from the eosinophils, thus preventing airway eosinophilic inflammation. [92][93][94] Mepolizumab (SB-240563, GlaxoSmithKline) was the first biological anti-IL-5 agent to be tested in randomized clinical trials (RCT) in 2000. 95 The first clinical trial of mepolizumab in patients with asthma showed a reduction in sputum and blood eosinophil count but no change in bronchial hyper responsiveness, and no effect on the late asthmatic response. 95 In the phase 2b/3 DREAM (Dose Ranging Efficacy And safety with Mepolizumab in severe asthma) much larger population trial, Pavord et al. 96 confirmed that mepolizumab reduced sputum and blood eosinophil counts, and also significantly reduced asthma exacerbation rates. Additionally, mepolizumab improved the asthma control questionnaire (ACQ) scores, and the asthma quality of life questionnaire (AQLQ) scores. 96 In the MENSA (MEpolizumab as adjunctive therapy iN patients with Severe Asthma) study, Ortega and colleagues, 97 showed that treatment with intravenous (IV) or subcutaneous (SC) mepolizumab decreased the rate of exacerbations by 47% and 53% respectively. It also reduced exacerbations requiring emergency room visits or hospitalization by 32% for IV and 61% for SC mepolizumab. In addition, patients in both IV and SC mepolizumab groups showed significant improvement in the quality of life, and asthma control as assessed by the St. George's Respiratory Questionnaire

The SIRUS (SteroId Reduction with mepoliz Umab Study) in patients with severe asthma and peripheral blood eosinophilia while on maintenance corticosteroid revealed that, patients on mepolizumab had a likelihood of reducing corticosteroid-dose 2.37 times greater than patients on placebo. 98 Patients on mepolizumab were also to reduce the corticosteroid dose by 50%, and had lower exacerbation rates, and improved asthma control despite receiving lower doses of ICS or OCS, thus demonstrating a steroid-sparing effect. 98 Recently, Chupp et al. 99 have confirmed a significant change in the St. George's Respiratory Questionnaire score at the 24 th week of treatment with add-on mepolizumab. Patients receiving mepolizumab showed improvement in symptoms, and health-related quality of life (HRQoL) scores, compared with control subjects receiving placebo. In summary, mepolizumab has a very good safety and tolerability profile. Add-on treatment with mepolizumab has been shown to improve the ACQ scores, AQLQ scores, SGRQ scores, and FEV1. Additionally, add-on mepolizumab has been shown to reduce the rate of exacerbations, and the dosage of corticosteroid or use of other drug modifiers. [96][97][98][99] Mepolizumab was approved by the FDA on March 23, 2015 for add-on treatment of eosinophilic asthma in adults and children aged ?12 years. 100 Meplizumab was also approved by the European Medicines Agency Committee for Medicinal Products for human use in December 2015. 101 Nucala is also indicated for the treatment of eosinophilic granulomatosis with polyangitis (EPGA/Churg/Strauss Syndrome). Mepolizumab is not indicated for treatment of the relief of acute bronchoconstriction and status asthmaticus or any other eosinophilic syndromes.

The recommended dose is 100 mg administered subcutaneously every 4 weeks, and it is well tolerated and has been found to be safe. 100 The most common adverse effects with Nucala include injection site reaction, headache, backache, fatigue, muscle weakness, nasopharyngitis, and upper respiratory tract infection. Acute and delayed systemic reactions, including anaphylaxis, urticarial rash, angioedema, bronchospasm, and hypotension

may occur. Anaphylaxis is rare (<1%), but patients need to be monitored after treatment for these adverse effects.

Eosinophils play an important role in protection against parasitic infection, including helminth infestation. Patients with pre-existing helminth infections should be treated for the infection before mepolizumab therapy. If individuals become infected whilst receiving treatment with Nucala and do not respond to anti-helminth treatment, temporary discontinuation of mepolizumab should be considered.

8 VIII.

9 Reslizumab

Reslizumab (Cingair®), previously known as SCH55700 (Scherig-Plough), is a fully humanized, IgG4/k monoclonal antibody with high affinity for 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. 102 Several randomized clinical trials (RCT) have been conducted on the safety and efficacy of reslizumab. Kips et al. 103 in the first phase 2 pilot study, in patients with severe persistent asthma showed that reslizumab lowered sputum and eosinophil levels, and induced a transient increase in FEV1. A larger phase 2 trial, conducted by Castro el al. 104 showed that treatment with reslizumab significantly increased FEV1, and improved symptoms control, especially in patients with very high eosinophilia and concomitant nasal polyps. Two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials by Castro et al. 105 demonstrated that reslizumab decreased the annual rate of asthma exacerbation by 50-59% in severe asthmatics with blood eosinophil count >400 cells/ml. Reslizumab also improve asthma symptom control and slightly improved FEV1. 105 Bjermer and colleagues, 106 in phase 3 trial, have shown that therapy with reslizumab resulted in significant increase in pulmonary function (FEV1), including airflow limitation in peripheral airways, i.e., increase in forced expiratory flow at 25-75% of forced vital capacity (FEF25-75%). Treatment also improved self-reported asthma control, and quality of life. Brusselle and colleagues have also reported that reslizumab is able to reduce asthma exacerbations, and improve lung function in patients with late-onset eosinophilic asthma. 107 Reslizumab was approved on March 23, 2016 by the FDA for patients aged ?18 years as add-on maintenance therapy for severe uncontrolled eosinophilic asthma. 108 The approved dosage for reslizumab is 3 mg/kg intravenously infused over 20-50 minutes every 4 weeks. It is safe and well tolerated by the patients. The most common side effects of Cinqair include headache, nasopharyngitis, myalgia, and fatigue. Anaphylaxis occurs in about 0.3% of the patients, 109 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. If the patient experiences a severe reaction including anaphylaxis, reslizumab infusion should be discontinued immediately, and the patient should be treated for the adverse event.

Eosinophils play an important in combating helminth infections. Treat patients with pre-existing helminth infections before initiating Cinqair. If patients become infected while receiving treatment with reslizumab and do not respond to anti-helminth treatment, discontinue treatment with reslizumab until parasitosis resolves.

10 IX.

11 Benralizumab

Benralizumab (Fasenra®), formerly called MEDI-563 (AstraZeneca-MedImmune) is a humanized afucosylated IgG1/k monoclonal antibody, developed via hybridoma technology, which selectively recognize the isoleucin-61 residue of domain 1 of human IL-5R?, located near IL-5 binding site. 110,111 As a result, the interaction of benralizumab with its recognition site on IL-5R? block IL-5 binding to target cells, thus preventing hetero-dimerization of IL5R? and ?c subunit, and the subsequent activation of IL-5-dependent signaling pathway. 112 Through the constant Fc region, benralizumab bind to the Fc?RIII? membrane receptor expressed by natural killer cells, which upon activation release the pro-opoptotic proteins granzyme D and perforin, which are responsible for eosinophil apoptosis implemented via antibody-dependent cell-mediated cytotoxicity. [113][114][115] All these effects cause a reduction in eosinophil numbers in the airway mucosa, submucosa, sputum, blood, and bone marrow. 116 Preliminary RCT have shown that treatment with benralizumab results in a decrease in blood eosinophil count to almost depletion, which is associated with reductions in the rate of exacerbations, and improvement in the ACQ-5 scores. 117,118 The SIROCCO RCT showed that treatment with benralizumab significantly reduced exacerbation rates, and improved lung function, and asthma control in patients with severe asthma uncontrolled on high-dose inhaled corticosteroids and long-acting ?-agonists. 119 FitzGerald and colleagues in the CALIMA study showed that treatment with subcutaneous benralizumab 30 mg every 4 weeks resulted in a 36% reduction in exacerbations, and a significant increase of 125 ml in FEV1. 120,121 The ZONDA phase III oral corticosteroid-sparing trial, demonstrated that add-on benralizumab treatment resulted in up to 51% reduction in annual asthma exacerbation rates versus placebo. There was also a significant improvement in lung function as measured by FEV1. The FEV1 increased by 159 ml, and the improvement in lung function was seen as early as 4 weeks after the initiation of the treatment. 122 Additionally, there was a 75% median reduction in daily oral corticosteroid (OCS) use, and discontinuation of OCS in 52% of the eligible patients. 122

Noteworthy, the BORA RTC revealed that long-term use of add-on benralizumab was associated with a very good safety and tolerability profile. 123 In real-life daily clinical practice, the therapeutic effects of Fasenra may even be better than what is observed in randomized, double-blind clinical trials. 124 Benralizumab was approved by the U.S. Food and Drug Administration on November 14, 2017, as add-on therapy for people with severe eosinophilic asthma aged 12 years and older, and those whose asthma is not controlled with current asthma medication. 124 Benralizumab has a half-life of 15-18 days, and is available as a single-dose pre-filled syringe. The recommended dose is 30 mg/ml injection subcutaneously every 4 weeks for the first three doses, thereafter every eight weeks. The most common adverse effects of Fasenra include headache (8.6%), nasopharyngitis (4%), arthralgia (3.9%, cough (3.3%), injection site reaction (2.2%), urticaria rash. Other rare adverse events include chills, nausea, dysgeusia, asthenia, tremor, dizziness hot flushes, and hyperhidrosis.

It is not known if Benralizumab will influence helmith infestation or response to anti-helminth treatment. The manufacturers recommend treatment of the parasitosis before initiating Fasenra, and if patients become infected while receiving Fasenra and do not respond to anti-parasitic agents, to discontinue benralizumab until the infection resolves.

12 X. Criteria for Initiation of Interleukin-5 Antagonists

Biologics should be recommended early in the management of established eosinonophilic asthma diagnosed using pharmacodynamic biomarkers, such as sputum and blood eosinophil counts, fractional exhaled nitric oxide (FeNO), serum perisostin, dipeptidyl peptidase-4, and osteopontin. [126][127][128][129][130] Long-term treatment with biologics, such as omalizumab (anti-IgE), 131,132 and mepolizumab, 132 significantly reduce airway wall and reticular membrane thickening. Phipps et al. 133 have reported that mepolizumab is associated with significant reductions in tenascin and lumican deposition in the reticular basement membrane in human atopic skin. 133 If mepolizumab and other anti-IL-5 antagonists exhibit similar effects in eosinophilic airways inflammation, they may be capable of preventing subepithelial fibrosis, and progressive decline in lung function in patients with eosinophilic asthma.

The GINA guidelines, 1 and NAEPP 19 yardsticks for step-up treatment for severe refractory asthma, recommend initiation of biologics, such as anti-IgE, and anti-interleukin (IL)-5 monoclonal antibodies for patients with eosinophilic asthma at step 5. The latest ERS/ATS Task Force guidelines, 134 recommend using anti-IL-5 and anti-IL-5 receptor ? for severe uncontrolled adult eosinophilic asthma phenotypes, using a blood eosinophil cut-point of 150 cells.µL -1 to guide anti-IL-5 initiation in adult patients with severe asthma. The guidelines also suggest specific eosinophil ?260 cells.µL -1 , and FeNO 19. F response to anti-IgE therapy. Table **??** shows the three anti-Il-5 antagonists and their weekly costs.

There are few reports on the pharmacoeconomical aspects of the newly introduced biologics for the treatment of severe steroid-resistant eosinophilic asthma. Bogart et al. 135 using a hypothetical model estimates that mepolizumab without bronchial thermoplasty (BT) was the most cost-effective option for biological responders, with a 10-year-per-patient cost of US$116,776. In patients who do not respond to eosinophilic targeted biologics, bronchial thermoplasty is more cost-effective option. Similarly, an indirect comparison of BT with omalizumab in patients with moderate-to-severe allergic asthma in the USA reported greater than 60% chance that bronchial thermoplasty was cost-effective relative to omalizumab and standard therapy at the willingness-to-pay of $100,000 per qualitylife years (QALY). 136 However, bronchial thermoplasty is a complex sophisticated procedure which requires critical selection of the patients, experienced pulmonologist, and anesthetists, excellent bronchoscopic skills, and dedicated intense postprocedural management and follow-up. [137][138][139][140] XI.

13 CONCLUSION

Eosinophilic asthma is a well characterized phenotype of asthma, which is driven by Th2 cytokines, such as IL-4, IL-4, IL-13, IL-25, IL-33, and TSPL. Interlekin-5 plays a central role in the differentiation, proliferation, maturation, survival, and activation of eosinophils. Activated eosinophils secrete cytotoxic cationic proteins, radical oxygen species, cytokines, chemokines, and growth factors which are responsible for epithelial injury, airway inflammation, AHR, and airway remodeling. Targeting IL-5 and its receptor with biologics, such as mepolizumab, reslizumab, and benralizumab is a novel therapeutic strategy for the treatment of severe refractory, steroid unresponsive eosinophilic asthma. Early use of anti-IL-5 antagonists may prevent the progressive decline in lung function, and improve the quality of daily living.

14 Conflicts of interest

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.1 Abbreviations:

LT, leukotriene; IL, interleukin; MMP, matrix metalloproteinases; TIMP, tissue inhitors of metalloproteinases; MIP, macrophage inflammatory protein; MCP, monocyte chemoattractant protein; GM-CSF, granulocyte macrophage colony-stimulating factor; TGF?, transforming growth factor-?; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor.

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