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Monoclonal antibody therapy for the treatment of asthma and chronic obstructive pulmonary disease with eosinophilic inflammation

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ABSTRACT

Eosinophils have been linked with asthma for more than a century, but their role has been unclear. This review discusses the roles of eosinophils in asthma and chronic obstructive pulmonary disease (COPD) and describes therapeutic antibodies that affect eosinophilia. The aims of pharmacologic treatments for pulmonary conditions are to reduce symptoms, slow decline or improve lung function, and reduce the frequency and severity of exacerbations. Inhaled corticosteroids (ICS) are important in managing symptoms and exacerbations in asthma and COPD. However, control with these agents is often suboptimal, especially for patients with severe disease. Recently, new biologics that target eosinophilic inflammation, used as adjunctive therapy to corticosteroids, have proven beneficial and support a pivotal role for eosinophils in the pathology of asthma. Nucala® (mepolizumab; *anti*-interleukin [IL]-5) and Cinquair® (reslizumab; anti-IL-5), the second and third biologics approved, respectively, for the treatment of asthma, exemplifies these new treatment options. Emerging evidence suggests that eosinophils may contribute to exacerbations and possibly to lung function decline for a subset of patients with COPD. Here we describe the pharmacology of therapeutic antibodies inhibiting IL-5 or targeting the IL-5 receptor, as well as other cytokines contributing to eosinophilic inflammation. We discuss their roles as adjuncts to conventional therapeutic approaches, especially ICS therapy, when disease is suboptimally controlled. These agents have achieved a place in the therapeutic armamentarium for asthma and COPD and will deepen our understanding of the pathogenic role of eosinophils.

Abbreviations: ACQ-5, Asthma Control Questionnaire-5; ACQ-6, Asthma Control Questionnaire-6; ADCC, antibody-dependent cell-mediated cytotoxicity; AG, antigen; AHR, airway hyper-responsiveness; AQLQ, Asthma Quality of Life Questionnaire; B, B cell; Bas, basophil; BrO^-, hypobromite; C1q, complement component 1, subcomponent q; CCL, chemokine ligand; CCL11, CC-chemokine ligand 11; CCL13, CC-chemokine ligand 13; CCL17, CC-chemokine ligand 17; CCL22, CC-chemokine ligand 22; CCL24, CC-chemokine ligand 24; CCL26, CC-chemokine ligand 26; CCR, chemokine receptor; CCR3, Chemokine (C-C Motif) Receptor 3; CD, cluster of differentiation protein; CDC, complement-dependent cytotoxicity; COPD, chronic obstructive pulmonary disease; CTL, cytotoxic T lymphocyte; DC, dendritic cell; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; Eos, eosinophil; EPO, eosinophil peroxidase; Fab, fragment antigen-binding; Fc, fragment crystallizable; FcγRIIIa, fragment crystallizable gamma receptor IIIa; FEG, free extracellular granules; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FGF, fibroblast growth factor; GINA, Global Initiative for Asthma; GM–CSF, granulocyte-macrophage colony-stimulating factor; HER2, human epidermal growth factor receptor 2; HMGB1, high-mobility group box protein 1; H_2O_2, hydrogen peroxide; ICS, inhaled corticosteroids; IFN, interferon; IgE, immunoglobulin E; IgG_1, immunoglobulin G1; IgG_2, immunoglobulin G2; IgG_4, immunoglobulin G4; IgM, immunoglobulin M; IL, interleukin; IL-3, interleukin-3; IL-3R, interleukin-3 receptor; IL-4, interleukin-4; IL-4Rα, interleukin-4 receptor α; IL-5, interleukin-5; IL-5R, interleukin-5 receptor; IL-5Rα, interleukin-5 receptor α; IL-11, interleukin-11; IL-13, interleukin-13; IL-25, interleukin-25; IL-33, interleukin-33; ILC, innate lymphoid cell; ILC2, innate lymphoid cell, type 2; ILR, interleukin receptor; LABA, long-acting β_2 agonist; LT, leukotriene; LTB4, leukotriene B4; LTC4, leukotriene C4; LTD4, leukotriene D4; LTE4, leukotriene E4; mAb, monoclonal antibody; Mac, macrophage; MAC, membrane-attack complex; MBP, major basic protein; MCP-4, monocyte chemoattractant protein 4; MOA, mechanism of action; mRNA, messenger ribonucleic acid; NGF, nerve growth factor; NK, natural killer; O_2, superoxide; OCS, oral corticosteroids; PGD_2, prostaglandin D_2; PDGF, platelet-derived growth factor; PGE_2, prostaglandin E_2; PMN, polymorphonuclear cell; RANTES, regulated on activation, normal T cell expressed and secreted; scFv, single-chain variable fragment; SGRQ, St. George's Respiratory Questionnaire; TARC, thymus- and activation-regulated chemokine; TCR, T-cell receptor; Th2, T-helper 2; scFv, single-chain variable fragment; TGF, transforming growth factor; TGFβ1, transforming growth factor β1; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor; VEGF-A, vascular endothelial growth factor A.

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Contents

1. Asthma and chronic obstructive pulmonary disease with eosinophilic inflammation

1.1. Asthma

Asthma is one of the most common chronic diseases, with an estimated 300 million patients afflicted by this disease worldwide. The Global Initiative for Asthma (GINA) 2004 estimated that more than 10% of the population in Australia, Brazil, Canada, New Zealand, Peru, England, and United States had asthma. The prevalence of asthma is expected to increase, and there may be an additional 100 million people with asthma by 2025 (Masoli et al., 2004). A 2012 survey revealed that 25.5 million people in the United States alone, including 6.8 million children younger than 18 years, had a diagnosis of asthma (Centers for Disease Control and Prevention, 2015). Moreover, asthma prevalence has increased from 3.1% in 1980 (Moorman et al., 2007) to 8.3% in 2012 (Centers for Disease Control and Prevention, 2014).

The widespread use of inhaled corticosteroids (ICS) as monotherapy, and particularly as combination therapy with long-acting β_2-agonists (LABA), has been accompanied by a marked reduction in the burden of disease and a substantial reduction in asthma mortality (Chauhan et al., 2015; Chong et al., 2015). However, as with most pharmacotherapies, population data with ICS or ICS–LABA combinations display a Gaussian distribution, with a substantial percentage of patients responding suboptimally or not at all. Furthermore, poor adherence to medication plays an important role in treatment failure (Gamble et al., 2009). By definition, as the requirement for treatment increases, so does the severity of the disease (Global Initiative for Asthma, 2016). In its worst form, severe refractory asthma – which affects 3.6% of patients with asthma – accounts for a disproportionately high burden of suffering and health care costs (Hekking et al., 2015). Suboptimal control in these patients manifests as daytime symptoms, nighttime awakenings, and increased propensity to suffer more frequent and more severe exacerbations, which, in extreme cases, can be fatal.

Increasingly, experts recognize that moderate to severe asthma is a disease encompassing several distinct endotypes characterized by the shared presence of cellular and molecular biomarkers. Linking asthma endotypes with clinical phenotypes has greatly advanced our understanding of asthma pathobiology and the development of novel targeted therapeutics (Anderson, 2008). For more details on this subject, we refer the reader to the reviews by Wenzel, 2012, 2013, 2016; Lötvall et al., 2011. One of the best-characterized endotypes of asthma is the patient population with eosinophilic airway inflammation, which accounts for approximately 40–60% of patients with severe asthma (Wenzel et al., 1999; Douwes et al., 2002; Zhang & Wenzel, 2007; Schleich et al., 2013).

Several important observations in human initially supported the hypothesis that eosinophils play a critical role in the pathogenesis and severity of asthma. An increased eosinophil count is associated with increased asthma severity, frequency of exacerbations and mortality in patients with asthma (Bousquet et al., 1990; Tran et al., 2014; Zeiger et al., 2014). A 1995 report quantified the risk of dying from asthma as 7.4-times greater for patients with eosinophilia than without eosinophilia (Ulrik & Frederiksen, 1995). Several studies have demonstrated that sputum eosinophils increase during exacerbations and that increased numbers of eosinophils in the peripheral blood and airways of patients with asthma correlate with disease severity. Perhaps most importantly, persistent, eosinophilic airway inflammation increases the risk of subsequent exacerbations (Jatakanon et al., 2000; Louis et al., 2000; Di Franco et al., 2003; Miranda et al., 2004; Wenzel, 2005; Scott & Wardlaw, 2006; Zhang & Wenzel, 2007; Malinovschi et al., 2013; Schleich et al., 2014). For example, markers of eosinophilic airway inflammation increase well before the onset of exacerbations induced by corticosteroid withdrawal, and sputum eosinophil number predicts loss of asthma control after corticosteroid reduction or discontinuation (Pizzichini et al., 1999; Jatakanon et al., 2000; Deykin et al., 2005). In addition, activated eosinophils, recognizable by degranulation and upregulation of biochemical effector pathways, are found in the airways of patients who have died of acute severe asthma. Necropsy results identified two distinct pathogenic inflammatory mechanisms of fatal asthma (Restrepo & Peters, 2008). Patients dying suddenly exhibit a neutrophilic airway infiltrate, whereas postmortem examination of patients who exhibit more protracted asthma crises, which precipitate 80–85% of all fatal events, reveals an intense eosinophilic infiltrate (James et al., 2005; Restrepo & Peters, 2008).

Another line of evidence comes from the partial success of eosinophil management strategies with corticosteroids. The English general physician Harry Morrow Brown is credited with making the initial observation that only patients with asthma with eosinophilic inflammation responded to oral steroids (Brown, 1958), which was soon afterward extended to the first effective inhaled steroid, beclomethasone dipropionate (Brown et al., 1972; Brown & Storey, 1973). A more comprehensive study demonstrated that a strategy aimed at managing sputum eosinophils through the controlled use of corticosteroids achieved a greater reduction in the number of severe exacerbations for patients with moderate to severe asthma than a traditional management strategy based on British Thoracic Society guidelines (Green et al., 2002a). More recent studies aimed at controlling sputum eosinophils through adjustments in ICS have provided similar benefits (Chlumský et al., 2006; Jayaram et al., 2006). Although these studies do not prove a cause and effect relationship, as the benefits of controlled corticosteroid management may be mediated through different mechanisms, the findings lend validity to eosinophilic airway inflammation being a surrogate marker for exacerbation frequency. It is unclear how corticosteroids reduce eosinophilic inflammation. Some studies suggest that corticosteroids reduce IL-5 receptor (IL-5R) expression on eosinophils, rendering them less responsive to IL-5. Other studies propose that corticosteroids increase eosinophil apoptosis and stimulate phagocytic elimination of apoptotic eosinophils (Her et al., 1991; Meagher et al., 1996; Liu et al., 1999).

These initial discoveries in humans of a pathogenic role for eosinophils in asthma were confirmed by application of mouse genetics. Two