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Biopharmaceutical Aspect Of Reslizumab in Asthma : A Review

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Abstract
Eosinophils are primary proinflammatory cells that have an important role to the inflammation in allergic diseases including asthma. Eosinophilic asthma is a phenotype of asthma which characterized by the persistence eosinophils in the airways. Interleukin-5 (IL-5) plays a key role in eosinophil activation and survival. Elevated numbers of blood eosinophils are risk factor for asthma exacerbations. The complexity of chronic severe asthma with various underlying mechanisms suggests that phenotyping patients with severe asthma and individualized therapy could lead to improved treatment outcomes and fewer side-effects. Reslizumab which is a human monoclonal antibody that disrupts eosinophils maturation dan promotes apoptosis estimated can be a potential treatment for poorly controlled eosinophilic asthma. Recently, more clinical trials have been performed to evaluate the effects of anti-interleukin (IL)-5 antibodies in eosinophilic asthma as since 2016, an intravenous formulation of reslizumab was approved by FDA as add-on maintenance treatment for patients aged ≥ 18 years with severe eosinophilic asthma. However, a confirm conclusion has not been well established. In this study, we aimed to review the use of Reslizumab in patients with inadequately controlled, moderate-to-severe asthma.

Keywords: *Asthma, Eosinophil, Anti Interleukin 5, Reslizumab*

A. INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning (GINA, 2012). Asthma can be divided into different clinical phenotypes. Eosinophilic asthma is the most predominant phenotype, accounts for approximately 50 to 60 % of the total asthma population which which characterized by increased blood or sputum eosinophils (Wang & Xiong, 2016). Inflammation is the most important pathophysiological mechanism underlying the development of asthma, involving a complex interaction between lymphocytes from the adaptive immune system and various cell types in the innate immune system, including innate lymphoid cells, mast cells, basophils, neutrophils, eosinophils, and dendritic cells. If not sufficiently treated, chronic inflammation of the airways will cause mucus hypersecretion, airway hyperresponsiveness, and bronchial remodeling, including airway thickening, fibrosis, and angiogenesis (Maspero, 2017).

Eosinophils play an important role in the pathophysiology of asthma including promoting airway inflammation, airway wall thickening, fibrosis, and angiogenesis (Corren & Weinstein, 2016). Assessment of eosinophilia in patients with severe asthma is an important tool for monitoring asthma control and guiding therapeutic decisions. Increased numbers of eosinophils in the airways, peripheral blood, and bronchoalveolar lavage (BAL) fluid have been detected in patients with chronic asthma. Increased blood and sputum eosinophil have been correlated with increased asthma severity and are independent risk factors for future asthma exacerbations. Treatment strategies that aim to reduce the level of eosinophils in the sputum have resulted in improved control of asthma symptoms and reduce exacerbations (Castro & Sameer, 2011; Maspero, 2017).

Although most patients with asthma are controllable with with bronchodilators and low to moderate doses of inhaled corticosteroids, some patients remain uncontrolled on high doses of corticosteroid. Patients with inadequately controlled asthma remain at risk of asthma exacerbations (Li & Lin, 2016). IL-5 is a cytokine responsible for eosinophil maturation, differentiation, recruitment, and survival and also prevention of eosinophil apoptosis (Wang & Xiong, 2016). Clinical studies with anti-IL-5 therapies have demonstrated decreases in eosinophil levels so thus bring a significant improvements in many of the clinically relevant parameters associated with eosinophilic asthma. One such therapy is reslizumab, a monoclonal antibody that inhibits IL-5. Recently, the Federal Drug Administration (FDA) approved reslizumab as an add-on maintenance therapy for adults with severe asthma with an eosinophilic phenotype (Walsh, 2013).

B. EOSINOPHIL MEDIATED INFLAMMATION IN ASTHMA AND ROLE OF IL-5

Eosinophils are multifunctional leucocytes that are recruited from the circulation into the airway, in response to various stimuli and play important role in asthma (Lim & Nair, 2014). Eosinophils have been involved in epithelial dysfunction, airway remodelings including airway thickening and fibrosis, and angiogenesis, hyper responsiveness,and late-phase allergic response (Bjermer & Lemiere, 2016). Activated eosinophils will able to release leukotrienes, platelet activation factor, major basic protein, eosinophil cationic protein, eosinophil peroxidase, eosinophil-derived neurotoxin, and other cytokines that are toxic to the bronchial epithelium and lead to airway inflammation and bronchospasm (Maselli, Velez, & Rogers, 2016). Previous studies also showed that eosinophils can produce cytotoxic granules, lipid mediators like leukotriene C4 and TGF-β that may, respectively, lead to airway hyper-responsiveness, bronchoconstriction and remodeling (Lim & Nair, 2014). Eosinophilic asthma is a phenotype of the asthma conditions which characterized by increased blood or sputum eosinophils (Walsh, 2013). The number of eosinophils in the blood and sputum can correlate with disease severity and are independent risk factors for future asthma excerbations. Treatment regimens that can reduce the level of eosinophils in sputum and blood have resulted in improvement of asthma symptoms and reduce exacerbations (Corren & Weinstein, 2016).

The activated T-helper cells are the main sources of IL-5, although eosinophils, mast cells, and other cellular lines produce this cytokine at varying degrees. The production of IL-5 is increased upon activation of TH2 cells after antigen exposure. IL-5 stimulates the production and maturation of eosinophil precursors in the bone marrow. Pheriperally, it participates in terminal maturation and activation of eosinophils. It also has a role in diapedesis of eosinophils by helping the adhesion and chemotaxis, and migration. Briefly, IL-5 has a key role in eosinophil proliferation, differentiation, maturation, migration, survival, and prevention of eosinophil apoptosis. IL-5 comprises of a functional site for binding to the specific receptor subunit, IL-5Rα, and a separate motif for binding to the signalling subunit, β-chain. The IL-5Rα subunit is specific only to IL-5 binding; the β-chain also binds the cytokines IL-3 and granulocyte-macrophage colony-stimulating factor. Targeting IL-5 is a great promise for the treatment of asthmatic patients and may have a beneficial effect by preventing tissue damage that cause by eosinophil in patients with asthma (Garcia & Taile, 2013).

C. PHARMACOLOGY OF RESLIZUMAB

Reslizumab is a humanized monoclonal antibody that binds with high affinity to circulating human IL-5 and downregulates the IL-5 signaling pathway so it can disrupts the maturation and survival of eosinophils. It neutralizes IL-5 by binding the region *ERRR* (glutamic acid, arginine, arginine, arginine) corresponding to amino acids 89–92 on IL-5 and prevents it from interacting with IL-5Rα (Maselli, Velez, & Rogers, 2016). Its molecular weight is 146 kDa and it has a high affinity to IL-5 (Kd of 20 pmol/l) in vitro and inhibitory effect (IC50 0.5 nmol/l) (Lim & Nair, 2014). When characterized in various populations, the pharmacokinetic profile of reslizumab was similar across groups. Plasma concentrations of reslizumab were dose dependent and serum concentrations of reslizumab accumulated by approximately 1.5- to 1.9 fold in multiple dose administration. Peak serum concentrations of reslizumab are achieved at the end of intravenous infusion and then decline in a biphasic manner. Weight-based dosing is recommended so the drug can achieve a steady-state condition across patients with various bodyweight (Maspero, 2017).

Reslizumab has a small volume of distribution (5 L), and it degrade into small peptides and amino acids via enzymatic proteolysis. The clearance is approximately 7 ml/h and its half-life is around 25–30 days. Reslizumab are unlikely to affect cytochrome P450 1A2, 2B6, or 3A4 enzyme activity. According to population pharmacokinetic analyses, the pharmacokinetic of reslizumab were not significantly altered by mild hepatic impairment, mild or moderate renal impairment, or the concomitant use of leukotriene antagonists or corticosteroids, or by age and gender (Deeks & Brusselle, 2017; Maspero, 2017).

D. CLINICAL TRIALS OF RESLIZUMAB

Reslizumab was initially evaluated in humans in a small study that enrolled patients, 18 years or older, with symptomatic severe persistent asthma despite using high-dose ICSs or oral corticosteroids. The patients received either placebo or reslizumab intravenously (IV) at a single dose ranging between 0.03 and 1.0 mg/kg. At doses of 0.03 and 0.1 mg/kg, there was no significant effect on eosinophil counts. But, at doses of 0.3 mg/kg, there was a significant decrease in circulating eosinophils, but in patients who received 1.0 mg/kg, the response was more profound. Importantly, in the last group of patients, the effect was sustained for 30 days. There were no significant differences

in forced expiratory volume in 1 second (FEV1), FEV1/forced vital capacity ratio, or symptom scores among the study groups (Kips & O'Connor, 2003). This study has important implications as it was the first to demonstrate that reslizumab can effectively and safely decrease eosinophil counts in patients with asthma (Maselli, Velez, & Rogers, 2016).

A recent Phase II, randomized, placebo-controlled, multicenter trial conducted by Castro *et al.* evaluated intravenous reslizumab in patients with poorly controlled asthma who had a sputum eosinophilia greater than 3% and uncontrollable with a high-dose inhaled corticosteroids. Compared with placebo (n = 53), the reslizumab group (n = 53; 3.0 mg/kg) showed a trend favoring better asthma control (reslizumab, −0.7; placebo, −0.3) although it was not statistically significant ($P = 0.054$) as assessed by the Asthma Control Questionnaire score, the primary study endpoint (Castro & Sameer, 2011). In patients with concomitant nasal polyposis, reslizumab treatment was associated with a significant improvement in asthma symptoms (reslizumab, −1.0; placebo, −0.1; $P = 0.012$). There was a nonsignificant reduction in asthma exacerbations in the reslizumab group while the adverse event profile for reslizumab and placebo were similar without evidence of rebound eosinophilia (Castro & Sameer, 2011). In this study, patients were selected based on their sputum eosinophil counts so that it demands certain expertise when collecting the sample, and is not widely available. Because of that reason, sputum eosinophil counts may not be the ideal way of identifying eosinophilic asthma. On the other hand, blood eosinophil counts are readily obtained in an automated, inexpensive method and give more reliable results. For these reasons, the following studies evaluating the effectiveness of reslizumab have used blood eosinophil counts to define the eosinophilic asthma phenotype (Walsh, 2013; Lim & Nair, 2014).

To assesed the efficacy of anti-IL-5 therapy using blood eosinophil counts, two replicate, double-blind, multicenter, randomized, placebo-controlled trials evaluated the efficacy of reslizumab in patients with uncontrolled asthma. These patients had to have at least one blood eosinophil count of 400/μL and were receiving at least medium-dose ICS with or without a second controller. At the end, 953 patients aged 12–75 years were randomly assigned to receive reslizumab at a dose of 3 mg/kg or placebo IV every 4 weeks for 13 doses. Patients who received reslizumab showed a reduction in the rates of asthma exacerbations compared to placebo (0.84 vs 1.81 events per patient per year, rate ratio 0.86 [0.37–0.58], $P<0.001$). The time of first exacerbation was significantly longer in the treatment group, with a probability of not having an exacerbation were 61% and 73% (95% confidence interval) in studies 1 and 2 compared to 44% and 52% (95% confidence interval) in the placebo group. The improvement in FEV1 and ACQs scores in the treatment group happened as early as 4 weeks after therapy was started. The adverse events reported were similar in both treatment and placebo groups. The results of this study provide evidence that blood eosinophil counts are more suitable to discriminate different asthma phenotypes (Castro & Zangrilli, 2015).

To determine the impact of the baseline blood eosinophil count, a randomized, double-blind, placebo-controlled, multicenter study was designed to evaluate the use of reslizumab in uncontrolled asthmatics with a wide range of blood eosinophil levels. A total of 496 patients aged 18–65 years were randomized to determine the group, either reslizumab group (3.0 mg/kg IV every 4 weeks for 16 weeks) or placebo group. Only 20% of the patients had blood eosinophil counts >400/μL. The mean change in FEV1 from baseline at week 16 was similar in both the study groups (reslizumab 255 mL compared to placebo 187 mL, standard error 49.5, P=0.170). In subjects with eosinophil counts >400/μL showed an improvement in pulmonary function and ACQ scores. This study confirmed that patients with a non-eosinophilia asthma do not suitable to have reslizumab therapy (Corren & Weinstein, 2016).

More recently, a study was held to explore the efficacy of two different doses (0.3 and 3.0 mg/kg IV) of reslizumab in asthmatics with a blood eosinophil count of at least 400/μL. This multicenter, double-blind, placebo controlled study had 315 subjects aged 12–75 years with uncontrolled asthma and at least using medium-dose ICS. After 16 weeks of therapy, patients who received the 3.0 mg/kg dose had clinically significant improvements in pulmonary function and quality of life compared to placebo group. Similar with the previous studies, the response was observed as early as 4 weeks, and a significant decrease in the blood eosinophil count was detected. Although there was a significant response with the 0.3 mg/kg dose, the effect was superior in the 3.0 mg/kg dose. No increased rates of adverse reactions were observed in both dose compared to placebo (Bjermer & Lemiere, 2016).

Based on that four studies, the FDA approved reslizumab as an add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype in March 2016. Reslizumab has been shown to reduce blood and sputum eosinophils, improve pulmonary function, and reduce asthma exacerbations in patients with elevated

sputum eosinophils or blood eosinophil counts ≥400 cells/μL The suggested dosage regimen is 3 mg/kg interavenous over 20–50 minutes every 4 weeks (Walsh, 2013). The use of corticosteroid can be reduced gradually once reslizumab has been initiated and should not abruptly discontinued (Deeks & Brusselle, 2017).

E. SAFETY DATA OF RESLIZUMAB

Reslizumab is generally safe and well tolerated. The most common side effects include headache, nasopharyngitis, upper respiratory tract infections, and fatigue, although these not significantly different compared to placebo (Li & Lin, 2016; Maselli, Velez, & Rogers, 2016). Reslizumab can cause an anaphylaxis so patients must be monitored closely after the administration. The drug should be discontinued immediately in those who experience anaphylaxis. Reslizumab is contraindicated in patients who known hypersensitivity to the drug. Future evaluation studies are still needed to add the information about the risks of malignancy and safety during pregnancy (Maselli, Velez, & Rogers, 2016).

F. CONCLUSION

Asthma is a chronic and complex inflammatory disease of the airways. The selections of the initials treatment is depend on the basis of the asthma severity and according to the level of asthma control. For the patients with severe asthma who continue to experience exacerbations with the use of standard therapy, the more personalized asthma therapy seems give a great promise with targeted biological aggents like reslizumab. Intravenous Reslizumab is a valuable add-on therapy options for adults with severe eosinophilic asthma which uncontrollable with standard therapies and it is generally safe and well tolerated.

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