New Therapeutic Options in Asthmatic Patients

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Abbreviations:

ACQ-5 – Asthma Control Questionnaire

FeNO – Fractional exhaled nitric oxide

FEV1 – Forced expiratory volume in 1 second

FVC – Forced vital capacity

GINA – Global Initiative for Asthma

ICS – Inhaled corticosteroid

IgE – Specific immunoglobin E

IL-4 – Interleukin 4

IL-5 - Interleukin 5

IL-5r - Interleukin 5 receptor

IL-13 – Interleukin 13

LABA – Long-acting beta agonist

LAMA – Long-acting muscarinic antagonist

OCS – Oral corticosteroids

SGRT - St. George's Respiratory Questionnaire

TH2 – T-helper 2 cells

WHO – World Health Organization

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Abstract

Despite the widespread burden of asthma among all ages and regions of the world, until a number of years ago the treatment of asthma has been nonspecific, and largely unchanged. Growing knowledge about the molecular pathology of this disease and new strides in medical technology have opened the door to the development of better treatments. These new treatments are disease specific to various phenotypes of asthma and have proven to be useful and effective in treating asthma patients who were previously unable to gain control of their symptoms and disease progression with traditional medications.

Key words: asthma, severe asthma, phenotype, treatment, biologic therapy,

Sažetak

Unatoč globalnom opterećenju astmom, pacijenata svih dobi u svim regijama svijeta, do prije nekoliko godina dostupna terapija je bila nespecifična i nije se drastično mijenjala. Boljim razumjevanjem molekularne patologije same bolesti i razvojem medicinske tehnologije otvorila su se vrata ka razvoju boljih terapijskih opcija. Nova terapija je bazirana na specifičnim fenotipovima astme što se pokazalo korisnim i efektivnim u liječenju onih pacijenata s astmom koji nisu dostupnom maksimalnom terapijom postigli kontrolu bolesti i stoga im bolest progredira.

Introduction

Asthma has been known as a very important respiratory disease for many years. In modern times there has been a significant increase in the number of cases of asthma worldwide and shows a definite need for investigation and research into the disease and its treatments. With new advances in technology a better understanding of the disease has been revealed through molecular methods, genetics, and treatment studies. These developments have led to the identification of specific phenotypes of asthma that have unique characteristics, and require different, more effective treatments.

The development of monoclonal antibodies has revolutionized medicine, and offers exciting new possibilities for efficiently treating diseases. Asthma has been one such disease that is the focus of developing new treatments using monoclonal antibodies. The complex pathways involved in asthma made it difficult to treat, but also offers many potential sites of interest. This paper will review the features of asthma, and the new therapies available for the treatment of specific types of asthma that cannot be adequately managed by traditional methods.

2. Disease overview

2.1 Definition and History of Asthma

Asthma is a complex disease with multiple etiologies and clusters of symptoms. According to the Global Initiative for Asthma (GINA), asthma can be defined as, "a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation."(1) This definition of the disease is a very concise expression of the broad range of phenotypical expressions, and underlying causes of airway inflammation and their various biomarkers that is seen in asthma.

2.2 Epidemiology

According to the World Health Organization (WHO) there is an estimated number of 262 million cases of asthma worldwide and it is reported to be the cause of 455,000 deaths annually. (2)Studies have found that there is an increased incidence of asthma in western countries, and there is high level of mortality in developing countries, as well as a rise of cases in countries that continue to adopt western trends and urbanize. (3)

Among patients with asthma there is a slightly higher incidence in children than adults, with a trend of increasing prevalence through adolescence, and a decrease in cases of asthma among the adult population. (4) In addition to the variances seen between age groups, there are observable differences in the incidence of asthma between races, and socioeconomic classes. (3)

2.3 Etiology

Due to the heterogeneous nature of the disease, it has been difficult to find a single cause for the development of asthma. Many theories have been proposed to explain what the most likely reasons are, and most experts have concluded that asthma is the result of complex interactions between a patient's genetics and their environment. Heritability of asthma has been long know, yet without a single identifiable cause. Asthma does not follow Mendelian inheritance patterns; rather it is thought to be the result of interactions between multiple genes that are responsible for the asthma phenotype, and its severity. (5) New advances in genetic sequencing have led to the hopes that specific combinations of genes can be identified, and associated with the various phenotypes of asthma, but at this time no successful studies have been performed.

Beyond the genetic aspects of asthma, many theories have been given to explain which environmental factors are responsible for the activation of the genes causing the disease. Various risk factors have been identified for individual stages of life. Many possible factors in the pre- and peri- natal period have been identified and researched including deficiencies of specific nutritional factors such as omega-3 polyunsaturated fatty acids, micronutrients such as vitamins D, E, C, and zinc, and increased sugar intake. Beyond dietary considerations, the most apparent and significant prenatal risk factor for the development of asthma is maternal smoking. (6) Perinatal factors suspected to increase the risk of developing asthma include the mode of delivery, breastfeeding, and prematurity. Some correlations have been found with these factors, but studies of these variables have shown conflicting evidence, and further research is needed. (7–10)

Childhood is when most cases of asthma develop, and it is therefore critical to look at the numerous environmental factors that are present, as some have shown strong correlations to the development of asthma. One of the most popular and well-studied

theories of the role of environment and asthma is the hygiene hypothesis. It has been long known that childhood asthma is correlated with atopy and allergic diseases, and this theory suggests that changes in exposure to various microbes causes a shift in the development the immune system that results in elevated levels of specific IgE. (11–13) Despite some promising evidence in this line of research the results are not entirely conclusive, and are conflicted by the span of time between improved hygiene in western countries and the only modest improvement in hygiene practices in less developed regions where asthma is still on the rise. (14) Another possible risk factor that is of importance is the amount of time spent indoors. With changes to lifestyle and living space design in the 20th century, more time was spent indoors, and home conditions were more favorable for exposure to allergens such as dust mites, cockroaches, and mold. (14) Others have postulated that factors such as environmental pollution, exposure to toxins, and climate change have caused the increase in incidence of asthma in children. Although these theories have evidence the supports and contradicts these findings it is likely that there is a complex interplay between many of these environmental factors that cause the activation of pro-asthmatic genetic pathways.

Asthma that develops in adulthood also has its own set of possible environmental triggers. One of the most significant environmental factors related to the development of asthma in adults is exposure to tobacco smoke. Studies involving the relationship between active and passive smoke inhalation suggest tobacco smoke is highly correlated with development of adult asthma (15–17), and is also related to the reactivation of resolved childhood asthma. (18) Other studies have suggested that obesity is a possible cause of adult asthma (19), but it is unclear if many of these cases are true airway obstruction or dyspnea unrelated to asthma. (20)

2.4 Pathophysiology and Pathogenesis

The characteristic physiological features of asthma are the variable obstruction of airflow in the lungs, bronchiolar hyperresponsiveness, and the hypersecretion of mucus.(21) Although these common features are shared in different asthma phenotypes, the underlying pathology is highly variable and results in multiple phenotypes, each containing a number of possible pathways of activation.

Although there is some conflicting terminology involving the phenotypes of asthma, a succinct way to group them is into allergic and non-allergic asthmas. Allergic asthma is the most common and most typical presentation of the disease.(1) Individuals with allergic asthma develop sensitivity to allergens through a complex immune pathway. Allergens are presented by dendritic cells to lymphocytes, and this process results in development of specialized type 2 helper T cells (TH2 cells). These TH2 cells release cytokines, most importantly IL4, IL-5, IL-13, that stimulate production of more TH2 cells, eosinophils, and the maturation of B cells into plasma cells that produce IgE antibodies. These IgE antibodies attach to mast cells, and when activated by the sensitized allergen cause degranulation. This degranulation of mast cell mediators, most importantly: histamine, prostaglandin D2, and various leukotrienescauses theearly phase hypersensitivity response of bronchoconstriction, and hypersecretion.(22) The late phase reaction in asthma typically occurs 4-6 hours after the initial reaction, and it is thought to be caused by the release of cytokines from immune cells, specifically TH2 cells and eosinophils that act directly on the smooth muscle of the lungs. (21) In addition to these short-term responses, the secretion of cytokines and accumulation of immune cells in the mucosa of the lungs cause structural changes to the lung tissue over time. Prolonged inflammation from asthma results in hypertrophy and hyperplasia of smooth muscle in the airways, thickening of the respiratory endothelium, and proliferation of mucus

secreting cells. The process of airway remodeling is very clinically relevant because it is a permanent change to the structure of the airways and makes treatment with traditional therapies less effective. (21)

Another very important asthma phenotype, that is currently the field of much research, is eosinophilic asthma. Eosinophilic asthma can be allergic, or nonallergic, and is characterized by hyperproliferation of eosinophils and invasion into airway mucosa and poor response to corticosteroids. This proliferation and recruitment into respiratory mucosa causes a thickening of the basement membrane and is an important aspect of airway remodeling. Proliferation and recruitment of eosinophils is primarily stimulated by interleukin 5 (IL-5) with other cytokines and growth factors playing a role as well. When eosinophils in the respiratory mucosa are activated they release their granules which contain multiple proteins and inflammatory modulators that lead to short term bronchoconstriction and play a role in the long-term remodeling of the airway.

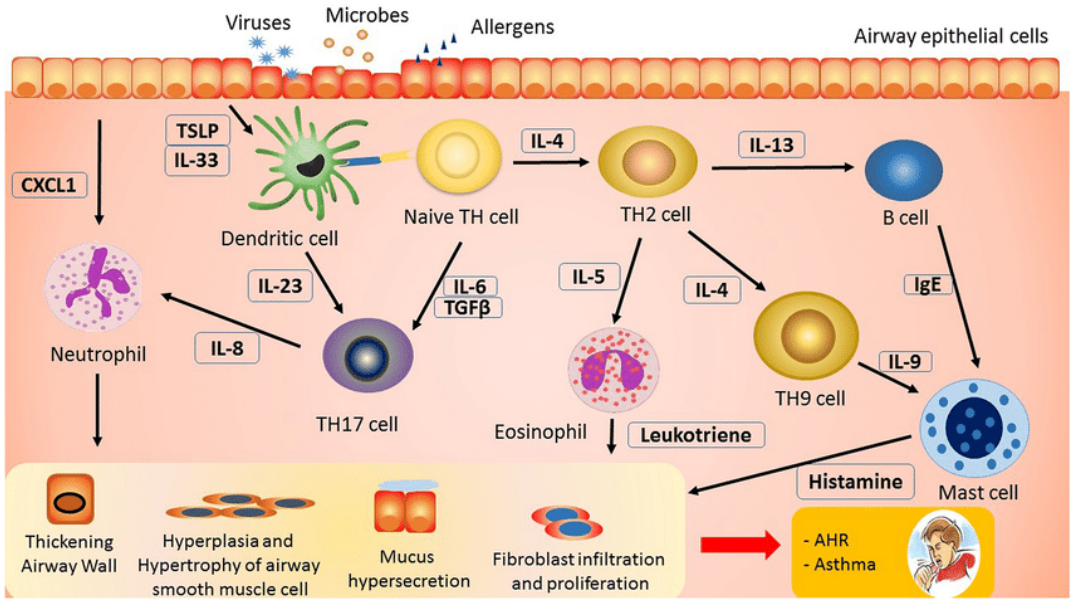

Figure 1. Diagram of immune response in asthma, and its effects on lung tissue. Adapted from Springer Nature

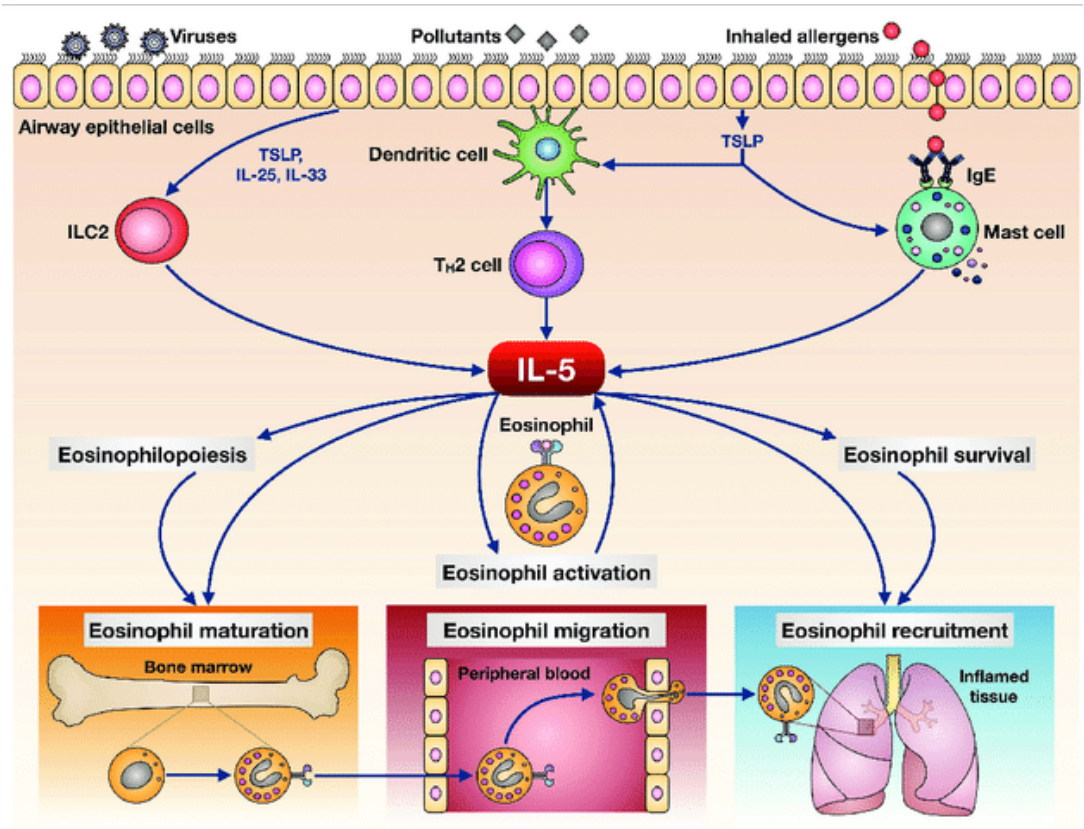

Figure 2. Diagram of mechanism of eosinophil activation an infiltration responsible for eosinic phenotypes of asthma, adapted from Frontiers in Physiology

2.5 Clinical Picture

The clinical picture of asthma can be quite varied between individuals but has a number of common features. The primary symptoms of asthma include wheezing, shortness of breath, chest tightness, and cough. An important differentiating feature of asthma is the frequency of symptoms. Asthma commonly involves patients having one or more of these symptoms occurring in episodes separated by time and with variance in intensity.(1) Patients with asthma generally report these symptoms occurring at night or when waking up, or after certain triggers. Common triggers for asthma include exposure to allergens, cold air, viral infections, exercise/ exertion, and inhalation of smoke, pollution, or other chemical fumes. Another common feature of patients with asthma is a history of

atopy and allergies.

2.6 Diagnosis

In diagnosing asthma, a number of factors should be considered. A medical history with the relevant respiratory symptoms indicative of asthma is the first step in making a proper diagnosis. When the patient's history is suggestive of asthma the next step for confirmation is with lung function tests.

Spirometry should be the first test performed, with special attention paid to forced expiratory volume in 1 second (FEV1) measured, and the ratio of this volume to the forced vital capacity (FEV1/FVC). (1)If there is a confirmation of limited expiratory airflow, as seen by a value of FEV1 <80%, and FEV1/FVC <75-80% of predicted variability should be assessed. A bronchodilator response test should be performed where spirometry is remeasured 15 to 20 minutes after administration of a short acting beta agonist. If there is an increase in FEV1 that is ≥12% and ≥200ml. If spirometry does not show limited expiration, bronchoprovocation tests can be used to confirm the variability of lung function. A methacholine challenge test showing a fall of ≥20% are confirmation of lung function variability and are positive confirmations of an asthma diagnosis. (1)

After the primary diagnosis of asthma is made treatment should be initiated. If patients do not respond to high levels of treatment a reconfirmation of asthma should be performed, and possible tests for determining the phenotype of asthma are indicated. Testing for asthma phenotypes is done using biomarkers. There are no absolute biomarkers of the various phenotypes of asthma but tests can be highly suggestive.(23) In diagnosing severe allergic asthma, useful indicators for further treatment are skin prick tests for specific allergens, blood tests to determine levels of IgE, and blood tests to confirm the presence of specific IgE to various allergens. A very important phenotype of asthma that is

commonly difficult to treat is eosinophilic asthma. Tests for the diagnosis of eosinophilic asthma include blood tests to determine absolute and relative levels of eosinophils, evaluation of sputum samples for the presence of eosinophils, and fractional exhaled nitric oxide measurements that indicate elevated levels of eosinophils in the airway.(1)

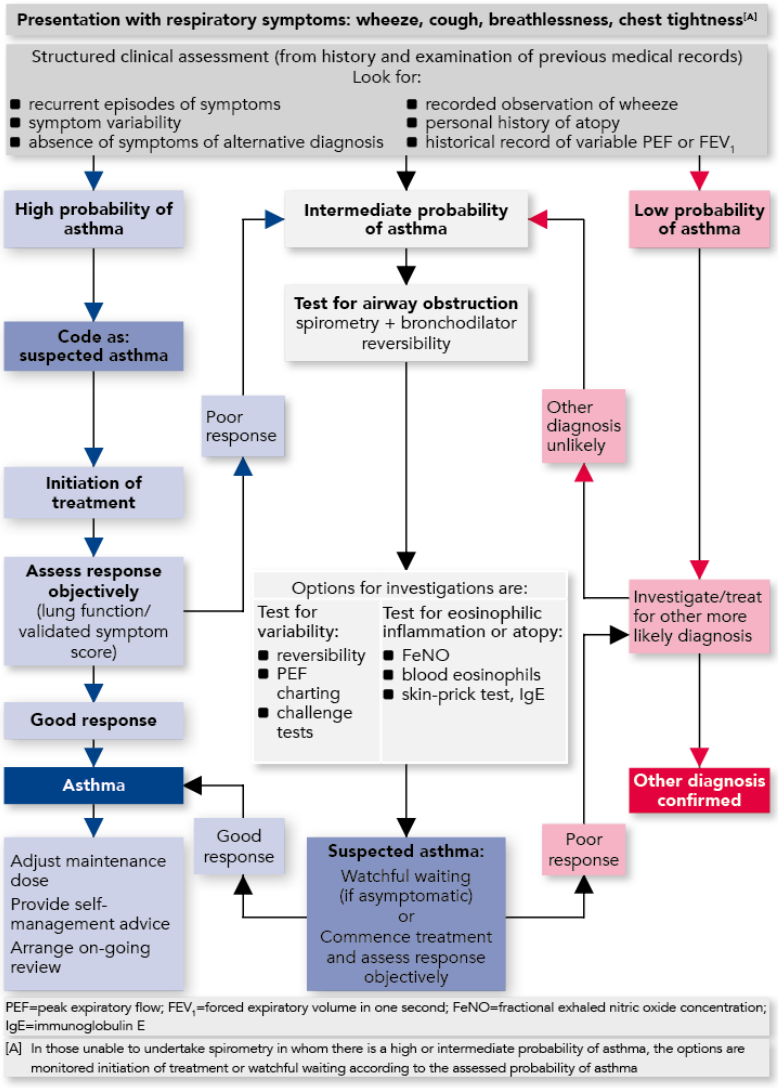

Figure 4. Diagnosis of asthma algorithm, adapted from GINA 2022 (1).

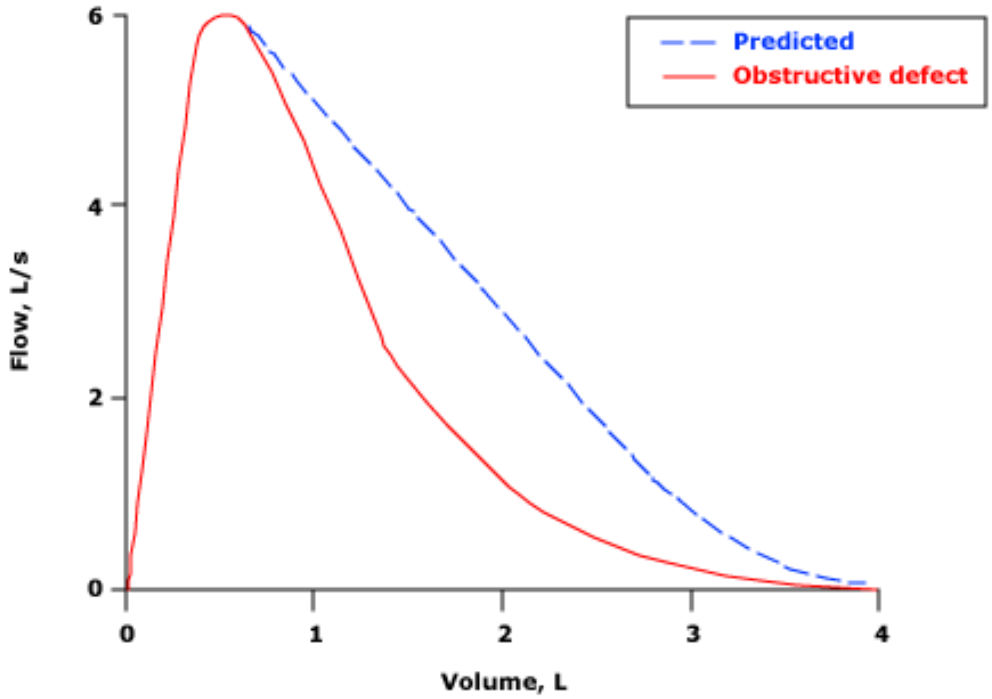

Figure 5. Spirometry showing predicted expiration compared to expiration observed in obstructive lung diseases. Adapted from, UpToDate

3. Overview of traditional asthma treatments

Treatment of asthma is individualized for patients and is guided on a stepwise basis, determined by the frequency and severity of symptoms. The goal of treatment is to achieve adequate symptom control and reduce the risk of exacerbations at the lowest effective dose. (1) The least severe cases of asthma (Steps 1 and 2) have a recommended combination treatment of low dose inhaled corticosteroids with a fast acting beta2 agonist (FABA), only formoterol, as needed. For patients with asthma that is not controlled using as needed treatment, regular use of the combination low dose ICS with LABA is indicated (step 3). Step 4 treatment is indicated for patients whose asthma is persistent despite maintenance use of combination low dose ICS/ LABA, these patients should be given moderate strength ICS/ LABA, with short course oral corticosteroids when severe symptoms are present. The last step available for asthma treatment is for patients who are still experiencing symptoms or have frequent exacerbations despite medication. Traditional treatment options available for patients in the step 5 category are limited to supplementing current therapy with the addition of a long acting muscarinic antagonist, or regular courses of OCS. Despite these intense therapies some patients still do not experience symptom relief, and can face many side effects from long term steroid use. Because of these circumstances, the development of new treatments is needed, which can be accomplished with the recent advances in biomedical technology.

4. New treatment options

With the development of immunotherapies, several emerging treatments for asthma have been created. These new treatments are very promising for a variety of reasons. Biologics target specific pathways in the pathogenesis of asthma. By targeting these specific points, the underlying cause of the disease can be treated and stop the chain reaction of inflammation which is very important in severe and difficult-to-treat asthma and shown to be highly effective. The specificity of these treatments allows for more effective control in the different phenotypes of asthma.

4.1 Anti-IgE

Omalizumab (Xolair) is a recombinant monoclonal antibody and the first immunotherapy that was approved for use in the treatment of asthma. Omalizumab is a step 5 treatment for controlling allergic asthma in patients ≥6 years old according to GINA guidelines and is given subcutaneously in weight dependent dosages every 2-4 weeks.(1) This drug primarily works by binding to free IgE antibodies at the site where they would normally bind to IgE receptors on mast cells.(24,25) This binding to free IgE forms immune complexes that are unable to attach to mast cells and can be cleared by the liver. By eliminating IgE on mast cell surfaces they are no longer able to be activated by allergens. In addition to eliminating free IgE, omalizumab has a secondary effect of decreasing the expression of the IgE receptor FCER1 which is present on mast cells, thereby potentiating its efficacy in controlling allergic asthma. (26)

Omalizumab has been shown to increase the quality-of-life scores of patients in trials, and had a significant effect on the reduction of asthma exacerbations while being treated, hospitalizations, and the required dosages of inhaled corticosteroids. (24,27)Trials of

omalizumab in patients with moderate to severe allergic asthma who were given subcutaneous omalizumab were shown to have a reduction from 26% to 16% chance of an asthma exacerbation. The reduced number of exacerbations in the omalizumab group was also accompanied by a reduction in risk of hospitalizations to just 0.5% compared to a 3% risk in placebo groups. (27) This is a major improvement in the quality of life for patients with allergic asthma taking omalizumab, and a promising improvement in overall control of the disease.

With the specificity of the treatment target of immunotherapies it is important to evaluate the specific phenotype of asthma that is being treated. Omalizumab is only approved in asthma treatment for moderate to severe allergic asthma. By having these designations, it is important to properly screen potential patients to ensure it is an appropriate treatment and will benefit the patient. Eligibility for treatment with omalizumab requires patients to have positive findings in allergy testing such as skin prick tests, total serum IgE levels, or high levels of specific IgE.(1) The ability to predict a positive outcome from treatment with omalizumab is an important area of study, and continues to be researched. Predictive factors identified to indicate successful treatment thus far include childhood onset, having primarily allergy driven symptoms, and various biomarker levels. (1) Important biomarkers that are tested and can be predictive of treatment efficacy are exhaled FENO levels ≥20 ppb (1), high ratios of specific IgE to total IgE (28), and elevated levels of eosinophils(29). Despite the effectiveness in reducing the severity of allergic asthma, other therapies needed to be researched to help treat patients who did not respond well to this treatment, and for patients with non-allergic phenotypes of asthma.

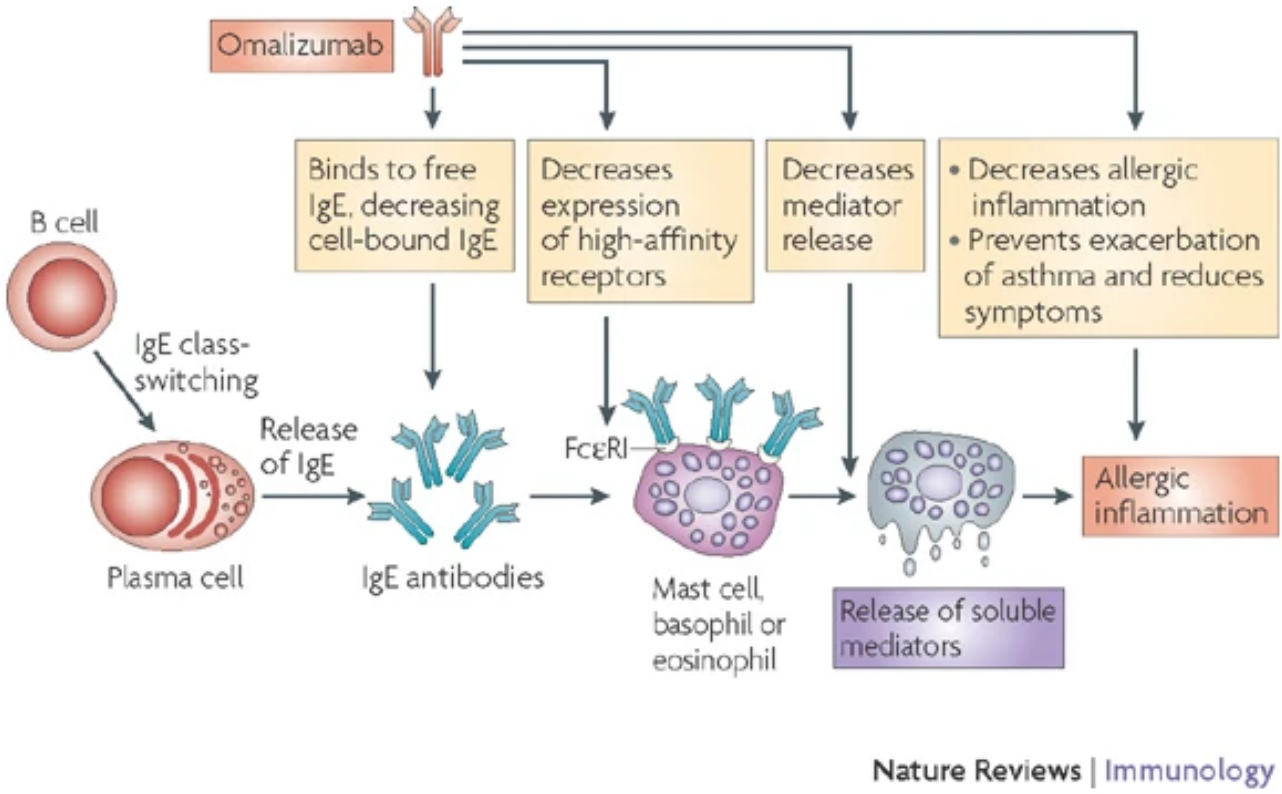

Figure 6. Mechanisms of action of omalizumab in allergic asthma. Reprinted by permission from Adapted from Nature Review Immunology

4.2 Anti-Il5

Among emerging immunotherapies for asthma, an important target being studied is Il-5. There are numerous drugs acting on these targets including mepolizumab (Nucala), and reslizumab (Cinqaero). Interleukin 5 is a cytokine that is responsible for the proliferation and activation of eosinophils. This opens up a very important target for the treatment of asthma because it can be used to cover multiple phenotypes. Unlike immunotherapies that only target IgE, by targeting IL-5 these drugs can be used to treat allergic eosinophilic phenotypes of asthma, including those with IgE thresholds below indications for anti-IgE therapies, in addition to non-allergic eosinophilic asthma phenotypes.

Mepolizumab is a humanized IgG1 monoclonal antibody that binds directly to Il-5, making it unable to attach to the high affinity Il-5 receptors on the surface of eosinophils. Mepolizumab is approved for the treatment of patients ≥12 years of age with moderate to severe eosinophilic asthma that is not well controlled with traditional therapies and is administered subcutaneously every 4 weeks. (1) Patients with frequent exacerbations (>4/ year) despite therapy and those needing continued oral corticosteroids (OCS) have been shown to greatly benefit from mepolizumab therapy. Randomized, double blind trials have shown mepolizumab to be associated with 32% reduced rate of annual exacerbations, a mean increase in FEV1 of 100 ml, and a very significant decrease in OCS dose averaging a 50% reduction. Patients also reported an increased quality of life and improvements of asthma control rated by SGRQ and ACQ-5 scores. (30,31) Positive predictive factors for good response were increased frequency of exacerbations in the previous year, adult onset of asthma, and blood eosinophils ≥300/μL, with effectiveness correlated to levels of eosinophils. (1,32)

Another monoclonal antibody treatment that targets IL-5 is reslizumab. Reslizumab has a similar mechanism of action as mepolizumab but is an IgG4 antibody and binds with a higher affinity to IL-5. (26) Reslizumab is approved for patients with uncontrolled eosinophilic asthma who are ≥ 18 years old and have blood eosinophils ≥400/μL. Reslizumab is given every for weeks as an intravenous injection with a weight dependent dosage. (1) Use of reslizumab in studied showed similar effectiveness to mepolizumab, with a mean reduction of OCS use of 50%, and a 30% reduction in the number of annual exacerbations, and a similar improvement in quality of life. (33)

4.3 Anti-IL-5R alpha

Biologic therapies directly targeting IL-5 have proven to be effective but are not the only pathway in treating eosinophilic asthma. Another drug, benralizumab (Fasenra), also inhibits eosinophils but targets the IL-5R alpha receptor present of eosinophils instead of the circulating cytokines.(34) By targeting the receptor, benralizumab is able to have a more broad effect on the immune activation pathway than by directly targeting free IL-5 alone. The effect of targeting the receptor directly causes two distinct mechanisms for the reduction of eosinophils and their activation. When these antibodies bind to the receptor, they become inactivated and are unable to bind to IL-5 for activation; this effect has a similar outcome to the binding of Il-5 directly. In addition to this, the binding of this receptor effectively induces the process of antibody-dependent cell-mediated cytotoxicity. (34,35) By inducing the cellular response of NK cells and macrophages, the eosinophils and basophils expressing the IL-5R are destroyed, with the clinical significance of greatly lowering the number of cells responsible for asthmatic inflammation instead of merely inactivating them. (34)

Benralizumab is approved for patients ≥12 years of age, with blood eosinophils ≥300/μL, and is given as a fixed dose subcutaneous injection every 8 weeks, after 3 injections every 4 weeks. (1) Treatment with benralizumab was demonstrated to be highly effective, with patients experiencing a 50-70% reduction in exacerbations, a 75% decrease in OCS use, and improved prebronchodilator FEV1 and ACS-5 scores. ((36–38)

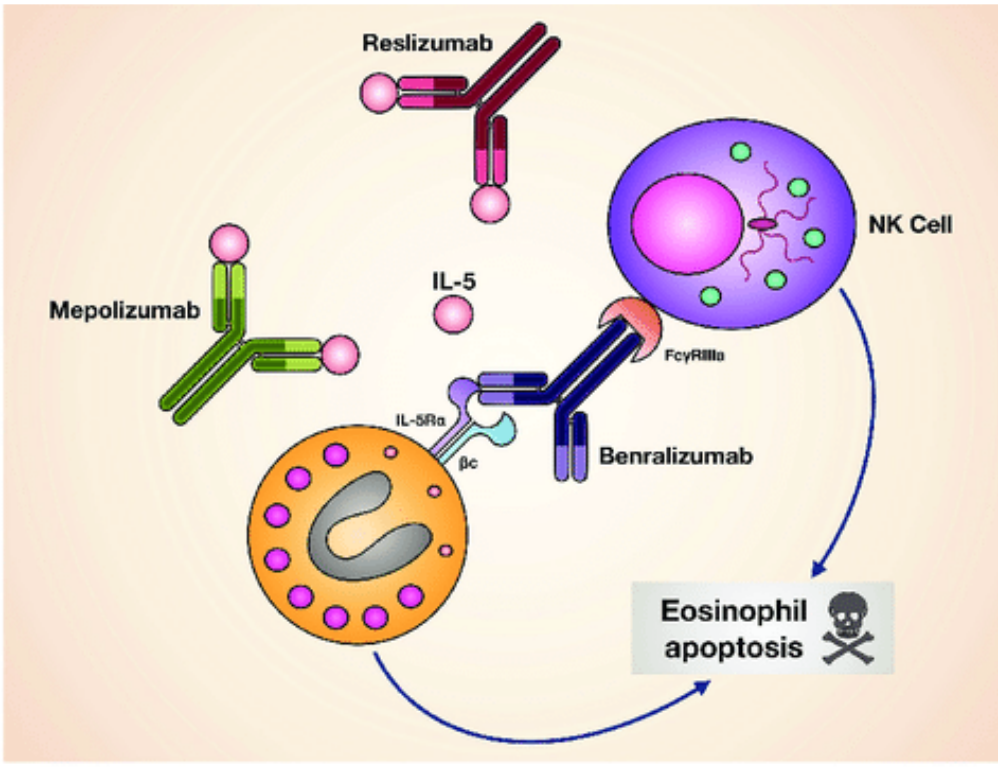

Figure 7. Comparison of active sites and cytotoxic mediation between Il-5R and Il-5 monoclonal antibodies. Adapted from Frontiers in Physiology

4.4 Anti-IL-4R alpha

Another important target for treating asthma is the receptor protein IL-4R alpha. This receptor subunit is needed for the activation of pathways for both IL-4 and IL-13. The monoclonal antibody treatment dupilumab (Dupixent) acts on this site to prevent its downstream effects. The action of IL-4 and IL-13 is to cause class switching in B cells to produce IgE antibodies, and stimulate the production of Th2 cell lines while inhibiting Th1 cell proliferation. (39) Inhibition of this pathway is able to reduce the number of cells and proinflammatory mediators released in a broader manner than therapies specifically targeting only eosinophils, giving dupilumab a wide range of asthma phenotypes it is indicated to treat. (40)

Dupilumab is given as a subcutaneous injection every two weeks for patients > 12 years of age, with uncontrolled moderate to severe asthma or moderate to severe asthma with concomitant uncontrolled atopic dermatitis. (25) Dupilumab has been shown to be most effective in patients with FeNO >25 ppb, but, importantly, was shown to be effective with or without elevated blood eosinophils. (41) Trials conducted on dupilumab showed a mean improvement of 50-70% in reduction of exacerbations, as well as a 50% decrease in oral corticosteroid use. (41–43) These studies also indicated that patients using dupilumab had a significant increase in lung function as measured by FEV1 and reported an increased quality of life. The efficacy of dupilumab, in concert with the broad range of phenotypical indications for asthma makes it a very important new drug in the treatment of this disease and a possible starting point for increasingly more effective treatments to be developed.

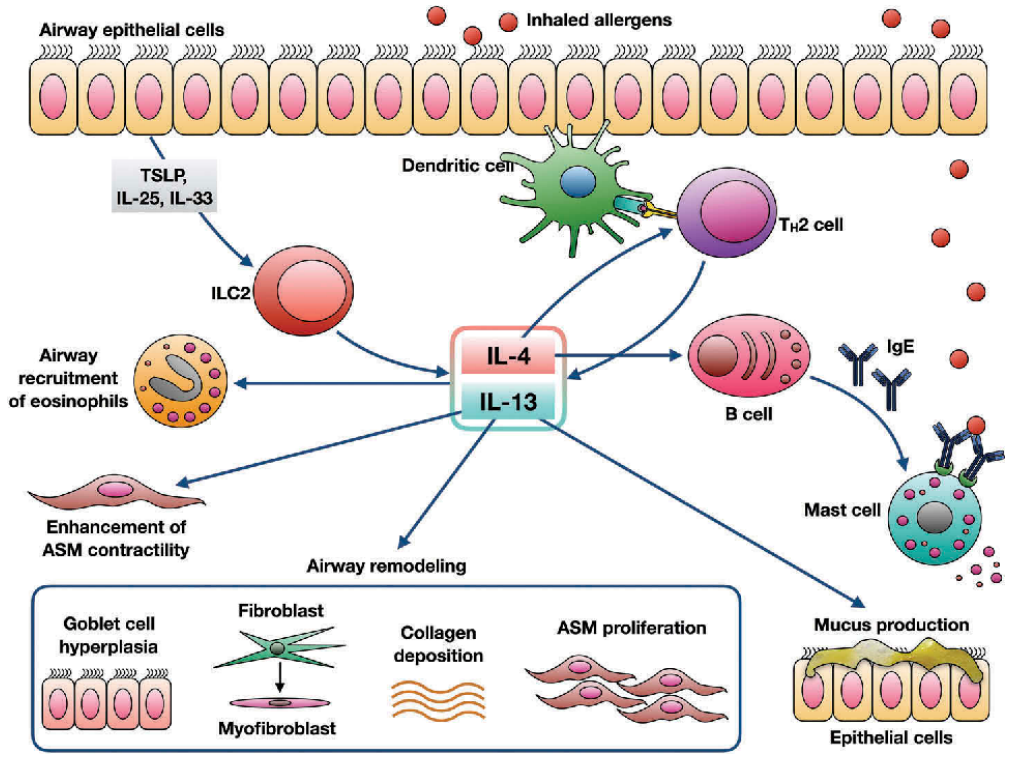

Figure 8. Pathway of immune activation in asthma via IL-4 and IL-13. Adapted from Frontiers in Immunology.

5. Discussion

The disease complexity and variability of asthma has made it hard to treat at times. New technologies have allowed us to get a better picture of the molecular basis of the pathogenesis of asthma and have identified potential points of treatment, specifically IgE, IL-5, and IL-5R. Despite having different mechanisms of action, current biologic therapies available acting on these targets show many similarities. There is considerable overlap between these therapies and their indications for use. It can also be seen that when compared to each other, there are not significant differences in the benefits or efficacy of these medications. This similarity in success for all of these treatments shows promise for patients who may be able to reach the expected level of benefit if a previously tried monoclonal antibody treatment for a different target molecule failed.

6. Conclusion

New treatments using monoclonal antibodies have proven to be useful and highly effective. Patients with severe asthma and those refractive to other treatments have been given new hope by this developing technology. The currently available biologic treatments for asthma have been of great use and indicate a positive trend in the treatment of multiple phenotypes of asthma. However, despite their ability to treat these phenotypes of asthma relatively well, there remain other phenotypes that are not treated by the current targets and pathways, and groups of patients who are still not responsive to these currently available therapies despite having a seemingly correct phenotype for the treatment. This highlights the need for continued research into other possible mechanisms for the treatment of asthma using immunotherapy and other new techniques.

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Biography

I am from Buffalo, New York. After high school I went on to study biomedical engineering at Boston University. After 3 years of study, I decided to change course and pursued a degree in Medicine at the University of Zagreb. I have plans to continue my medical career in the United States, and specialize in Family Medicine.