

Noval Biological Therapies in Allergic Asthma

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1. Abstract

Asthma is an intricate chronic inflammation. The airways distinguish by bronchial hyper responsiveness and irregular airflow limitation. Asthma affect 300 million people in the world. Asthma varies 60 to 80% genetically and 20 to 30% due to environmental contributions. Allergens trigger Th2 cell proliferation, Th2 cytokines and interleukin IL-4, IL-5, IL-13. Long lasting therapies aims to attain to control symptoms and reduce the danger of future inflammation. The old treatments of asthma like Inhaled corticosteroids, inhaled bronchodilator and use of other saving drugs are sufficient to reduce asthma inflammation, but these have much side effects. Scientists are trying to make biologic that has very few side effects. Omalizumab is an approved biologic and currently best biologic to treat severe asthma. Moreover, Fevipiprant is in its last stage which reduce asthma exacerbation. Biomarkers give precise clinical details about asthma phenotype. Biomarkers are under research to treat asthma. These novel biologics are promising for future.

2. Introduction

Asthma is a long-term disease of the lungs. It makes airway inflamed and narrow. Moreover, it results in difficult breathing. Severe asthma can cause trouble talking or being active. Some people refer to asthma as bronchial asthma [1]. Asthma is a long-term exacerbation. There are new biological treatments that help to treat allergies in efficient way. The new biological therapies that precisely block cytokines either directly or indirectly via their receptors [2]. This suggests a wide spectrum of effective treatments for inflammatory diseases. To understand the disease, it requires

deep study for the use of advanced treatments in order to make it effective. Scientists observe that asthma is not uniform but it is a heterogeneous inflammatory disease with various phenotype [3]. There are two categories of asthma i.e., Intrinsic and extrinsic. Intrinsic is a non-allergic asthma and extrinsic is allergic asthma [4]. Type 2 (Th2) lymphocytes support the pathophysiology of allergic asthma which coordinate the immune inflammatory response of asthmatic airways. In Th2 pathways, the new biological therapies target many mediators (IgE, IL13, IL5, and IL4).

3. Prevalence of Asthma

Asthma is a heterogeneous inflammatory disease which affect the airways of the lungs. It is the long-term disorder which narrow the airways. The airways of lungs distinguish by bronchial hyper responsiveness and irregular airflow limitation. Asthma affects 300 million people in the whole world [2, 5]. It affects 8% of North Americans and also 7.0 million children in United States, and recent survey determined that the prevalence of disease increases in the whole worldwide [6]. The signs which arise in patient are breathlessness, coughing, pain in chest, sleep problems because of breathlessness and some other symptoms that arises daily specially at night time such as wheezing and chest tightness [3]. Asthma varies heritably 60 to 80% and 20 to 40% due to environmental contributions. Allergic asthma caused by pollens, dusts, mold and pets. Non-allergic asthma is caused by environmental factors like cold air, some environmental pollutions, and powerful smells these are some causes that triggers non allergic asthma [7]. Asthma also triggered by heavy physical work, strong feelings, and stress (Figure 1).

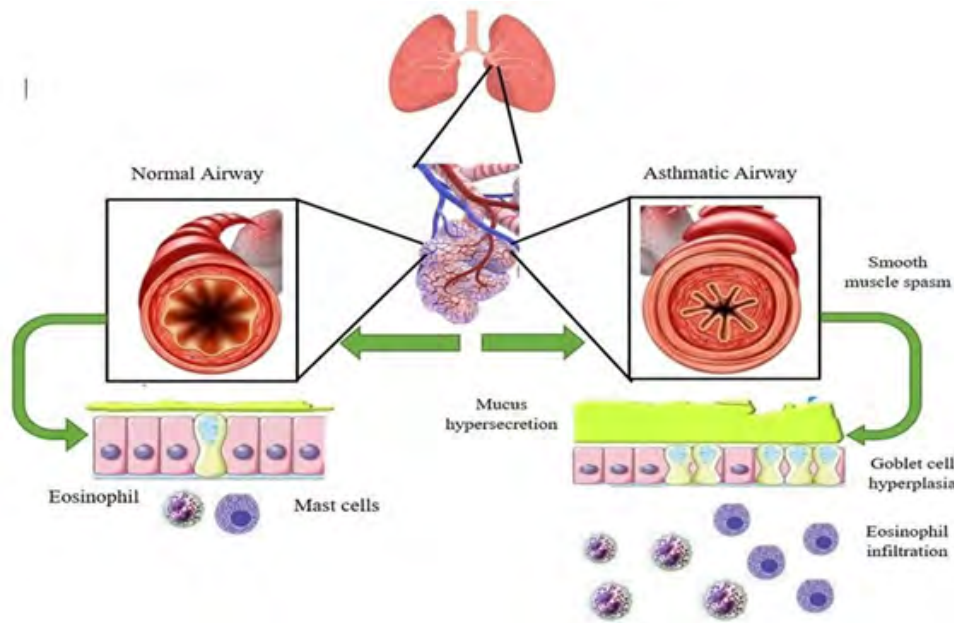


Figure 1: The airways of asthma patients are more complex as compared to normal individuals because of mucus hypersecretion, expansion of goblet cell number and also expansion of eosinophils in plasma.

4. Pathophysiology of Serve Asthma

Asthma starts from childhood due to house dust mites, fungi and pollen allergies. These allergens trigger Th2 cell proliferation, th2 cytokines, interleukin IL-4, IL-5 and IL-13 [8]. Research has been determined that asthma inflammation was a key to pathology of the disease.

4.1. Histopathophysiology of Asthma

Asthma is treated as nonspecific hyperreactivity and heterogenous exacerbation [9]. Impact of wide mucus struggling in bronchus, segmental and peripheral airways lungs are typically overinflated. Lung parenchyma stay relatively intact in [10] subjects who die in exacerbation known as status asthmatics [11, 12]. Goblet cell and squamous cell metaplasia the epithelium of the lungs naturally displays sloughing of ciliated columnar cells. The improved thickness of subepithelial basement membrane is there. True basal lamina is made of normal thickness. When thickness of SBM develop it is associated with the assembling of other components beneath the basal lamina [13]. IL-13 contributes in regulating exacerbation of lungs in asthma [14].

Researchers simply picked (BAL) specimens and lungs tissue from the patients with airway inflammation. Research had determined that both specimens play a role of cytokinesis produced by Th2 of CD4+T cells in asthma pathology [15, 16]. In some years, interest in remodeling of airway wall mechanism increases which also explain that only airway inflammation does not describe the hyper-sensitivity and chronicity of asthma. The remodeling of lungs wall may be treated in terms of extracellular matrix deposition. Wounded epithelium behave frequently stimulus to airway remodeling.

Remodeling has slight effect on mechanics of respiratory base-line and extracellular matrix accumulation so as a result specific amount of narrowing of (ASM) contraction [17]. Patients have more thick walls. Thickness is due to high ASM mass and mucus. Unexpectedly, physical power generated by ASM activate remodeling of airways in patients. More research is needed between remodeling and chronicity of asthma [18] (Figure 2).

When Th2 and ILC2 stimulate so as a result IL-4, IL-13, IL-5 and IL-9 discharge and type 2 exacerbation develop.

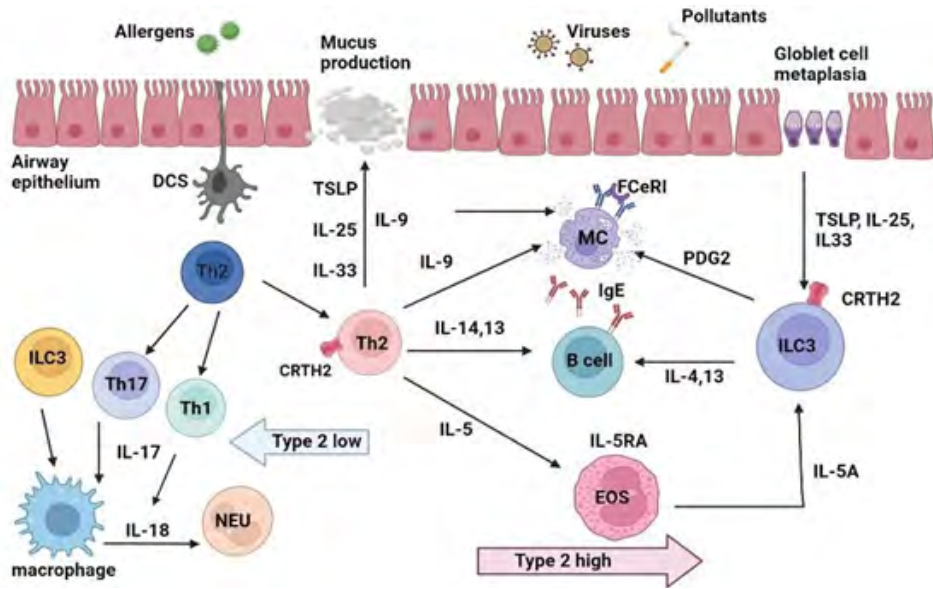


Figure 2: A schematic overview of pathophysiology. In type 2 low exacerbation, when epithelial cell and Mo cell stimulate Th1, Th17, ilc3 and CRth2 show on Th2 cell and ILC2. In type 2 high allergens, viruses and other pollutants are entered through epithelium and discharge TSLP. IL-33 and IL-25 stimulate dendritic cell and ILC2.

4.2. Epithelium

The codependent inflammation and remodeling cause physical change in airways of lungs [19]. In this process the mucus secretions increase in epithelium cells. The inflammation allow injury to the epithelium cells and after some time remodel in the injury repair cycle. Some recent researches determined that patients with infected epithelium cells have low profiling markers and wide damage, due to inhaled agents and inflammation the breakdown in epithelial injury cycle is exposed [19]. Epithelial damage results in continuous development in EGf receptors, that results in epithelium locked in a repair phenotype. During repairing the cells make profibrotic mediators, TGF- β , fibroblast growth factor and endothelin, which modulate fibroblast and myofibroblast they release some substances which make airway wall thicker. Eosinophils also help to remodel airway of lungs, because they discharge eosinophils derived TGF- β , cytokines and relation with mast cells. The features also trigger mesenchyme cells and epithelium so these features help in remodeling [20]. The Th2 response of cytokinesis eosinophils stimulate TGF- β 1 which perform as a stimulus to extracellular production. EMT TGF- β 1 improved remodeling of airway and treatment with anti TGF- β 1 stop EMT in airways [21]. The epithelium acts as a hurdle against foreigner from the environment, but in asthma patients the epithelium is defective and do not function properly. Strong and healthy function is significant to avoid sensitization and progress in many allergic diseases [22].

4.3. ASM

Huber and Koesser in 1922 defined the structural irregularities of ASM in asthma. They described that patient who died with acute exacerbation, have more extra smooth muscle as compared to those who died from another illness. Restriction in breathing is

due contraction of muscle and it is the major symptom [10]. ASM role in asthma is necessary. Irregular assemblies of SMC cells is alternative mechanism of remodeling [23]. In animals' research have been determined that if allergens are long term so it also increase the thickness of smooth muscles. Myosin binding and plasticity have different mechanisms [24]. They have ability to develop relation and also have a vital effect on the contractual volume of ASM and possible to cause extreme narrowing of the airways.

ASM also trigged when ASM makes a bond with intracellular calcium ions. Intracellular calcium ions which come from extracellular atmosphere and form sarcoplasmic reticulum stores. Intracellular Ca²⁺ come over voltage dependent calcium channel. We noticed in cardiac, skeletal and muscle cells that the origin of ca²⁺ in airway smooth muscle mostly construct intracellular sarcoplasmic reticulum stores relatively extracellular Ca²⁺. Acetylcholine and methacholine are ligands GPCR means G-protein coupled receptors, which cause stimulation of phospholipase C (PLC), and start forming inositol triphosphate. IP3 arises because it helps to release ca²⁺ from SR stores then ca²⁺ makes a C-C complex (calcium-calmodium) and then it stimulates MLC Which phosphorylates RMLCs formed forming phosphorylated-MLC [25]. The stimulation of actin and myosin cross bridges result in shortening and tightening.

Secondly, SM can cause calcium sensitivity through Ras homolog gene family, member A RhoA/Rho kinase pathway [26]. RhoA stimulates Rho-kinase which phosphorylates MLCP. When RhoA/Rho kinase signaling pathway regulate it can cause blockage of MLPC, so as a result the level of p-MLC and contraction force are enhanced. the RhoA protein and mRNA treated through cytokines, such as IL-13 and IL-17A that increase the contraction

of ASM. IL-17A alter integrin $\alpha\beta 8$ on DCs which show reduce response against IL-17A-induce antigen challenge [26]. ASM also play a role in airway remodeling. Immunoglobulin E change ASM cells into a proliferative, SM proliferation induced by (MMP)-2. Matrix metalloproteinase recommend that ASM play a role in airway remodeling [27].

4.4. EMTs on Asthma

EMT is a process in which (EP) cells decrease their action and bonding. It induced weak connection between them. Antagonistic characteristics alter their cell creation to mesenchymal cells [28]. EMTs observe more significantly in asthma than before. Mesoderm formation and neural tube formation is necessary for processes because it take part in wound healing in cancer metastasis. The phenotype of both cells is different and found in embryogenesis. It is divided into 3 types Type I, Type II and Type III. Type II take part in wound healing and also remodel the airways of lungs. Type II observe that the epithelial tissues show plasticity [28]. It is Started by extracellular signals and connections with growth factors such as TGF- β and EGF. TGF- β involves in EMT and airway remodeling. TGF- β cause the formulation of smooth muscle actin and vimentin and also decreases E-cadherin [29]. The physical effect of TGF- β signaling in the structure exposed to depend on microenvironment. (BMP)-7 flopped to reduce TGF- β that activate EMT, and BMP-4 member take part in EMT in the airway [29, 30]. TGF- β cause reduction of wound fixing and intercellular adhesion which are found in EMT which can also increase by (TNF) α tumor necrosis [31]. In long-lasting house dust mite-exposure model, the epithelial cells exposed to raise the formulation of nuclear phosphorylated Smad3 and TGF- β . Collagen α smooth muscle actin show when tight connection of protein was diffuse. When inhaled allergens is with cytokinesis it alters EMT [32].

4.5. MCs and EO

Mast cells cause the stimulation of mesenchymal cells [33]. During process fibroblast propagation enters to cut and stimulate protease R-2 along with fibroblasts [34]. Mast cells discharge plasminogen activator inhibitor type 2 which contribute in remodeling of the airways. $\alpha\beta 6$ integrin is a Mice deficient which are protected from inflated airway contraction.

Mast cells protease 1 in mouse activate by allergen in (WT) mice and Mmcp-4 enhanced $\beta 6$ deficient baseline which is present in Mice. The proteolytic substrates of MCPs modulate airway hyper-reactivity [35]

Eosinophils are mixing granulocytes and only 3% present in white blood cells [36]. They released toxic granule proteins cytokines, lipid mediators and ROS. Proinflammatory mediators play a major role in pathogenesis of asthma, such as asthma exacerbation, epithelial cell damage etc.

Eosinophil also take part in remodeling of airways and they discharge TGF- β , cationic proteins secretions, and cytokines [4].

4.6. Extracellular Matrix

The airways express extra growth of extracellular matrix components [37, 38]. In mast cells and fibroblasts, the cellular interactions are triggered by receptor-2. It takes part in as irregular mesenchymal cell explosion and enhanced the number of fibroblasts and myofibroblasts that are present in airways. Myofibroblasts play important role in airway remodeling and its numbers are also improved in airways [39]. SM have ability to change extracellular matrix environment. Reticular basement membrane contains plexiform deposition of immunoglobulin such as types I and III collagen, tenascin and fibronectin [40]. Extracellular remodeling methods are less recognized as compared to thickening of lamina reticularis [38]. Asthma activities exist with irregular superficial elastic fiber in which fiber are fragmented [41]. Overlying of elastic fiber is also irregular because the fiber is frequently twisted, irregular and condensed. Research with electron microscopy observe that, in patients elastolytic process happens and in some other disturbance of fiber is detected. Asthma is incurable because of destruction in elastic fiber [42]. Research proved that volume of airway changes mostly in those patients which serves long term asthma. More research indicate that SM transformation is linked with asthma severity [43].

4.7. Immunological Responses

4.7.1. Hypersensitivity: Allergic sensitization is a result of intricate interaction between allergens and host in a certain environmental situation. Hygiene hypothesis give a point that why the number of patients increasing with the passage of time. The conclusion is that the opposite response of Th1 cells is not activate initially in life leaving the body to modify Th2 disease [44]. It has been determined that children of the bigger families have fewer fever and eczema. The Th1 immune response is originated by various bacteria and viruses which cause the downregulation of Th2. The prevalence in urban ruler established more firmly in children because of their environment, they raised in the environment with broad diversity of microbial exposures, because they safe children from childhood asthma and immediate allergic reactions [45]. Basic mucosa is a specific population of (APCs) and it is known as DCs. DCS carries allergens and show minor peptides from them. DCs change allergens into minor peptides and show innate immune response, and show them through MHC class I and MHC class II and it is recognized through T cell receptors. In patients, it is upgrade by allergic interaction, Fc ϵ RI is big affinity receptor for IgE [46]. DCs is not present in the airway of lungs when a person born. Stimulation of the respiratory epithelium is the main catalyst that began the acceptance of DCs. Immature DCs and present in the bone marrow and discharge chemo kinase C-C and then moves towards epithelium and basic mucosa [47].GM-CSF discharged when IL-4 and TNF- α is present and cause DCs maturation to totally sufficient as APCs. In the beginning when allergens enter in and sensitizing the airways of lungs, Th2 lymphocyte T naïve cells

need IL-4 discharge. Mouse research determined that, in Th1 and Th2 responses microRNA-21 plays a crucial role in stability within Th1 and Th2. It can attach the gene coding promoter IL-12P35 and stops stimulation of Th2 profile. Low levels of microRNA-21 lead DCs to generate extra IL-12 and also T cells to generate new IFN- γ . It produces low IL-4 which leads to increase delayed hypersensitivity [48].

4.8. DCs Stimulation

DCs developed their actions into EP cells and lumen and make a compact junction to recognize allergens [49]. In mouse the subcategories of DCs are explained according to the manner of myeloid conservative (DCs cDCs, CD11c⁺) and plasmacytoid DCs CD11c. CD11c⁻ pDCs and CD11c⁺ myeloid DCs are subcategories of human [50]. Proteolytic tasks also trigger allergens. After interaction with allergy the (TLRs) activate on DCs and regulate chemokine receptors. The subcategories of cDC manage antigen presentation. When DCs mature it form an immunological junction with T lymphocyte to begin a Th response. Th with B-cell follicle moderate class switching IG from IgM and IgE and others pull back to mucosa which is found in airways of lungs and cause Th2 response by the excretion of proallergic cytokines. TLRs moderate the response to pathogens (PAMPs) which are present in the form of fungal, viral products also endotoxins which is detected by TLR4 such as proteins TLR2 and TLR6, RNA (TLR3 and TLR7/8) and DNA (TLR9 [51]. To enhance Th2 immunity inflammatory DCs is effective. With the help of basophiles, the DCs increase Th2 immunity. Collaboration of EP and DCs manage the progress in asthma, Th2 stimulation need DCs mediated antigen. In the absence of DCs allergens remains inactive [47]. Molar concentration of DCs increases by TRLS along cytokines (IL-25, IL-33, GM-CSF).

4.9. Viruses

Asthma increases if Individuals have multiple allergens [52]. Rhinovirus infection is the main reason of acute disease. If an individual is genetically at risk of asthma, initial whistling due to rhinovirus also increase the risk of asthma, when individual becomes 6 years old[53]. IFN is an interferon that inhibit viral replications. Infected epithelial cells accept to damage through infection, the cells produced large amount of Th2 (TSLP) which trigger dendritic cells and enhanced allergies, however exogenous IFN- β utilize antiviral characteristics [54].

4.10. Cellular Immune Response

Asthma is typically th2 disease. Th2 stimulation need Dendritic cells, DCs contribute in maintenance of airway exacerbation. Tentative models of asthma showed that IL-13 plays an important in pathology of asthma. it seems that now asthma is not basically a Th2 disease. CD4 is an effector cells stating IL-17A, IL-17F and supposed to signify a diverse T-cell line. It helped in the initial modification of Th1/Th2 pattern of immunity. Polarity of naïve T cells generate the impression of ROR γ t when IL-6, TGF- β exist.

IL-17 expressed along Smad 2/3, STAT 3 and NF- κ b. NT cells can distinguish various cell categories and have a definite immunity to discharge cell type specific cytokines. Th17 contribute in the regulation of neutrophilic and macrophage exacerbation. Currently they have been recommended to involve in asthma and other. On the other hand, their variation is controlled by Th1 and Th2 as well as IFN- γ , IL-4, and IL-13. Precisely CXCL8 is an effective chemokine whose impression is high in airways and precisely imply Th17 cells in neutrophilic airway exacerbation. IL-17A increases the contractility force of Airway smooth muscle. Hypersensitive mice have deficiency of integrin α v β 8 on dendritic cells so as a result they express less stimulation of IL-17A linked path. SM contraction is flexible to IL-17A and express the connection of IL-17A on airway hyperresponsive. Allergens cause a powerful Th17 response with airway neutrophilia and hypersensitivity. The response is revoked in IL-17F busted mice. In humans the contribution of IL-17A and IL17F is not authentic but play a role for IL-17A and IL-17F in mediate to severe disease. The subclasses of Th2 memory and effector cells in human beings expressed GATA3 and ROR γ t together and generate Th17 and Th2. Research have been determined that the amount of Th17 cells and plasma accumulation of IL-17 or IL-22 is improved. In human asthma influence of Th17 has not been recognized sufficiently. More research in needed to clear the role of Th17 in human asthma

4.11. Cytokines

(IL)-4, IL-5, IL-9 and IL-13 are interleukins which are generated by type 2 (ILC2) cells [55]. They distinguish themselves from primogenitor cells when (TSLP), IL-33 and IL-25 occurs. Th2 and ILC2 shows both ST2 and prostaglandin D2 receptors. Moreover, it is determined that weaken epithelial barrier causes more stimulation of ILC2 and Th2 17, so that's why they enhanced Status Asthmaticus [56]. IL-4 contributes in isotype switching of b cell and synthesized IgE. IgE connects to its high-affinity receptor at the surface of mast cells and brings their activation as well as degranulation. Instant discharge of preformed mediators like histamine, tryptase and heparin in addition to de novo production of various lipid mediators together with prostaglandins and leukotrienes resultantly bring it to bronchoconstriction [57]. IL5 is crucial for development and subsistence of eosinophils. IL-9 mediates mast cell and eosinophil buildup. Eosinophilia relates to airway remodeling and mucus manufacturing. IL-13 contributes in bronchial hyper-reactivity, goblet-cell metaplasia and mucus construction along within fibrosis [58-60].

5. Improvements in Current Treatments

Long lasting therapies aims to attain to control symptoms and reduce the danger of future inflammation that stable the restriction in the airflow and aftereffects of therapies [61]. A complete method which contains nonpharmacological actions. It is step-by-step method which enhanced the dosage of medicines. ICS is frequent-

ly in sequence with a second controller and beginning with β_2 agonist and then ultimately totaling leukotriene receptor antagonists or theophylline beforehand the usage of systemic corticosteroids [61]. Inhalation method regulates asthma therapies [62].

About 5 percent asthmatic patients require escalation to phase 5 and the usage of systemic steroids stayed uncontrolled which describes them as asthmatic patients with acute severe asthma under ERS/ATS measures.

Present goals for type 2 asthma are IgE Omalizumab, IL-5 mepolizumab and Reslizumab, IL-5Ra benralizumab and IL-4Ra dupilumab are the drugs which control acute severe asthma [62].

Omalizumab is an improved monoclonal antibody, which is fixed in case of IgE and it was the first biological treatment which is present in clinical situations ultimately 2000s. It is approved medicine to mediate acute severe allergic asthma in patients which is less than 6 years old with IgE more than 30 IU/L [63]. Omalizumab stops IgE to attach with (Fc ϵ RI) which is affinity receptor, and present on mast cells and basophils which inhibit their allergic responses.

It also decreases the impression of IgE receptors on mast cells. Various random control trials (RCTs) and actual research shown that Omalizumab decrease asthma inflammation [64]. It reduces 25% hospital entries of children's and adults. Omalizumab also decrease virus-associated inflammation, and is well approved, with lonely 0.1 danger of anaphylaxis [65-67] (Figure 3).

Mepolizumab and Reslizumab targets IL-5, avoiding it to attach with its receptor. They are approved drugs [64]. Mepolizumab also decrease asthma inflammation by approximately 50%, minor development in the function of airways and QoL [65]. In asthmatic patients with OCS, mepolizumab decrease its amount by 50% in similar with a decrease of inflammation and through no damage of asthma control. It has a protective profile which is parallel to a placebo [66, 67].

Reslizumab also decrease asthma inflammation which is parallel to mepolizumab and it enhance FEV1 in 4 weeks [68] Reslizumab is the only one circulatory monoclonal antibody. Reslizumab dose is weight based and it is well approved with negative effects, which is parallel to placebo, while three patients of anaphylaxis have been noted [65].

Dupilumab attack IL-4a receptor and inhibit the motioning of IL-4 and IL-13. It monitors in mediated severe asthma and almost decrease 50% asthma inflammation and boost the function of lungs (FEV1) among 2 weeks [69]. Asthma patients have steroid-dependent inflammation, dupilumab decrease 70% usage of OCS, and it also decrease 60% inflammation and enhanced the function

of lungs [70].

Benralizumab focused averse to IL-5Ra. Because of its afucosylation, benralizumab interrelates with Fc γ RIIIa receptor in NK cells make an antibody-dependent, cell-mediated cytotoxicity so as a result in quick decrease of eosinophils [71]. It also decreases asthma inflammation which is parallel to another anti-IL-5 biologics. It has oral steroids-sparing effect which decrease 70% inflammation [72].

The result of RCTs is it decreases asthma inflammation, OCS effects and also decrease the amount of hospital entries. The results of another clinic trail the function of the lungs is not absolute [1]. Omalizumab exposed nominal or ambiguous development in the function of lungs. Stage three study of A Dupilumab expose the development in FEV1 equal to 0.32/L at 12 weeks [69]. This research illuminate that the further research is required in future to estimate the result of biologics in lung weakness.

All biological treatments stated above protect patients from acute severe asthma. Through biologics, a good long-term suggestion occurs for anti-IgE therapies without any trouble till now. Until no long-term data is present for anti-IL-5/5Ra and anti-IL-4Ra [64]. At this time, eosinophils also play a significant role in exacerbation.

Further studies for next-generation biological treatments are continue. Tezepelumab is a monoclonal antibody that attach with TSLP, it is alarmin that plays an appropriate role in asthma pathogenesis and it is an ambitious effector T2-high pathobiology pathways [73]. The clinical trials openly exposed that patient with severe asthma who accept Tezepelumab had less inflammation and moderate asthma dissimilar to blood eosinophils and FeNO [74]. It is reported that the license of Tezepelumab is approved.

Iptekimab antibody target IL-33 and it is an alarmin which is related to TSLP, leading to the stimulation of T2-high inflammatory pathway [75]. Clinical trials are continued, but initial results are not satisfactory in severe asthma when it is related with dupilumab or dupilumab alone.

Tralokinumab and lebrikizumab are the antibodies that target IL-13. The outcomes of stage 3 research are unsatisfactory in Oder to reduce inflammation and OCS [76]. In the last concern about Th2-low asthma is mostly categorized by a neutrophilic airway's exacerbation, attempts are concentrating on its pathogenic issues which is related to cytokines, for example IL-1beta, IL-17 and IL-23. Various monoclonal antibodies such as canakinumab targets anti IL-1beta, Brodalumab attack anti IL-17 receptor and Risankizumab attack anti IL-23, all these interleukins are under research [77, 78].

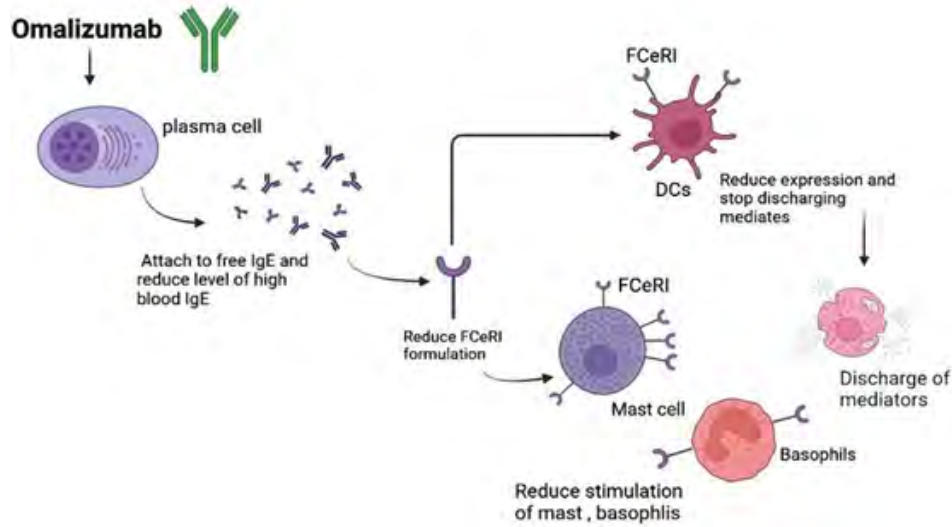


Figure 3: Omalizumab attached with free IgE which cause reduction in the level of blood IgE and inhibit their connections with FcεRI which is showed by dendritic, mast and basophils. It also reduces the activation of mast cells and basophils stop releasing mediators.

6. Chose a Biological Therapy

Omalizumab is always first choice when we choose a biological treatment for allergic asthma. Inversely individuals with a non-allergic serve asthma should be handle with an anti-IL-5 medication.

In last anti- IL- 4/IL-13 should be saved for asthmatic patients with severe eosinophilic type 2 asthma. However, the accurate biological treatments are still unknown and further research is continued [73] (Table 1) (Figure 4).

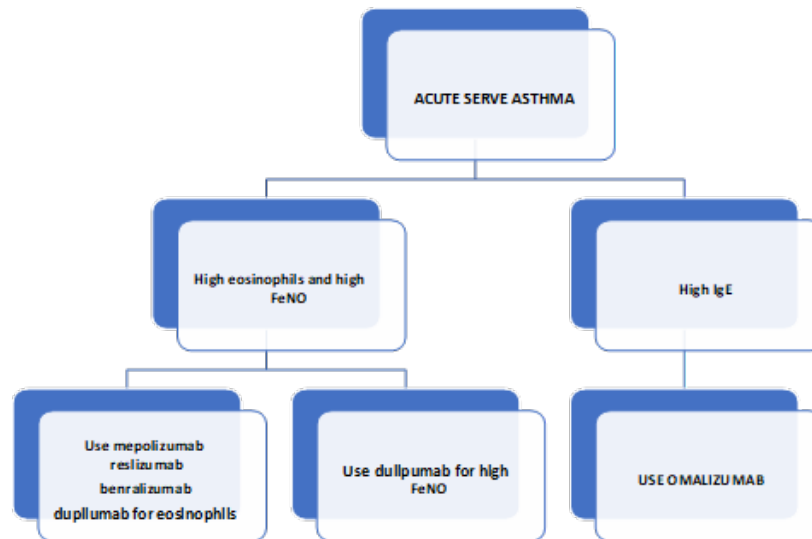


Figure 4: Procedure of Choosing absolute biological therapy for serve asthma.

Table 1: Biological therapies that are recently accepted.

MEDICINE	ACTION	LISENCE	Negative effects
Omalizumab	Target IgE	It is approved drug	0.1% anaphylaxis
Benralizumab	Targets IL-5Ra	50% improved	Rare hypersensitivity
Dupilumab	Targets IL-4Ra	It is approved	18% risk of IR and rare hypersensitivity
Mepolizumab	Targets IL-5	Approved drug	Induce hypersensitivity
Reslizumab	Targets IL-S	50% improved	0.3% risk of anaphylaxis
Tezepelumab	Targets TSLP	In stage 2	----
Fevipirant	----	Under research	----
Brodalumab	Attack anti IL-7	Under research	----
Risankizumab	Attcak IL-23	Under research	----

The table shows the novel and licensed medicines which are useful to reduce exacerbation and that are under research.

7. Future Therapies of Serve Asthma

The involvement in rising future targeted therapies has been increasing day by day mostly for type 2 exacerbation. A new exciting approach is to adjust the distribution of monoclonal antibodies in airways [79]. Recently, a nebulized biological treatment method that attack IL-13 is under development [80]. Fevipiprant is a drug which decrease exacerbation and it is on its last phase of research [81]. Establishment of biomarkers to recognize appropriate patients and predict to identify the response to these medications is important for the future. Biomarkers give precise clinical details about asthma phenotype [82].

8. Conclusion

The pathology of asthma generally contains the collaboration of lymphocytes and EP cells. Subsequently, the most capable medications to cure allergic asthma is now licensed or under progress to overcome the type 2 immunity. Mostly patients do not require biological therapies, if they use their general medicines daily or in a week. Yet, the most appropriate biological treatment for acute severe asthma with lapping phenotypes is quite blurred, hence needing more deleterious and prophesy biomarkers which tolerate a well patient selection.

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