Biologics in the Treatment of Severe Asthma

By

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Declaration

It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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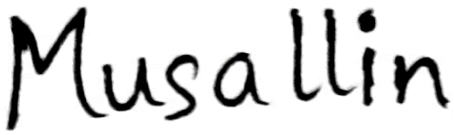

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Approval

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Ethics Statement

This project is a review article and it does not involve any animal trials or clinical trials on humans.

Abstract

At present, asthma is one of the major chronic respiratory diseases that distorts the daily life of nearly 300 million people around the globe and almost 5–10% of these people experience severe or uncontrolled asthma. Asthma is a condition in which the airways undergo chronic inflammation resulting in wheezing and difficulty in breathing. It is predominantly triggered due to an irritant or an allergen, virus exposure, exercise and emotional stress. Contemporary treatment of asthma includes inhaled corticosteroid (ICS) with montelukast or theophylline as additional controllers and oral corticosteroids and inhaled long-acting beta 2 agonists (LABA) are administered in case of insufficient control of symptoms. The advent of biologics became pivotal since the conventional treatment alternatives were ineffective in the control of severe asthma. Omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab and tezepelumab are the biologics that have been implemented successfully in treating severe asthma patients. This enabled patient specific, safe and effective treatment for asthmatics.

Keywords: Asthma; Biologics; Eosinophil; Phenotype; Omalizumab; Severe asthma.

Dedication

Dedicated to my beloved family members, faculties and friends.

Acknowledgement

I would like to begin by expressing my utmost gratitude to the Almighty Allah (Subhanahu Wa Ta'ala) for showering me with His boundless mercy, blessings and kindness which provided me the strength, patience and hope for completing this project.

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List of Acronyms

ICS	Inhaled Corticosteroid
LABA	Long-Acting Beta 2 Agonist
NCD	Noncommunicable disease
FEV	Forced Expiratory Volume
PEF	Peak Expiratory Flow
FeNO	Fractional exhaled Nitric Oxide
IgE	Immunoglobulin E
Th2	T helper type 2
DC	Dendritic Cell
IL	Interleukin
TSLP	Thymic Stromal Lymphopoietin
ILC2s	Group 2 Innate Lymphoid Cells
NO	Nitric Oxide
CS	Corticosteroid
TNF-a	Tumor Necrosis Factor alpha
SABA	Short-Acting β2-Agonist
AE	Adverse Event
ILO	Intermittent Laryngeal Obstruction

COPD	Chronic Obstructive Pulmonary Disease
GERD	Gastroesophageal Reflux Disease
EMA	European Medicines Agency
US FDA	The United States Food and Drug Administration
mAb	Monoclonal Antibody
GINA	Global Initiative for Asthma
IND	Investigational New Drug
IgG1k	Immunoglobulin G1 kappa
mIgE	membrane-bound form of Immunoglobulin E
OCS	Oral Corticosteroids
NICE	National Institute for Health and Clinical Excellence
MENSA	Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma
IL-5Ra	IL-5 Receptor a
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
iNOS	Inducible Nitric Oxide Synthase

Chapter 1

Introduction

Asthma is a major noncommunicable disease (NCD), affecting both children and adults. It is a chronic respiratory disease, affecting millions of people and also a cause of death if not managed properly, occurring mostly in low- and lower-middle income countries. Among children, asthma is found to be the most common chronic disease. Inflammation and narrowing of the small airways in the lungs cause asthma symptoms, which can be any combination of cough, wheeze, shortness of breath and chest tightness (WHO, 2021)

1.1 Asthma

Asthma is defined as a chronic inflammatory disease affecting the airways which is heterogeneous in nature and chronic airway inflammation, mucus hypersecretion, airway hyper responsiveness and bronchoconstriction are some of its characteristics (Rogliani et al., 2020). If the symptoms of asthma remain uncontrolled after administration of high dose inhaled corticosteroids (ICSs) along with systemic corticosteroids as adjuvant therapy, then this condition is termed as severe asthma (Rogliani et al., 2020).

1.2 Subtypes of Asthma

The classification of asthma in a broader perspective includes the intermittent and persistent categories in terms of the severity of the disease. Among these, the persistent category can further be sub-classified into mild, moderate or severe. The regular anti-inflammatory asthma therapy is not required in case of intermittent asthma patients and this can be used to distinguish these patients from the other three categories. The frequency of daily symptoms in these patients is less than twice a week and in case of nighttime symptoms, it is less than twice a month along with an FEV1 of >80%. Although not regularly, the daytime symptoms of mild

persistent asthma patients are exhibited greater than two times per week, in case of nighttime symptoms, it is greater than two times per month but fewer than one time per week along with a >80% of FEV1. Asthma patients with moderately persistent symptoms experience daytime and nighttime symptoms more than a single time per week or have an FEV1 ranging from 61% to 79 %. Continuous symptoms are displayed by severe persistent asthma patients with recurrent sleep disturbances or an FEV1 of <60% (Padem & Saltoun, 2019).

Incidence: Globally, around 300 million people are affected by asthma, and patients with severe or uncontrolled asthma account for approximately 5–10% of all asthmatics. Hospitalization and elevated mortality, higher health care expenses and diminished quality of life are all affiliated with this condition (Rogliani et al., 2020).

Symptoms: Some general symptoms of asthma are breathlessness, chest tightness, wheezing and cough with varying expiratory flow limitation (Kusumoto & Mathis, 2021).

Diagnosis: The gold standards for the diagnosis of asthma worldwide include assessment of airflow within the airways, specifically inside the lungs, as the prime factor and evaluation of thresholds of respiratory efficiency along with existence of signature symptoms. Recurrent symptoms of cough, wheezing, chest tightness, paroxysmal dyspnea, limitation of reversible airflow, atopy, airway inflammation, airway hyper responsiveness, and absence of other diseases are established as key criteria to diagnose the presence of asthma in adult patients. Peak expiratory flow (PEF) and FEV1 are used to measure reversible airflow limitation and asthma is confirmed in patients if there is a 12 % or greater increment in FEV1 after a β-agonist inhaler is administered. Nitric oxide (FeNO), histamine and acetylcholine thresholds are used in the assessment of airway hyper-responsiveness and on the other hand, eosinophil and mast cell counts in sputum are examined to detect airway inflammation. In case of juvenile-onset asthma, greater emphasis is provided in total serum IgE levels and on family history of the

disease in order to aid diagnosis although the symptoms displayed are similar to adults (Kusumoto & Mathis, 2021).

Novel treatment alternatives have become available in the management of asthma in recent years and distinguished phenotypes of asthma have been characterized with the aid of specific biomarkers. Biological drugs are prescribed for severe asthma patients whose condition does not improve with the conventional treatment options. These medications effectively control the symptoms of asthma, decreases exacerbation and reduce use of systemic steroids which are affiliated with common adverse events and these agents mostly work by targeting the components of type 2 inflammatory pathway (Rogliani et al., 2020).

1.3 Rationale

Asthma, a type of chronic respiratory disease, has been an issue of great concern for the past few decades in the field of medical science as appropriate treatment modalities to completely cure this disorder still continue. The advent of biologics, however, have brought a revolutionary hope in this aspect since this novel treatment option provides potential to relieve this non-communicable disease. Among the new treatment methods, biologics along with their biosimilars have shown great promise as new alternatives. This systematic review intends to evaluate the usefulness of biological drugs that have been approved or are in clinical trials for the treatment of severe asthma. This article does not associate any experiments carried on human volunteers or animals and is entirely based on literature and reviews.

Chapter 2

Methodology

This study involves extensive literature review on biologics used in the treatment of severe asthma and the secondary data required for this paper was obtained from peer-reviewed research articles, news articles, academic published papers and authentic web-sites. The articles from distinguished journals such as Springer, Nature, MDPI, Elsevier, etc., were analyzed for this study. The web sites which facilitated the compilation of information for this review includes PubMed, ResearchGate, ScienceDirect, etc. Numerous publications were studied to gather relevant information and data along with their insights which aided to identify the necessity of biologics that are approved for the treatment of asthma. The information of this review paper was compiled and referenced properly. This study also involved significant attempts to identify gaps or missing information within the existing literature.

Chapter 3

Etiology, Pathogenesis and Biomarkers

Asthma is a chronic condition affecting the airways, leading to wheezing and difficulty in breathing. It causes the inner walls of the airways, or the bronchial tubes, to be inflamed. There are several triggers such as exposure to viruses, an irritant or an allergen, emotional stress, and exercise. However, some of the most common triggers include dust mites, outdoor air pollution, tobacco smoke, pests such as cockroaches and mice, mold, and pets.

Asthma accounts for a range of heterogeneous phenotypes which are distinct in terms of pathophysiology and etiology, where several components of the host, environment and genetics are considered as potential risk factors for the different phenotypes. Although the prevalence of the disease in the family is a prime risk factor, the reason for the development of asthma might not include it. The asthma epidemic is primarily governed by environmental alterations and an asthmatic patient at different times may suffer from asthma differently due to these environmental stimulations and the respective risk factors varies with time. It is established that genetics have a pivotal role in the development of asthma (Subbarao et al., 2009).

Asthma, which is a chronic disease of the airway, is highly diversified with respect to severity of symptoms, clinical manifestations, pathogenesis and outcomes. The different phenotypes of asthma which are characterized by specific biomarkers have been identified recently due to a better understanding of the underlying pathogenesis along with the inclusion of biology, genetics and clinical features. The phenotypes Th2- high and Th2-low, which are the two major groups of asthma phenotypes, have been acknowledged and differentiated based on the associated inflammatory pathway. The prime characteristic of the Th2-high phenotypes is the Th2-high-related inflammation along with late-onset eosinophilic asthma and early-onset allergic asthma. The Th2-low phenotypes include obesity-related asthma and neutrophilic

asthma (De Ferrari et al., 2016). The undifferentiated CD4 T cells differentiate into Th2 cells when they encounter the allergens presented by the dendritic cells (DCs) in case of allergic asthma. Cytokines derived from respiratory epithelium and chemokines that includes interleukin (IL)-25, IL-33 (also called alarmins) and thymic stromal lymphopoietin (TSLP) are released as a countermeasure to several harmful stimuli such as microbes, air pollutants or glycolipids in case of nonallergic eosinophilic asthma (Brusselle et al., 2013). The alarmins bind to the receptors on the lymphoid cells (ILC2s) that are innate to the type-2 inflammatory system. The cytokines IL-4, IL-5, and IL-13 are generated by the activated forms of both Th2 cells and ILC2s and these cytokines function as chief effectors of type 2 inflammation. The most precise trigger for eosinophils is IL-5 as it induces the maturation of eosinophils in bone marrow, potentiates recruitment and activation. The synthesis of allergen-specific immunoglobulin (Ig) E is triggered by the activation of the IL-4Ra subchain which is present in the IL-4 and IL-13 cytokines (Varricchi et al., 2016). The structural and functional changes in the bronchial wall are induced by the potentiated release of mediators due to the interaction between the FceRI receptor and IgE. This FceRI receptor is present in various cells of the immune system. The nitric oxide (NO) synthase present in its inducible state in the epithelium is triggered by IL-13 which brings about increased airway NO production, airway smooth muscle contractility, secretion of mucus by the goblet cells and the expression of periostin in fibroblasts and lung epithelial cells (Rogliani et al., 2020).

Atopy, high total IgE, polysensitization to allergens, increased sputum and blood eosinophils, prominent levels of fractional exhaled NO (FeNO) and enhanced airway periostin are characteristic features of the early-onset allergic phenotype of asthma. The Th2-high-related inflammation biomarkers include FeNO, eosinophils, elevated levels of periostin and IgE of the airways. Among these biomarkers, the phenotype of late-onset eosinophilic asthma is associated with FeNO and eosinophils. Due to acceptable accuracy in detection, FeNO and

eosinophils are regarded as valid noninvasive biomarkers in case of type 2 asthma although infections, smoking habit, age, gender, height and exposure to steroids and allergens can affect their levels (Parulekar et al., 2016). Despite this, significant research interest is garnered as type 2 asthma is well correlated with sputum eosinophil count of ≥ 3%. The late onset eosinophilic phenotype accounts for about 25% of all severe asthma patients and its key feature is an insignificant response upon treatment with corticosteroids (CSs). Hence this serves as a confirmation that patients with the early-onset allergic phenotype does not involve the Th2 process and the utilization of blood/sputum eosinophilia as a biomarker could be done for the selection of potential patients that are appropriate for the anti-IL-5 modality and other anti-eosinophilic therapies (Pavord et al., 2012). Besides, there is an infrequent connection of chronic sinusitis and nasal polyps with adult eosinophilic asthma in patients with unclear history of atopy. A frequent infection, immunity driven by Th1- and Th17, oxidative stress and inflammation due to neutrophils are characteristic features of th2-low phenotypes. Systemic inflammation, which includes elevated levels of various cytokines such as IL-6, leptin and tumor necrosis factor alpha (TNF-a), and obesity are also interlinked to these phenotypes (Rogliani et al., 2020).

The classification of etiopathogenetic pathways that depicts the features of severe asthma have led to the identification of distinct biomarkers for distinct phenotypes. Focusing on the specific molecular targets will allow the achievement of prognostic and therapeutic information and this method might facilitate the optimum treatment of this heterogeneous and complex disorder (Rogliani et al., 2020).

Biomarkers: Several biomarkers have been identified for asthma and these have been briefly discussed below.

Eosinophils: In asthma, the chronic inflammation is maintained and stimulated by this type of cells. Asthma patients who have elevated peripheral blood eosinophils experience greater degree of exacerbations and inadequate overall asthma control. Eosinophilic inflammation can be highly suggestive where out of the total cell amount, greater than 2–3% accounts for sputum eosinophil or about 300 cells/μL is accounted by blood eosinophil count although this standard cut-off is not approved till now (Ciprandi et al., 2017).

FeNO (fractional exhaled nitric oxide): The corticosteroid-responsive and IL-13 driven inflammation of the airway can be determined by FeNO which is a non-invasive and simple indicator. The generation of FeNO is increased due to the activation of nitric oxide which is induced by the release of IL-13 (Katial et al., 2017).

Immunoglobulin E (IgE): The allergic phenotype is detected in about 70 % of asthma patients which is categorized by the ratio of IgE to aeroallergens and the increment in total serum IgE. The immunoglobulin E is an allergen specific antibody which is the core element in the pathogenesis of atopic asthma. Both the specific IgE and total IgE measurements are recommended in the diagnosis of allergy. These biomarkers facilitate in the screening of allergic bronchopulmonary aspergillosis which is associated with very high serum total (Santus et al., 2019).

Periostin: The formation of periostin, an extracellular matrix protein, secreted primarily by the epithelial cells present in bronchus is induced by the IL-4 and IL-13 and this protein circulates in the peripheral blood. It is assumed that periostin is involved in airway remodeling, eosinophil recruitment, mucous production regulation in the goblet cells and fibrosis in the sub-epithelial cells (Carpagnano et al., 2018). In case of the type 2 endotype of asthma, periostin is of key importance and its serum concentration along with blood eosinophils, IgE and FeNO provides pivotal indication in eosinophilic asthma about the presence of airway inflammation (Berry &

Busse, 2016). In severe eosinophilic type 2 asthma, high amounts of periostin in the condensate of exhaled breath is considered as a prominent indicator compared to serum periostin sampling according to recent studies (Santus et al., 2019).

Chapter 4

Conventional Treatments for Asthma

The general treatment procedure is comprised of an inhaled corticosteroid (ICS). Additional controllers such as montelukast and/or theophylline, or an inhaled long-acting beta 2 agonist (LABA) are included when there is insufficient control of asthma. Oral corticosteroids for example prednisolone are added if this therapy becomes inadequate to control asthma (Lommatzsch & Virchow, 2014).

Limitations of conventional therapies: Inhaled short-acting β2-agonists (SABAs), the most usually administered conventional therapy, is acknowledged to induce a deterioration of asthma control, potentiate airway inflammation and infrequently elevate the risk of asthma mortality upon daily use as the only treatment option for asthma. Similar scenario of elevated risk of asthma mortality is also observed when the only treatment option used is inhaled long-acting β2-agonists (LABAs) (O'Byrne et al., 2019).

Chapter 5

Management of Asthma using Biologics

At present, it is acknowledged worldwide that asthma is a diversified syndrome which is the outcome of several mechanistic pathways of inflammation rather than a simple characteristic disease with a general changing clinical presentation (Khalaf et al., 2019).

Control over symptoms, better functionality of the lungs, reduced exacerbations and deduced adverse events (AEs) from long term therapies are the primary endpoints in the management of asthma although this generally implemented treatment approach is rather unsuccessful since asthma is heterogenous in nature and there is diversified response in patients with asthma when available medications are administered. Moreover, in spite of strict adherence to therapy, a large number of patients suffer from frequent exacerbations and continue to face poor control over symptoms (Sulaiman et al., 2018). Novel therapies have been developed in recent years due to a better understanding of the mechanisms involved in etiopathology of various endotypes and phenotypes of severe asthma. The natural history of severe asthma has been modified by the advent of biologics among the innovative treatment procedures and most of these biological drugs target molecules associated with the type 2 inflammatory pathway (Rogliani et al., 2020). The implementation of biological therapies has been verified to be effective in the management of asthma as they provide reduced exacerbations, reduced requirement for steroid bursts and maintenance of control over the symptoms of asthma along with prevention of conventional adverse effects connected to the use of steroid (Rogliani et al., 2020).

Biologics modify the natural course of severe asthma by deducing the inflammation of the airways while preventing the collateral damage due to corticosteroids usage as these medications work against molecules associated with the type 2 inflammatory pathway.

Omalizumab is the first among the biologics and it is an anti-IgE monoclonal antibody that works through several mechanisms on the pathways of allergy. Another class of biologics used in the treatment of severe asthma contains three more approved biologics which includes mepolizumab, reslizumab and benralizumab. This class of biologics target the interleukin-5 (IL-5) pathway and the first two, mepolizumab and reslizumab, target the interleukin itself and the last one, benralizumab, targets its receptor. The monoclonal antibody dupilumab works by blocking interleukin-4 (IL-4) receptor which inhibits the signaling pathways involved in IL-4 and IL-13 (Dragonieri & Carpagnano, 2021).

Before initiating treatment with biological agents, accurate diagnosis of severe asthma is essential and other potential conditions with similar symptoms for example intermittent laryngeal obstruction (ILO), COPD (chronic obstructive pulmonary disease), hypersensitivity pneumonitis and bronchiectasis that might overlap with asthma must be eliminated. Assessment and eventual treatments of comorbidities should also be done. Aspiration, ILO, rhinosinusitis, GERD (gastroesophageal reflux disease), obstructive sleep apnea, cardiovascular comorbidities and infections are the most common comorbidities linked to asthma (Rogliani et al., 2020).

5.1 Omalizumab

The European Medicines Agency (EMA) and US FDA (Food and Drug Administration) approved omalizumab for severe asthma treatment which is the first among biologics. Omalizumab is a recombinant humanized mAb (monoclonal antibody). It works by blocking immunoglobulin E (IgE) and reduces IgE levels in blood by selectively binding to IgE molecules in the systemic circulation (Busse et al., 2001). Omalizumab is approved for use in patients of minimum 6 years of age by Global Initiative for Asthma (GINA) and the FDA and EMA who suffer from moderate to severe allergic asthma. These patients generally have

elevated levels of blood IgE, minimum sensitization to a perennial allergen and their asthma is primarily induced by IgE which remains uncontrolled in spite of GINA step 4 treatment. Omalizumab is prescribed for subcutaneous injection every 2–4 weeks while considering the total baseline IgE level and body weight. Patients should be reexamined after treatment with this drug for 16 weeks in order to evaluate this drug's efficacy before progressing with the therapy even though the European label of this biologic states that this drug is appropriate for use in the long-term (Rogliani et al., 2020).

The IgE specific humanized monoclonal antibody omalizumab was initially synthesized from a murine (mice) source. IgE gets neutralized by this antibody and downregulates the IgE receptor on basophils which prevents the activation of the inflammatory pathways. The formation of free circulating IgE results from the IL-4 and IL-13 mediated switching of IgG class along with stimulation of IgE positive B cells by allergen. The pathway that activates both basophils and mast cells short circuits upon driving down this response which lowers T-cell activation thresholds and prevents inflammation that induces the responses of Th2 (Froidure et al., 2016). Hence omalizumab inhibits continuous activation of the responses of Th2 by downregulating the activation of the immune system which are responsible for both the histological modifications observed in asthmatic airways and the exacerbations (Kusumoto & Mathis, 2021). The Global Evaluation of Treatment Effectiveness carried out a meta-analysis which showed improvement in symptoms after four to six months treatment with omalizumab in 77% of severe asthma patients (Kusumoto & Mathis, 2021).

GBR 310 (Omalizumab biosimilar) Glenmark Pharmaceuticals received approval for investigational new drug (IND) application from the FDA to initiate clinical trials of GBR 310 in human which is a proposed biosimilar of the reference drug omalizumab (Xolair) produced by Novartis. The GBR 310 is a recombinant humanized DNA-derived immunoglobulin G1

kappa (IgG1k) monoclonal antibody. This drug binds to a membrane-bound form of IgE (mIgE) present in mIgE-expressing B lymphocytes. It also interacts with the free human immunoglobulin E (IgE) present in the interstitial fluid and in the blood. It is currently in phase II of clinical trial (*Proposed Xolair Biosimilar Gets FDA Approval for Clinical Trials*, 2017).

5.2 Mepolizumab

Mepolizumab, also a monoclonal antibody, approved as an adjuvant treatment by the EMA for 6 years and older patients and FDA approved it for 12 years and older patients who suffer from the severe eosinophilic phenotype of asthma which stays uncontrolled in spite of GINA step 4 therapy. This biologic works against IL-5 and is prescribed for patients who have at least 150 eosinophil cells per µl of blood during first administration or a count of ≥ 300 eosinophil cells per µl blood in the previous year and asthma exacerbations experienced is at least 2 times which required the use of steroid bursts in the past year (Haldar et al., 2009). Mepolizumab is also prescribed for patients who have a blood eosinophil count of ≥ 300 cells/µl in the past year and asthma exacerbations of at least four times which required the use of systemic steroid or constant OCSs identical to at least 5 mg per day of prednisolone in the past 6 months in correspondence with the specification provided by the National Institute for Health and Clinical Excellence (NICE) of the UK. The administration of mepolizumab is done at a constant dose of 100 mg every 4 weeks via the subcutaneous route of injection (Rogliani et al., 2020).

The N-glycosylated IgG1 kappa chains from humans are used to produce this monoclonal antibody and mepolizumab is highly specific to IL-5 due to the neutralization of its binding ability to IL-5 receptor alpha. This results in impairment of eosinophil maturation in the bone marrow which in turn reduces the eosinophil levels in bronchial mucus and blood (Faverio et al., 2018). Important immune pathways may be compromised which are involved in antiparasitic response as a side effect due to the highly effective IL-5 neutralizing capacity of

mepolizumab and this event must be considered within pediatric patients or developing countries (Giovannini et al., 2019). Subcutaneous administration of mepolizumab resulted in a decrease in exacerbations by 53% compared to placebo whereas intravenous administration resulted in a 47% decrease and a 100 mL increase in FEV1 in the MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma) study involving 576 patients (Nixon et al., 2017). Eosinophil count in both sputum and blood were reduced in mild asthma patients after administration with mepolizumab and similarly, eosinophil count also reduced in the blood, the bone marrow and the bronchoalveolar fluid of mild atopic asthma patients with mepolizumab administration. Mepolizumab is the pivotal add-on drug at present for treatment of patients aged 12 years and above suffering from the severe eosinophilic phenotype of asthma (Kusumoto & Mathis, 2021).

5.3 Reslizumab

The mechanism of reslizumab is also identical to mepolizumab as reslizumab is also a monoclonal antibody targeted against IL-5. Reslizumab is approved by FDA and EMA as an adjuvant treatment in adult patients of age ≥ 18 years with uncontrolled severe eosinophilic asthma even after administration with high-dose ICSs and an added controller (Haldar et al., 2009). Patients with at least 400 eosinophil cell count per µl of blood and at least 3 asthma exacerbations in the previous year are prescribed with reslizumab for intravenous administration at 3 mg/kg every 4 weeks (Rogliani et al., 2020).

The mechanism of action of reslizumab in patients with severe asthma involves selective inhibition of IL-5α receptors which inhibits production of eosinophils in the bone marrow. Reslizumab has 24.5 to 30.1 days of terminal half-life and great affinity for IL-5α and is also a IgG4 kappa monoclonal antibody (mAb) for IL-5 (Pelaia et al., 2019).

5.4 Benralizumab

Benralizumab is an afucosylated humanized monoclonal antibody (mAb) targeted against IL-5 receptor a (IL-5Ra). The binding of benralizumab to IL-5Ra induces eosinophil apoptosis by incorporating natural killer cells which induces the process of antibody-dependent cell-mediated cytotoxicity (ADCC) therefore leading to depletion of peripheral blood eosinophil (Pham et al., 2016). Patients with uncontrolled severe eosinophilic asthma of age ≥ 12 years with blood eosinophil count of ≥ 300 cells/ µl are administered with benralizumab as an add-on treatment approved by the FDA. Benralizumab is indicated for subcutaneous administration at a dose of 30 mg every four weeks in the initial 3 months of treatment and then every 8 weeks in prolonged treatment modules (Rogliani et al., 2020).

The humanized recombinant mAb benralizumab was developed to prevent the IL-5 mediated eosinophil generation by blocking the IL-5 receptor-α which inhibits the differentiation of eosinophils in the bone marrow. Benralizumab directly reduces eosinophil count as opposed to mepolizumab and reslizumab, other IL-5-neutralizing biologics, by ADCC and it also attaches to macrophages, natural killer cells and neutrophils with its Fcγ-receptor in the heavy chain. Eosinophil population in both the tissue and systemic circulation is reduced by more than 95% as a result of these events (Dávila González et al., 2019). Despite this, benralizumab may provide inadequate control in eosinophilic asthma due to inflammatory factors which include age, genotype, weight, smoking exposure, gender and comorbidities which leads to higher degree of Type 2 inflammation. Moreover, IgE and FeNO levels are not adequate for physicians to rely on in order to monitor treatment studies reported insignificant variations in these biomarkers during treatment and there is no actual benefit of benralizumab in non-Type 2-related or non-eosinophil-mediated asthma (Izumo et al., 2020). Patients with at least three exacerbations in the last year and a predicted FVC of less than 65%, who were on oral

corticosteroids treatment of high doses, were diagnosed as adults and had polyposis demonstrated maximum response to treatment with benralizumab (Kusumoto & Mathis, 2021).

5.5 Dupilumab

Dupilumab is also a humanized monoclonal antibody which targets the A chain present on IL-4Ra. The IL-4 and IL-13 cytokines share this chain which enables dupilumab to suppress the signaling mechanism of both these interleukins. Dupilumab is approved as an add-on maintenance therapy by FDA for patients aged 12 years or more who suffer from moderate-to-severe asthma and have an oral corticosteroid (OCS)-dependent asthma or an eosinophilic phenotype. The EMA approved this biologic for severe asthma patients in adolescent age (≥ 12 years) for type 2 inflammation as adjuvant maintenance treatment which features elevated FeNO and/or elevated blood eosinophils along with poorly controlled symptoms using high-dose ICS (inhaled corticosteroids) and another medication for maintenance treatment. Dupilumab is prescribed for subcutaneous administration with 400 mg starting dose consisting of two 200 mg injections with accompanying 200 mg after every two weeks or 600 mg starting dose consisting of two 300 mg injections with accompanying 300 mg after every two weeks (Rogliani et al., 2020).

Dupilumab, a IgG4 monoclonal antibody used in the treatment of Th2-mediated asthma, inhibits the signal transduction through the IL-4R and IL-13 via JAK/STAT6 by specifically blocking the IL4 or IL-13 which is a co-receptor. The IgM to IgE class switching is stimulated by IL-4R and this induces infiltration of eosinophils inside the airways and precipitation of a type I allergic reaction. Inducible nitric oxide synthase (iNOS) and the epithelial mucus production is promoted by IL-13 which mediates constriction of the airways (Barranco et al., 2017). Additionally, it potentiates goblet cell hyperplasia which induces bronchial fibroblasts transformation into myofibroblasts. Hyper responsiveness of the airway which is the hallmark

of asthma symptoms are a result of these contractile cells which remodel the airway. Therefore, dupilumab specifically inhibits this pivotal inflammatory pathway. A decrease of 87% in exacerbation rate was reported upon treatment with dupilumab compared to a placebo in a study consisting of 104 asthma patients (Wenzel et al., 2013). The biomarkers of inflammation for example chemokines that regulate activation, serum and thymus IgE levels and FeNO concentration were all reduced upon administration of dupilumab and no major drug associated adverse events were observed (Kusumoto & Mathis, 2021).

5.6 Tezepelumab

Tezspire (tezepelumab-ekko) is an injectable approved as an adjuvant maintenance treatment by the FDA to relieve symptoms of severe asthma upon concomitant use with the patients current asthma medications. Tezepelumab is indicated for children ≥ 12 years of age and adults experiencing severe asthma that is uncontrolled using their current medication. Tezepelumab is the first approved biologic that targets thymic stromal lymphopoietin (TSLP), a molecule associated with airway inflammation, for the treatment of asthma. TSLP is an epithelial cytokine and its levels are associated with airway obstruction, severity of disease and resistance to glucocorticoids. AstraZeneca and Amgen acquired the rights to sell this biologic for pediatric patients (aged 12 years and above) and adults. The use of the biologic tezepelumab is not restricted to a certain type of severe asthma and it is the first of its kind. Tezspire provided a novel biologic alternative that has no phenotypic limitations and is irrespective of the levels of biomarkers. It is the first and only approved biologic that reduced asthma exacerbations constantly and remarkably in clinical trials phase 2 and 3 that involved a diverse population of patients with severe asthma who had variable levels of pivotal biomarkers which includes fractional exhaled nitric oxide, blood eosinophil counts and allergic status. Tezepelumab is indicated for subcutaneous administration by a healthcare professional once every 4 weeks. The typical adverse events associated with its use included upper respiratory tract infection,

nasopharyngitis and headache (*FDA Approves Maintenance Treatment for Severe Asthma | FDA*, 2021; *FDA Approves Tezepelumab for Severe Asthma*, 2021).

Tezepelumab, a humanized monoclonal antibody, binds to TSLP which prevents the interaction of TSLP with its receptor that is found on various immune cells involved in the type 2 inflammatory cascade. This biologic reduces the biomarkers of Th2 responses including immunoglobulin E, FeNO and eosinophil by targeting the pathways involving IL-4, IL-5 and IL-13 cytokines when used in the treatment of patients with severe asthma (Corren et al., 2017).

There have been significant changes in the recommended treatment approach of severe asthma in the last ten years. The biomarker-linked personalized medicine is derived on the basis of accurate identification of precise biomarkers and this approach has successfully substituted the typical approach which was based on bronchodilators and corticosteroids and other nonspecific drugs which were once considered blockbuster drugs. The detection of patients with severe asthma is enabled by the specification of molecular targets and thus these patients would benefit from personalized biological treatments (Rogliani et al., 2020).

Table 1. FDA approved Biologics for Severe Asthma (adapted from Rogliani et al., 2020)

Biologics	**Modality**	**Patient Category**
Omalizumab	Anti-IgE	Adults Children ≥ 6 years
Mepolizumab	IL-5 Inhibitor	Children ≥ 6 years Adults
Reslizumab	IL-5 Inhibitor	Adults
Benralizumab	IL-5 Inhibitor	Children ≥ 12 years Adults

Dupilumab	IL-4 and IL-13 Inhibitor	Children ≥ 12 years Adults
Tezepelumab	IL-4, IL-5 and IL-13 Inhibitor	Children ≥ 12 years Adults

Chapter 6

Challenges and Future Implications

Currently, a model comprised of greater complexity in the biological network of interrelating and distinct inflammatory pathways has substituted the previously considered single entity model of asthma. Numerous diseases with exclusive mechanistic pathways, known as endotypes and varying clinical presentations, known as phenotypes, is now being represented by the term asthma. The core component in the management of asthma is the explicit definition of these endotypes which is because of the inherent prognostic and therapeutic implications (Kuruvilla et al., 2019). The choice of personalized treatments can be facilitated by the determination of the existence of particular biomarkers which confirms the distinct endotype.

6.1 Challenges

The advent of new biologics indicated for severe asthma has made the selection of suitable treatment options more complex. Currently, there are no guidelines for the selection of biologic treatment options since there is no direct comparison available between the various classes of biologics. Both omalizumab and anti-IL-5 biologics, for example mepolizumab and reslizumab, qualify as treatment options in approximately 50% of severe asthma patients as they have both high IgE levels and blood eosinophil counts. Although the effectiveness of omalizumab for this particular group of patients is evaluated in different studies, no precise answer was acquired as to which choice of therapy is optimal in this regard (Humbert et al., 2018). Similarly, there is no direct comparison available between the biologics of the anti-IL-5 class and the conclusion reached from the comparisons of indirect treatment could be unreliable to determine the inferiority or superiority between different biologics of the anti-IL-5 class (Busse et al., 2019). Equivalent reduction rates in case of asthma exacerbations is observed in the trials conducted till now between anti-IL-4/IL-13 biologics and anti-IL-5

biologics. Dupilumab, which is the anti-IL-4/IL-13 biologic, could potentially have mechanistic benefit over anti-IL-5 biologics since it inhibits the signaling cascades involved in both IL-4 and IL-13 which leads to deactivation of smooth muscle contraction, mucus production within airways and remodeling and hence may potentially be more applicable for a broader group of severe asthma patients. This theory is not tested clinically as of yet. Moreover, dupilumab can also be used in severe asthma patients with nasal polyposis since this biologic has provided efficacious response in patients with basal polyps and chronic rhinosinusitis (Bachert et al., 2016). Currently, FENO, blood eosinophil count, sputum quantitative cytometry and periostin are the acknowledged T2 biomarkers which are suspected to represent the various pathways among the T2-high inflammation. The ability to predict the T2 endotype did not improve by the combination of these biomarkers. Blood eosinophil count gained widespread use since it is readily available, inexpensive and detects T2 endotype by providing specific cut-off. Anti-IL- biologics therapy is guided by at least 150 cells per µl of blood eosinophil count and a FeNO of at least 19.5 ppb. At least 260 cells per µl of blood eosinophil count was demonstrated to fairly predict the reduction in exacerbation with omalizumab use (Hanania et al., 2013). Individual patients may commonly experience suboptimal treatment response as the trials constantly demonstrate approximately 50% decrease in exacerbations although complete tapering off of systemic corticosteroids in prednisolone-dependent severe asthma patients account for only17–40%. In reality, targeting all the T2 pathways is impossible due to the hefty costs and the unknown adverse events associated with complete obliteration of T2 pathways that is the enhanced likelihood of malignancy and infections from opportunistic parasites. The T2-low severe asthma group on the other hand is highly heterogenous and unclassified. Improved clinical outcomes were not achieved by directing treatment against airway neutrophilia in T2-low severe asthma (Tan et al., 2020).

It is apparent that the definitions of endotypes of asthma are evolving and not definite since there are more cell types of the adaptive and innate immune system that are revealed to be important triggers of asthma. Currently the approach includes classification of patients into T2-high and T2-low asthma since the available therapies are directed against cytokines of the T2 inflammation consisting of comparatively simple biomarkers. The contributions in the clinical expression of disease and understanding of the microenvironment of inflammation in the descending airway are still incomplete which provides scope in severe asthma for critical unanswered questions (Kuruvilla et al., 2019).

6.2 Future Implications

The prominent future prospect includes the current research aimed at developing novel delivery modes and innovative targeted therapies that will potentially address the different phenotypes in T2-low or noneosinophilic asthma. Additional studies must be conducted to evaluate whether the biologics could be administered in the preliminary stages of the disease process and the application of these agents are disease modifying or not. The information from direct comparisons among the different class of biologics will be exemplary to aid physicians forge the most sophisticated treatment decisions when selecting among the biologics. There is significant importance of more studies that should be focused on pediatric patients in order to have better understanding of the impact of these drugs in this class of patients since the majority of the previously conducted trials had comparatively fewer number of patients under the age of 18 years (Krings et al., 2019). IL-1β, IL-6, IFN-γ, TNF-γ and other cytokines are a part of recent investigations in order to determine the potential biomarkers in case of neutrophilic asthma (Tan et al., 2020).

The advent of exemplary treatment alternatives for severe asthma patients became possible because of the current discoveries regarding the T2 inflammatory pathways and the class of

agents, monoclonal antibodies, that are developed targeting the T2 cascade which overall transformed the severe asthma management by paving the road for biomarker-driven personalized medicine (Dragonieri & Carpagnano, 2021). More research must be conducted in order to establish new potential molecular targets that would be employed as therapeutic and prognostic biomarkers since this will aid in developing treatment strategies that are explicitly customized according to the requirements of each patient (Rogliani et al., 2020).

Chapter 7

Conclusion

The continuous advancement in the treatment modalities for asthma and their respective development and consistent assessment ascertains the concept of asthma being heterogenous in nature. The heterogenous characteristic of asthma contributes to its global prevalence which raises great concern although novel therapeutic alternatives have been integrated in recent times. The pivotal aspect of this review is to convey the numerous progression in the molecular level concept of asthma pathophysiology and the advent of biologics which provided targeted therapeutic alternatives for the treatment of patients suffering from severe asthma who are maximized on recommended therapy but still have ineffective control over the disease. Despite such progressions, a single biologic is apparently ineffective in all types of asthma conditions. It is critical to detect the set of patients that will have the maximum therapeutic benefit from these biologics along with the assessment of efficacy of these agents. In this aspect, the role of biomarkers is of great significance in determining the subset of patients that will receive substantial benefits from these novel agents. Although the biologics provide insignificant adverse events, they are yet to be economical for their respective targeted patients. Despite such circumstances, the treatment approach for severe asthma patients have been transformed by the advent of biologics. Hence treatment options simply focused on improving symptoms should be substituted by aiming to develop disease-modifying therapeutics that contribute in the actualization of personalized medicine that provide patient specific treatment alternatives (Aberumand & Ellis, 2019).

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