.

Use of biological drugs in treatment of bronchial asthma: Meta analysis study

By

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DEDICATION

بِسۡمِ ٱللَّهِ ٱلرَّحۡمَٰنِ ٱلرَّحِيمِ

"يرفع الله الذين آمنوا منكم والذين أوتوا العلم درجات والله بما تعملون خبير "

أما بعد ..

بداية ؛ الحمد لله الذي سدد الخطى وشرح الصدر وساقنا لتحقيق الأماني ، بهذه الكلمات أود أن أعبر عن إمتناني العميق وشكري لله عز وجل ، على توفيقه لي في طيلة مسيرتي العلمية ، فبعد إنفاق كل جهدي ووقتي في سبيل العلم ، كلل الله لي هذا السعي بالنجاح والوصول للختام وتمام النعمة ، فالحمد لله الذي هدانا لهذا وماكنا لنهتدي لولا أن هدانا الله .

ثانياً ؛ أود أن أتقدم بجزيل الشكر والعرفان لمن كان فضلهم بعد الله عليا كبير ، أمي وأبي ، فهم أول من بدأو بتعليمي من كيف أمسك القلم ، حتى كيف أمسك العلم لأصل إلى المُبتغى ، جزاكم الله عني ألف خير وحفظكم الله وأمد الله في أعماركم وبارك لكم فيها .

ثالثاً ، أود أن أتقدم بالشكر والعرفان للمعلمين والدكاترة ، لمن وهبو وقتهم وجهدهم لتوجيهي وتعليمي ، فصدقاً لم تكونوا لي فقط معلمين ، فقد كنتم خيرملهمين ، فلم أنسى كل كلمة منكم كانت تحمل الدعم والإيمان والثقة بي ، فكلماتكم صنعت جزاً كبيراً من كياني وأحلامي .

لن أنسى فضل عائلتي الكريمة وأقاربي ، أصدقائي وزملائي ، شكراً على كل ما قدمتوه لي في رحلتي .

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ABBREVIATIONS

AAER: annualized asthma exacerbation

ACQ: Asthma Control Questionnaire

ACT: Asthma Control Test

ADCC: Antibody department cell mediated cytotoxicity

AHR: Airway hyper responsiveness

AQLQ: asthma quality of life questionnaire

BEC: blood eosinophil count

ERR: Exacerbation Rate Reduction

FDA: food and drug administration

FEV: forced expiratory volume

FeNO: Fractional Exhaled Nitric Oxide Improvement

FVC: forced vital capacity

HRQOL: Health Related Quality of life

Ige : Immunoglobulin E

LABA: long acting beta agonist

mAbs : monoclonal antibodies

OCS : Oral Corticosteroids

PEF: peak expiratory flow

SABA: short-acting beta-agonist

TSLP : thymic stromal lymphopoietin

ABSTRACT

Bronchial asthma is a chronic respiratory disease characterized by airway inflammation and hyper responsiveness. Despite the availability of conventional therapies, a subset of patients with severe asthma remains uncontrolled and experiences frequent exacerbations. In recent years, the emergence of biologic drugs has revolutionized the management of severe asthma by targeting specific inflammatory pathways.

This review aims to provide a comprehensive overview of the use of biologic drugs in patients with bronchial asthma. It begins by discussing the pathophysiology of asthma, highlighting the role of various inflammatory mediators and cytokines. Subsequently, it explores the mechanism of action and efficacy of different biologic agents, including monoclonal antibodies targeting immunoglobulin E (IgE), interleukin-5 (IL-5), and IL-4/IL-13 pathways.

Furthermore, this review examines the clinical evidence supporting the use of biologic drugs in the treatment of severe asthma. It summarizes the results of key clinical trials, highlighting the impact of biologic therapy on asthma control, exacerbation rates, lung function, and quality of life. Additionally, it discusses the safety profile and potential adverse effects associated with these agents.

In conclusion, the use of biologic drugs has emerged as a promising therapeutic approach for Patients with severe bronchial asthma. This review highlights the significant clinical benefits of biologic therapy in improving asthma control and reducing exacerbation rates. However, further research is needed to optimize patient selection, personalize treatment strategies, and explore the long-term outcomes of biologic therapy in this patient population.

Chapter I
Introduction

1. Bronchial asthma

Asthma is characterized by episodic, reversible bronchospasm resulting from an exaggerated bronchoconstrictor response to various stimuli. The basis of bronchial hyperreactivity is not entirely clear but it is widely believed to result from persistent bronchial inflammation. Hence, bronchial asthma is best considered a chronic inflammatory disorder of the airways. Clinically, asthma is manifested by episodic dyspnea, cough and wheezing. This common disease affects about 5% of adults and 7% - 10% of children [1].Current asthma management is aimed at reducing airways inflammation by using daily "controller" anti-inflammatory medications, minimizing proinflammatory environmental exposures and controlling co-morbid conditions that can worsen asthma.Less inflammation typically leads to better asthma control, including less need for "quick-reliever" asthma medication (B-agonist bronchodilators) and fewer exacerbation. Early intervention with systemic glucocorticoids can greatly reduce the severity of such episodes [2].

1.1. Pathophysiology

Airway inflammation is the primary problem in asthma. An initial event in asthma appears to be the release of inflammatory mediators (e.g. histamine. tryptase, leukotrienes and prostaglandins) triggered by exposure to allergens, irritants, cold air or exercise. The mediators are released from bronchial mast cells, alveolar macrophages, T-lymphocytes and epithelial cells. Some mediators directly cause acute bronchoconstriction termed the "early-phase asthmatic response". The inflammatory mediators also direct the activation of eosinophils and neutrophils and their migration to the airways, where they cause injury. This so called "late-phase asthmatic response "results in epithelial damage, airway oedema, mucus hypersecretion and hyper- responsiveness of bronchial smooth muscle. Varying airflow obstruction leads to recurrent episodes of wheezing, breathlessness, chest tightness and cough. The pathologic changes linked to persistent airways inflammation and hyper- responsiveness underlie the chronic basis of asthma [3].

1.2. Airways inflammation, hyperresponsiveness and remodeling

Asthmatic airways tissues have increased numbers of mast cells, activated eosinophils and activated helper T lymphocytes. Helper T lymphocytes that produce proallergic, proinflammatory cytokines (e.g. IL-4, IL-5, IL-13) and chemokines (e.g. Rantes, cotaxin) mediate this inflammatory process [2].

1.3. Diagnosis

Asthma should be considered in patients with a history of recurrent wheezing, cough (particularly if the cough is worse at night), recurrent shortness of breath or chest tightness. The diagnosis of asthma is also suggested if the symptoms worsen with exercise, viral illness, weather changes or exposures to airborne chemicals, dust, tobacco smoke or other allergens such as animal dander, cockroaches, house dust mites, mold and pollens. When the diagnosis of asthma is considered, reversible airway obstruction should be documented by spirometry performed before and after the administration of a short- acting bronchodilator. Airway obstruction is indicated by a forced expiratory volume in one second (FEV1) and a decreased ratio of FEV1 to forced vital capacity (FVC) relative to predicted values. Reversibility of obstruction is indicated by an increase in FEVI after bronchodilator treatment. In patients with asthma symptoms and normal spirometry, an assessment of the diurnal variation in peak expiratory flow (PEF) is useful in establishing the diagnosis [3].

1.4. Lung function testing: Measures of expiratory airflow are helpful in diagnosing and monitoring asthma and in assessing efficacy of therapy. Lung function testing is particularly helpful in asthmatics who are poor perceivers of airflow obstruction or when physical signs of asthma do not occur until airflow obstruction has become severe [2].

1.5. Spirometry: Measures airflow and lung volumes during a forced expiratory maneuver and is considered the gold standard measure of airflow in asthma. Its helpfulness as an objective measure in the initial evaluation and management of asthmatic [2]

1.6. Control of the environment will assist in lessening these influences:

- Smoke from personal smoking and second-hand smoke should be eliminated, as well as fumes from wood-burning fireplaces.
- Pet dander is a common allergen. Animals should not be present in the home of an asthma patient.
- Cockroaches should be controlled as much as possible.
- Air filtration and air conditioning should be used to minimize seasonal pollen and mold.
- Seasonal factors should be evaluated, including grass, ragweed, and other plants.
- Occupational concerns must be evaluated. Farmers are around molds and mites in hay and fungal agents in silage. Asbestos, dust, and chemical allergens and implicated
- Sports should be chosen that do not involve dusty environments.

  Swimming is a good sport for asthmatics [4].

1.7. Clinical manifestations

Asthma can present in a number of ways. It may manifest as a persistent cough. Most commonly it is described as recurrent episodes of difficulty in breathing (dyspnea) associated with wheezing.Diagnosis is usually made by a combination of a full history from the patient or patient's representative together with lung function tests before and after administration of bronchodilators.

Acute severe asthma is a dangerous condition which requires hospitalization and immediate emergency treatment. It occurs when broncho- spasm has progressed to a state where the patient is breathless at rest and has a degree of cardiac stress. This is usually progressive and can build up over a number of hours or even days [5].

1.8.Classification of asthma:- Based on the presence or absence of an underlying immune disorder So, bronchial asthma can be classified into:

1-Extrinsic asthma, in which the asthmatic episode is typically initiated by a type I hypersensitivity reaction induced by exposure to an extrinsic antigen

2-Intrinsic asthma, in which the triggering mechanisms are non-immune. In this from, a number of stimuli that have little or no effect in normal subjects can trigger bronchospasm. In general, asthma that develops early in life has a strong allergic (extrinsic) component, while asthma developing later in life is more often of the intrinsic subtype [1].

1.9. Pharmacotherapy of asthma

Medications used in the treatment of asthma may be divided into two categories: long-term control medications that are taken regularly and quick- relief medications that are taken as needed to relieve bronchoconstriction rapidly (the quick-relief medications are also known as rescue medications). Long-term control medications include anti-inflammatory medications (i.e. corticosteroids, cromolyn sodium, nedocromil and leukotriene modifiers) and long-acting bronchodilators. Quick-relief medications include shortacting beta2 agonists, anticholinergic and systemic corticosteroids. Any patient with persistent asthma requires treatment with both long-term control and quick- relief medications [3].

2. Biological drugs

Biologic treatments for asthma are medications made from cells of living organisms, such as bacteria or mice, that are modified to target specific molecules in humans also known as biologic drugs or monoclonal antibodies (mAbs), are specialized medications that target specific cells or molecules involved in asthma.

These treatments are designed to disrupt the pathways that lead to inflammation, which is the underlying cause of asthma symptoms Biologics can target various components of the immune system involved in asthma, including antibodies, inflammatory molecules, or cell receptors Biologics are used for patients with moderate-to-severe asthma who continue to experience symptoms despite using standard daily controller medicationsThe primary benefits of biologic treatments for asthma include a decrease in the frequency of asthma exacerbations, reduced asthma symptoms, improved lung function, and an overall improvement in the quality of life for patients[6].

Available Biologics: Currently, there are several FDA-approved biologics for the treatment of asthma, including:[7].

- Omalizumab
- Mepolizumab
- Reslizumab
- Benralizumab
- Dupilumab
- Tezepelumab

Most biologics for asthma are administered in a doctor's office either as a subcutaneous injection or as an intravenous infusion. The frequency of administration varies depending on the specific biologic, ranging from every two weeks to every eight weeks.

There are currently no set recommendations on how long a patient should be on a biologic. The duration of treatment is typically determined based on the individual patient's response and the control of their asthma symptoms.

Biologics have been shown to be generally safe, with common side effects including soreness at the injection site, headache, sore throat, and fatigue. However, some biologics may carry a small risk of anaphylaxis or certain infections, and precautions may be taken accordingly.

Biologic treatments for asthma tend to be more expensive compared to other controller medications. It is important for patients to discuss the cost and coverage with their doctor and insurance company before starting biologic treatment [7].

2.1. Types of Biological drugs:

- **Monoclonal Antibodies:**

- These drugs target specific proteins in the body, such as cancer cell receptors or inflammatory cells.
- They are used in the treatment of immune-related diseases and cancerous tumors.

- **Immunomodulatory Proteins:**

- These drugs enhance the activity of the immune system to fight diseases.
- They are used in the treatment of autoimmune diseases like lupus and rheumatoid arthritis.

- **Cellular Activators:**

- These drugs stimulate the growth and activation of immune cells.
- They are used in the treatment of certain types of cancers and other immune-related diseases.

- **Targeted Antibodies:**

- These drugs specifically target certain proteins in the body.
- They can be used in the treatment of immune-related diseases and cancerous tumors.

- **Biological Vaccines:**

- These vaccines contain biological components to stimulate the immune system for protection against specific diseases.
- They are used for immunizing individuals and boosting their immunity against infections [8].

Table 1 mechanism of action of biological drugs

Drugs	**Mechanism of action**
Omalizumab	Binds to IgE, preventing its binding to mast cells
Mepolizumab	Targets IL-5, reducing eosinophil production and survival
Reslizumab	Also targets IL-5, reducing eosinophilic inflammation
Benralizumab	Targets IL-5Rα, depleting eosinophils and basophils
Dupilumab	Inhibits signaling of IL-4 and IL-13, reducing inflammation
Tezepelumab	Blocks the interaction of TSLP (thymic stromal lymphopoietin) with its receptor

[9:10]

Table 2 Difference between biological medicines and traditional medicines in treating bronchial asthma

Aspect of Comparison	**Biological Medications**	**Conventional Medications**
Mechanism of Action	Target specific molecules or cells in the immune system to reduce inflammation and improve asthma control	Act on general pathways to reduce inflammation and bronchoconstriction
Target Patient Population	Primarily used for patients with severe asthma who do not respond well to conventional treatments	Used for a wide range of asthma severity, from mild to severe
Administration	Typically administered via injection or infusion	Usually inhaled or taken orally
Efficacy	Can provide significant improvement in asthma control, reducing symptoms and exacerbations	Can effectively control asthma symptoms and reduce exacerbations, but may not be as effective in severe cases
Side Effects	May have specific side effects related to immune system modulation, such as increased risk of infections or allergic reactions	Can have side effects such as oral thrush, increased heart rate with bronchodilators
Cost	Generally more expensive than conventional medications	Typically more affordable and accessible

[11:12]

Aim

This study was done by reviewing the literature to illustrate the biological drugs which approved by the FDA in the treatment of bronchial Asthma and the efficacy of some biological drugs in the treatment of bronchial asthma and the safety profile of these drugs.

Chapter II (Method)

Method

This study reviews articles to clarify the FDA approved drugs. Efficacy and safety of drugs used in the treatment of bronchial asthma. Was done by searching articles with meta analysis from year 2013 to 2023.

Chapter III
Results

Table 3 (Real world efficacy of treatment with benralizumab, dupilumab, mepolizumab and reslizumab for severe asthma (A systematic review and meta-Analysis)

Medications	**Results**
Benralizumab	Exacerbation rate Reduction (ERR) = - 3.79 Improvement Forced Expiratory Volum (FEV1) = 0. 21 L
Mepolizumab	(ERR) = - 3.17 (FEV1) = 0.17 L Fractional Exhaled Nitric Oxide Improvement (FeNO) = -14.23
Relizumab	(ERR) = - 6.72

[13]

This study illustrates better improvement by relizuumab by reduction in ERR to 6.72.

Table 4 Tezepelumab compared with other biologics for the treatment of severe asthma (a Systematic review)

Medications	**Results**
Dupilumab	Similar efficacy
Benralizumab	
Mepolizumab	
Reslizumab	
Omalizumab	

[14].

Table 5 Comparative Efficacy and safety of Tezepelumab and Other biologics in patients With inadequately controlled asthma According to Thresholds of Type 2 Inflammatory Biomarkers (A systematic Review and Network Meta-Analysis)

Medications	**Results**
Tezepelumab Mepolizumab Benralizumab Omalizumab Dupilumab Reslizumab	Tezepelumab showed significant improvement in asthma control, reduced exacerbation frequency , and decreased oral corticosteroid use.

[15].

Table 6 Clinical Characteristics and Treatment Outcomes of Severe Asthma Patients with a History of Multiple Biologic Drugs Use) (Observational study)

Medications	**Study results**	**P value**
Omalizumab Mepolizumab Reslizumab Benralizumab Dupilumab	Higher number of allergic airway comorbidities	
	Approximately half of the patients changed to different treatments due to uncontrolled comorbidities	
	Annualized exacerbation rates significantly improved after the latest biologic drug use	0.035
	Asthma control test (ACT) scores significantly improved after the latest biologic drug use	< 0.001
	Oral corticosteroids (OCS) dose significantly improved after the latest biologic drug use	0.038

[16].

The study highlights the challenges these patients face, and findings suggest that a history of multiple biologic drug use is associated with more severe disease and poorer treatment outcomes.

Table 7 A comparison of the effectiveness of biologic therapies for asthma (A systematic review and network meta-analysis)

Medications	Results
Dupilumab Mepolizumab Benralizumab Tezepelumab	They analyzed randomized controlled trials and observational studies and they found that biologic therapies were effective in reducing asthma exacerbations and improving symptom control.

[17].

Table 8 Hypersensitivity and immunologic reactions to biologics opportunities for theAllergist (systematic review)

Medications	**Results**
Omalizumab	Anaphylaxis in fewer than 0.1% of patients, many with delayed reactions
Rituximab	Hypogammaglobulinemia

[18].

Table 9 (Efficacy of Biologics in Severe Uncontrolled Asthma Stratified by Blood Eosinophil Count) (Efficacy of Biologics in Severe Uncontrolled Asthma Stratified by Blood Eosinophil Count) (A Systematic Review)

	Medications	**Results**
Baseline BEC ≥ 300 cells/μL	All biologics	annualized asthma exacerbation (AAER) reduction demonstrated
BEC 0 to < 300 cells/μL	Tezepelumab	Consistent AAER reduction demonstrated
BEC 150 to < 300 cells/μL	Tezepelumab, Dupilumab (300 mg dose only)	Consistent AAER reduction demonstrated
BEC 0 to < 150 cells/μL	Tezepelumab	AAER reduction demonstrated

[19].

Summary:

The study examined the efficacy of biologic therapies in treating severe, uncontrolled Asthma based on the baseline blood eosinophil count (BEC). They found that the Effectiveness of biologics in reducing asthma exacerbations varied depending on the Baseline BEC. Patients with higher BEC levels showed reduction in exacerbations with all biologics, while those with lower BEC levels experienced inconsistent Results. The study highlights the importance of considering baseline BEC when selecting biologic therapies for severe asthma

Table 10 The Safety and Efficacy of Anti-IL-13 Treatment with Tralokinumab (CAT-354) in Moderate to Severe Asthma) (A Systematic Review and Meta-Analysis)

Medications	**Results**	**Statistical note**
Tralokinumab at 300 mg every 2 weeks	Improved Absolute FEV = 0.14 L	Statistically significant
Tralokinumab at 600 mg every 2 weeks	Improved Absolute FEV1 = 0.20 L	Statistically significant
Tralokinumab at 300 mg every 2 weeks	Improved FEV1% changes = 5.82%	Statistically significant
Tralokinumab at 600 mg every 2 weeks	Improved FEV1% changes = 11.8%	Statistically significant
Tralokinumab at 300 mg every 2 weeks	Improved absolute forced vital capacity volume changes = 0.11 L	Statistically significant
Tralokinumab at 300 mg every 2 weeks	Improved percentage changes in forced vital capacity = 4.44%	Statistically significant
Tralokinumab treatment	Statistically improved Asthma Control Questionnaire 6 scores, but not clinically meaningful difference	Statistically significant
Tralokinumab treatment	No decrease in annualized asthma exacerbation rate in unselected patients with moderate to severe asthma	Not statistically significant
Tralokinumab treatment	Improved annualized asthma exacerbation rate in patients with severe asthma and high fractional exhaled nitric oxide levels: rate ratio = 0.72	Statistically significant
Tralokinumab treatment	No increased incidence of serious adverse events	Not statistically significant
Tralokinumab treatment	Increased incidence of mild injection-site reactions: odds ratio = 5.92	Statistically significant

[20].

Summary:

This study analyzed the effectiveness and safety of tralokinumab, an anti-IL-13 treatment, in adults with moderate to severe asthma. The analysis included six randomized controlled trials involving 2,928 patients. The results showed that tralokinumab improved lung function, as measured by FEV1 and FVC. Asthma control and quality of life did not significantly improve, but there was a reduction in asthma exacerbations in patients with severe asthma and high levels of fractional exhaled nitric oxide.

Table 11 (Cost -effectiveness and comparative effectiveness of biologic therapy for asthm (Systematic Review)

Medications	**Results**
Omalizumab Mepolizumab Reslizumab Benralizumab Dupilumab	Current pricing for all biologics exceeds measures of cost- effectiveness. Prices would have to be reduced by a minimum of approximately 60% to meet available measures indicating cost-effectiveness.

[23].

Table 12 Benralizumab from the basic mechanism of action to the potential use in the biological therapy of severe eosinophilic asthma (review)

	Medications	**Results**
Basic Mechanism	Benralizumab	Inhibits eosinophil differentiation in the bone marrow. Prevents eosinophilic infiltration of airways. Induces eosinophil apoptosis through Antibody department cell mediated cytotoxicity (ADCC) mediated pathway.
Clinical and Functional| Benralizumab	Benralizumab	Significant decrease in asthma exacerbations. Better symptom control . Reduction in oral corticosteroids intake. Attenuation of airflow limitation
Safety and Tolerability	Benralizumab	Very good safety and tolerability profile

[23].

Summary:The study discusses the potential use of benralizumab, a monoclonal antibody, as a therapeutic option for severe eosinophilic asthma and In this study, we found that Benralizumab reduced asthma exacerbations and was shown to be Effective and safe in asthma patients.

Table 13 Biological Therapy-Associated Adverse Reactions in Asthma Analysis of Reporting to the Portuguese Pharmacovigilance System

Medications	**Results**
Omalizumab	We found that it causes anaphylaxis and malignant neoplasms and abortions
Mepolizumab	We found that it causes Musculoskeletal connective tissue disorders

[25].

Table 14 Effect of biologic therapies on airway hyperresponsiveness and allergic response, the review Included 30 studies (a systematic literature review)

Medications	**Results**
Omalizumab	Reduced Hyper responsiveness (AHR) and allergic response early and late
Tezepelumab	Consistent reduction in AHR early asthmatic response
Mepolizumab	Did not have a significant effect on AHR or asthmatic response
Etanercept	Reduce AHR

[26].

Table 15 Reslizumab compared with benralizumab in patients with eosinophilia asthma (a systematic Literature review and network meta-analysis

Medications	**Results**
Reslizumab Benralizumab	Reslizumab significantly improved Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) scores compared with benralizumab once every 4 weeks.

[27].

Summary:

This study compared the effectiveness and safety of benralizumab and reslizumab in patients with eosinophilic asthma. They analyzed eleven studies and focused on subgroups with specific characteristics. Reslizumab showed significant improvements in Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) scores compared to benralizumab. It also had higher probabilities of being superior in terms of ACQ score, AQLQ score, and forced expiratory volume in one second (FEV1), and clinical asthma exacerbations.

Table 16 Use of dupilumab on the treatment of moderate to severe asthma (a systematic review)

Medications	**Results**
Dupilumab	Dupilumab is promising for the treatment of asthma, showing good response and improvement in lung function with few side effects.

[29].

Table 17 Real life effectiveness of mepolizumab in severe asthma (a systematic Literature review)

Medications	**Results**	**P value**
Mepolizumab	Reduction in annualized exacerbation rates (requiring oral corticosteroids (OCS) of 54-97%	$p < 0.05$ in all studies
	Reduced mean/median daily (OCS) doses and OCS discontinuation during follow-up (27-84% of patients)	$p < 0.05$ in all studies
	Improvements in lung function, asthma control, and Health Related quality of life (HRQoL)	$p < 0.05$ in all studies

[30].

Mepolizumab use led to a significant reduction in asthma exacerbations.

Table 18 Efficacy and safety of Biologics for oral corticosteroid dependent asthma (Asystematic review and Network Meta Analysis)

Medications	**Results**
Benralizumab every 8 weeks	Reduction in Oral corticosteroids (OCS) dose : 4.12 [95% CI: 2.22-7.64]
Benralizumab every 4 weeks	Reduction in OCS dose : 4.09 [95% CI: 2.22-7.55]
Dupilumab	Reduction in OCS dose : 3.25 [95% CI: 1.90-5.55]
Mepolizumab	Reduction in OCS dose : 2.39 [95% CI: 1.25-4.57]
Tezepelumab Reslizumab Tralokinumab	Ineffective in reducing OCS dose

[33].

Summary:

This study examined the effectiveness and safety of biologic medications for asthma patients who are dependent on oral corticosteroids (OCS). The researchers analyzed seven randomize controlled trials involving 1,052 patients. They found that benralizumab (administered every 8 weeks or every 4 weeks), dupilumab, and mepolizumab were effective in reducing the OCS dose, while tralokinumab, tezepelumab, and subcutaneous reslizumab were not effective. There were no significant differences in effectiveness among benralizumab, dupilumab, and mepolizumab. These medications also reduced asthma exacerbation.

Table 19 Efficacy and safety of dupilumab for the treatment of uncontrolled asthma (a meta-analysis of Randomized clinical trials)

Medications	**Results**
Dupilumab	Significant improvements in first-second forced expiratory volume (FEV1) = 4.29 L

[34].

Study 1

Effective management of severe asthma with biologic medications in adult patients (a literature Review and international expert opinion) [22].

Summary:

This study provides treatment recommendations for managing severe asthma using biologic Medications. When choosing the optimal biologic medication for patients with severe T2 asthma, Blood eosinophil count (BEC) and fractional exhaled nitric oxide (FeNO) levels can assist inSelecting anti-IL-5, like Mepolizumab and Reslizumab.Or anti-IL-5Rα like Benralizumab. Or anti-IL-4/13 like Dupilumab.If a patient does not respond well to initial treatment, alternative options targeting different inflammatory pathways or non-T2 disease should be considered. A trial period of 4 to 6 months is necessary to evaluate treatment response. Response assessment should be based on Predetermined goals shared with the patient and include oral corticosteroid reduction, symptom Control, lung function improvement, and minimizing exacerbations. Exacerbations are considered the most important outcome.

Study 2

Efficacy and safety of anti-interleukin-5 therapy in patients with asthma (a systematic review and meta-analysis) [24].

Summary:

A meta-analysis of 20 studies involving 7,100 patients investigated the efficacy and safety of anti-interleukin-5 (anti-IL-5) therapy in asthma patients. The analysis revealed significant improvements in several parameters, including increased first second forced expiratory volume (FEV1), improved FEV1% values, and enhanced Asthma Quality of Life Questionnaire (AQLQ) scores. Furthermore, anti-IL-5 therapy was associated with decreased blood and sputum eosinophils, a reduction in asthmatic exacerbations, and no increase in adverse events. However, there was no significant effect on peak expiratory flow (PEF), histamine PC20, or the use of short-acting beta-agonist (SABA) rescue medication. Overall, the study concluded that anti-IL-5 therapy is effective and safe for improving lung function, asthma control, and quality of life in asthma patients.

Study 3

Efficacy of Tezepelumab in Patients with Moderate-to-Severe, Uncontrolled Asthma (Randomized controlled Trail) [28].

Summary:

Tezepelumab, a medication for asthma, was studied in 1,334 patients with moderate-to-severe, uncontrolled asthma. Compared to placebo, tezepelumab reduced asthma exacerbations by 60% Overall. It was effective in patients with both low and high blood eosinophil counts, with Reductions of 48% and 63% respectively.

Study 4

Adverse events of benralizumab in moderate to severe eosinophilic asthma (A meta-analysis) [31].

Summary:

This study aimed to evaluate the adverse events associated with the use of benralizumab in patients with moderate to severe eosinophilic asthma. The researchers analyzed data from eight Randomized controlled trials. The results indicated that patients treated with benralizumab had a Lower risk of overall adverse events, serious adverse events, asthma exacerbation, bronchitis, and sinusitis compared to those who received a placebo. However, it was found that patients treated with benralizumab had a higher risk of experiencing headache and fever (pyrexia) Compared to the placebo group. Importantly, the study did not find any increased incidence ofdeath or other adverse events, such as hypersensitivity reactions, injection-site reactions, Respiratory tract infections, or musculoskeletal pain, when comparing benralizumab to placebo.

Study 5

The efficacy and safety of tezepelumab in the treatment of uncontrolled asthma (A systematic

Review and meta-analysis of randomized controlled trials) [32].

Summary:

This meta-analysis examined the efficacy and safety of tezepelumab in the treatment of uncontrolled asthma. The analysis included four randomized controlled trials with a total of 1600 patients. The findings showed that tezepelumab significantly reduced the rate of annual asthma exacerbations compared to placebo, indicating its effectiveness in controlling asthma symptoms. Additionally, tezepelumab demonstrated improvements in asthma control as measured by the asthma control questionnaire score (ACQ-6), suggesting better overall asthma management.

Chapter IV (Discussion and conclusion)

DISCUSSION

Bronchial asthma is chronic disease that managed by many drugs, this thesis concentrate on biological drugs efficacy and their safety profile .

Biologics approved by the food and drug Administration (FDA) include the following medications, omalizumab, Mepolizumab, Reslizumab, Benralizumab, Dupilumab, Tezepelumab [10].

These drugs are primarily used for patients with severe asthma who do not respond well to conventional treatments .[14] can provide significant improvement in asthma control, reducing symptoms and, exacerbations.[15]

The study entitled (Real world efficacy of treatment with benralizumab, dupilumap, mepolizumab and reslizumab for severe asthma) ,This study illustrates better improvement in relizumab by reduction of Exacerbation Rate Reduction (ERR). [16]

While in (Comparative Efficacy and Safety of Tezepelumab and Other Biologics in Patients With inadequately controlled asthma According to Thresholds of Type 2 Inflammatory Biomarkers) , study explains that Tezepelumab had significant improvement in asthma control, reduced exacerbation frequency, and decreased oral corticosteroid use. [18]

In the study (A comparison of the effectiveness of biologic therapies for asthma) ,The results tha biological therapies were effective in reducing asthma exacerbations, and improving symptom control. [20]

In the (Efficacy of Biologics in Severe Uncontrolled Asthma Stratified by Blood Eosinophil Count) , They found that the Effectiveness of biologics in reducing asthma exacerbations varied depending on the Baseline blood eosinophil count (BEC).
Patients with higher Baseline blood eosinophil levels showed a reduction in exacerbations with all biologics, while. those with lower BEC levels experienced inconsistent Results [22].

The study entitled (Benralizumab from the Basic Mechanism of Action to the Potential Use in the Biological Therapy of severe eosinophilic asthma) , was found that Benralizumab Inhibits eosinophil differentiation in the bone marrow and prevents eosinophilic infiltration of airways. Induces eosinophil apoptosis through Antibody department cell-mediated cytotoxicity (ADCC) mediated pathway and very good safety and tolerability profile, and Significant decrease in asthma exacerbations Better symptom control and Reduction in oral corticosteroids intake [26].

(Reslizumab Compared with benralizumab in Patients with Eosinophilia Asthma) was found Reslizumab showed significant improvements in Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) scores compared to benralizumab.[30]

The (Efficacy of Tezepelumab in Patients with Moderate-to-Severe, Uncontrolled Asthma) study showed tezepelumab reduced asthma exacerbations by 60% Overall. It was effective in patients with both low and high blood eosinophil counts, with Reductions of 48% and 63% respectively. [31]

Study entitled (Use of Dupilumab on the Treatment of Moderate to Severe Asthma) was found that Dupilumab is promising for the treatment of asthma, showing good response and improvement in lung function with few side effects. [32]

While in (Efficacy and Safety of Biologics for Oral Corticosteroid-Dependent Asthma), found that benralizumab, dupilumab, and mepolizumab were effective in reducing the OCS dose, while tralokinumab, tezepelumab, and reslizumab were not effective. [36]

In (Efficacy and safety of dupilumab for the treatment of uncontrolled asthma), Dupilumab treatment resulted in significant improvements in lung function, asthma control, and quality of life. [37]

Biologics are generally safe, with common side effects including soreness at the injection site, headache, sore throat, and fatigue. However, some biologics may carry a small risk of anaphylaxis or certain infections, and precautions may be taken accordingly. [10]

The study entitled (Clinical Characteristics and Treatment Outcomes of Severe Asthma Patients with a History of Multiple Biologic Drugs Use) was found these drugs Omalizumab, Mepolizumab, Reslizumab, Benralizumab, and Dupilumab caused a Higher number of allergic or eosinophilic airways. comorbidities and Approximately half of the patients changed to different treatments due to uncontrolled comorbidities. [19].

While in (Hypersensitivity and Immunologic Reactions to Biologics Opportunities for the Allergist) study illustrate Anaphylaxis for omalizumab and Hypogammaglobulinemia for Rituximab. [21]

(Biological Therapy-Associated Adverse Reactions in Asthma Analysis of Reporting to the Portuguese Pharmacovigilance System), was found that omalizumab caused anaphylaxis, malignant neoplasms, abortions, and mepolizumab caused musculoskeletal and connective tissue disorders. [28]

Final in the study (Effect of biologic therapies on airway hyperresponsiveness and allergic Response), were found omalizumab reduced hyperresponsiveness (AHR) and allergic response early and late, and mepolizumab did not have a significant effect on AHR or asthmatic response. [29] Biologic treatments for asthma tend to be more expensive compared to other control medications. It is important for patients to discuss the cost and coverage with their doctor . [10]

In the study entitled (Cost-effectiveness and comparative effectiveness of biologic therapy for Asthma) was found Current pricing for all biologics exceeds measures of cost-effectiveness. Prices would have to be reduced by a minimum of approximately 60% to meet available measures indicating cost effectiveness.[24]

Conclusion

Biological drugs, such as omalizumab, Mepolizumab, Reslizumab, Benralizumab, Dupilumab, and Tezepelumab, Tralokinomab, have been approved by the FDA for the treatment of severe asthma in patients who do not respond well to conventional treatments.

These biological drugs have shown efficacy in improving asthma control, reducing symptoms, and decreasing asthma exacerbations.

Different studies have demonstrated the effectiveness of specific biological drugs in reducing asthma exacerbations, improving symptom control, and reducing the need for oral corticosteroids.

The effectiveness of biologics may vary depending on the baseline blood eosinophil count (BEC) of patients. Higher BEC levels tend to show better response to biologics in reducing exacerbations.

Benralizumab, in particular, has been found to inhibit eosinophil differentiation and infiltration in the airways, leading to improved asthma control and a reduction in exacerbations.

Reslizumab has shown significant improvements in asthma control and quality of life compared to benralizumab.

Tezepelumab has demonstrated a significant reduction in asthma exacerbations, regardless of the blood eosinophil count.

Dupilumab has shown promise in the treatment of asthma, with improvements in lung function and asthma control.

Biologic therapies have generally been found to be safe, with common side effects such as soreness at the injection site, headache, sore throat, and fatigue. However, there may be a small risk of anaphylaxis or certain infections with some biologics.

The use of biologics in asthma treatment may incur higher costs compared to other control medications, and patients should discuss the cost and coverage with their doctor.

Current pricing for biologics may need to be reduced significantly to meet measures of cost-effectiveness.

These conclusions highlight the efficacy, safety, and varying effectiveness of different biological drugs in the management of severe asthma, providing valuable insights for healthcare professionals and patients making treatment decisions.

Chapter V (References)

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