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Review article

A NARRATIVE REVIEW ON BIOLOGICS IN THE MANAGEMENT OF ASTHMA: ASSESSING THE CURRENT LANDSCAPE.

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ABSTRACT.

Monoclonal antibodies (mAbs) play a crucial role in the treatment of severe asthma. Physicians rely on patient-specific characteristics to determine the appropriate asthma classification for treatment. Currently, there are five biological agents designed to target the 'TH2-high' asthma phenotype, characterized by inflammation primarily driven by type 2 T-helper cells (TH2). This subtype is associated with severe eosinophilic asthma, marked by elevated levels of immunoglobulin E, fractional exhaled nitric oxide (FeNO), and eosinophils. In contrast, the ' TH2-low' asthma phenotype, characterized by increased sputum neutrophil counts and activation of the TH17-mediated interleukin-17 pathway, remains less understood.
This review examines the role of mAbs in the management of severe asthma, with a focus on their efficacy in different asthma phenotypes. We analyze existing literature, clinical trials, and studies involving mAbs in severe asthma treatment, particularly those targeting thymic stromal lymphopoietin (TSLP).
Biologics targeting 'TH2-high' asthma have shown promising outcomes, effectively reducing symptoms and exacerbations. However, the management of ' TH2-low' asthma remains a challenge due to limited therapeutic options. Recent medical trials have explored the use of mAbs, specifically TSLP-targeting mAbs, which have demonstrated significant efficacy in improving asthma control, even in ' TH2-low' phenotypes.
Monoclonal antibodies have revolutionized the treatment of severe asthma, primarily focusing on the ' TH2-high' phenotype. While challenges persist in addressing ' TH2-low' asthma, recent developments, particularly TSLP-targeting mAbs, provide hope for more comprehensive asthma management across various phenotypes.
Further research is needed to expand our understanding of ' TH2-low' asthma and explore additional biologic agents that may be effective in its treatment. Clinicians should consider personalized treatment approaches, including mAbs, based on the specific asthma phenotype of each patient to optimize asthma management.

Keywords: *Biologics, Severe Asthma, Neutrophilic Asthma, Eosinophilic Asthma, Monoclonal Antibodies*
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INTRODUCTION.

In the management of severe uncontrolled asthma, a range of biologic agents can be utilized as supplementary therapeutic options alongside high-dose treatment involving inhaled glucocorticoids, as well as other controllers and relievers such as leukotriene receptor antagonists and long-acting inhaled β2-agonists. In the adult population, the presence of severe asthma is indicated when treatment by the Global Initiative for Asthma (GINA) levels 4 or 5 becomes necessary, and despite treatment adherence, satisfactory symptom control remains unattainable [1].
The risk factors related to the emergence of severe asthma in adulthood encompass several variables. These include being of the female sex, exhibiting persistent eosinophilic inflammation, presenting with nasal polyps and sinusitis, experiencing analgesic asthma, as well as suffering from recurrent respiratory infections [2]. Persistent uncontrolled asthma is associated with heightened susceptibility to exacerbations and the development of persistent, occasionally irreversible bronchial obstruction. Nevertheless, a significantly more prevalent condition compared to severe refractory asthma is the insufficiency of symptom management attributed to extrinsic factors, including erroneous inhalation technique, noncompliance with prescribed treatment, continual contact with allergenic substances or pollutants, or even an erroneous diagnostic evaluation [3]. It is imperative to thoroughly evaluate these potential etiological factors before escalating treatment with biologic agents.
The initial biologic therapy targeting immunoglobulin E (IgE), known as omalizumab, received approval 15 years ago, thereby establishing a foundation for the personalized treatment approach in managing severe asthma in the year 2005. Currently, there exists a repertoire of five monoclonal antibodies that have been developed and are now accessible for the therapeutic management of individuals suffering from severe asthma. In light of the expanding array of therapeutic interventions, the efficacy of biologic treatment hinges upon the meticulous identification of patients who exhibit a favorable likelihood of deriving benefits from the selected pharmaceutical agent, contingent upon their distinct

inflammatory endotypes. The findings of meta-analyses conducted on randomized controlled trials have revealed that all biologics approved for the treatment of asthma have shown a significant average reduction of 50% in exacerbation rates. However, it is important to note that this reduction is observed only when suitable patient individuals are meticulously selected [4]. In a casuistic manner, notable enhancements can be attained. The effectiveness of mAbs in treating various asthma phenotypes is the main emphasis of this review, which also explores their significance in the treatment of severe asthma. The review of the body of research on mAbs used in the treatment of severe asthma, including studies that target thymic stromal lymphopoietin (TSLP) and clinical trials.

METHODOLOGY.

A thorough literature search was undertaken to identify pertinent studies and articles that have been published in peer-reviewed scientific journals. The databases employed for this study were as follows: The databases utilized for this study included PubMed/MEDLINE, Embase, Cochrane Library, and Google Scholar.

Inclusion Criteria. The present study and relevant literature were incorporated if they satisfied the following predetermined criteria: This study primarily investigated the therapeutic efficacy of mAbs in managing severe asthma, with a specific focus on their role. The research involved the participation of human subjects. The present manuscript has been published in the English language. The accessibility of complete textual content articles.

Exclusion Criteria. Studies and articles were excluded if they failed to satisfy the predetermined inclusion criteria as delineated above. Furthermore, any investigations about animal subjects or those that do not possess a direct correlation to the subject matter of mAbs in the management of severe asthma were deemed ineligible for inclusion.

Data Collection. Pertinent data from the chosen studies were extracted and systematically organized. The following data was gathered:
The study population was characterized based on various demographic factors, including age, sex, and asthma phenotype. Various types of monoclonal antibodies, such as anti-thymic stromal lymphopoietin (TSLP) mAbs, have been identified and studied in the field of medicine. Dosages and administration protocols. The primary and secondary outcomes were evaluated in each study. Adverse events and safety profiles are critical aspects to consider in the realm of medical evaluation. In summary, the present study has yielded several noteworthy conclusions and key findings.

Data Synthesis. The data obtained from the chosen studies were synthesized narratively to present a comprehensive overview of the utilization of mAbs in the management of severe asthma. Special emphasis was placed on evaluating the effectiveness of mAbs in various asthma phenotypes, encompassing their influence on symptom management, reduction of exacerbations, and enhancement of quality of life.

Endotype determination.

Before commencing supplementary treatment utilizing biologics, it is imperative to ascertain the endotype of the individual afflicted with severe asthma. This is due to the recently authorized monoclonal antibody treatments mainly targeting responses to inflammation generated by TH2 cells. TH2 cells are actively involved in the immune response against extracellular microbes and facilitate the clonal proliferation of B lymphocytes that are specific to allergens. Upon antigen exhibition by dendritic cells, polarized TH2 cells secrete pro-inflammatory cytokines, such as interleukin (IL)-4, -5, and -13. Interleukin-4 (IL-4) exerts a significant impact on B cells, prompting them to engage in the process of immunoglobulin class switching, wherein the production of immunoglobulin M (IgM) is transitioned to immunoglobulin E (IgE).
In the "TH2-high" endotype, there is an increased presence of TH2 cells within the airways, leading to the commencement and perpetuation of eosinophilic inflammation. The determination of the TH2-high endotype can be achieved by assessing phenotypic features and biomarkers, including:

- Eosinophils equal to or greater than 150 µL in the blood
- FeNO $\geq$ 20 ppb and/or
- Eosinophils equal to or greater than 2 percent in the sputum
- Allergic asthma accompanied by elevated levels of total/specific IgE and
- A documented history of prolonged oral corticosteroid (OCS) therapy.

In the management of individuals suffering from unregulated severe eosinophilic asthma, the primary course of action entails the escalation of therapeutic measures through the augmentation of inhaled corticosteroids (ICS) dosage throughout 3 to 6 months. If symptom management continues to be insufficient, the contemplation of therapeutic intervention utilizing a suitable monoclonal antibody represents a viable course of action. The selection process ought to consider various factors, including but not limited to sensitization, IgE levels, exacerbation history, blood eosinophil counts, FeNO levels, comorbidities, and the pharmaceutical formulation of the treatment.

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Approved biologics.

IgE antibody.

Omalizumab, the initial mono-clonal anti-body sanctioned for the management of severe allergic asthma within the European Union, was approved in 2005. The compound exhibits a binding affinity towards IgE, thereby impeding its interaction with the FcεRI receptor. This receptor is predominantly expressed in basophils and mast cells. Omalizumab exerts a suppressive effect on the overall quantity of IgE liberated. To ascertain the appropriate dosage for a patient, it is imperative to assess the patient's total serum IgE levels before the commencement of treatment. Omalizumab is indicated for individuals diagnosed with asthma, particularly those who exhibit perennial allergen sensitization, have experienced exacerbations within the preceding 12-month period, possess total IgE levels not exceeding 1500 IU/mL, exhibit blood eosinophils equal to or greater than 260/mL, and have a history of childhood-onset asthma. The therapeutic agent demonstrates a substantial reduction in the incidence of exacerbations and hospitalizations [6].

IL-5 receptor antibodies.

Mepolizumab and reslizumab exhibit high affinity binding to interleukin-5 (IL-5), a cytokine that assumes a vital role in the activation of eosinophils. Similarly, the pharmaceutical agent benralizumab effectively inhibits the IL-5 receptor present in eosinophils and basophils. These agents are thus considered appropriate for individuals diagnosed with asthma who exhibit a significant increase in eosinophil count of at least 300/mL, relatively low levels of immunoglobulin E (IgE), asthma that develops later in life, and experience frequent exacerbations necessitating the use of systemic glucocorticoids for treatment. The administration of these therapeutic interventions has been observed to result in a notable decrease in the occurrence of exacerbations, with a range of 50-75% reduction reported [7]. Additionally, there are results to suggest that the utilization of these interventions can effectively decrease the reliance on oral corticosteroids. Mepolizumab has demonstrated efficacy in augmenting the rate of remission in Churg-Strauss syndrome, a condition characterized by the manifestation of severe allergic asthma primarily affecting the pulmonary system [8]. Reslizumab has been found to yield a notable decrease in the rate of exacerbations, but this effect is observed exclusively in patients exhibiting a blood eosinophilia level exceeding 400/mL [9]. The administration of antibodies targeting interleukin-5 (IL-5) has been observed to result in a decrease in the number of eosinophils present in both the bloodstream and sputum.

IL-4/IL-13 receptor antibodies.

Dupilumab is a biologic agent that effectively prevents the signaling of both IL-4 and IL-13 by precisely binding to the α-subunit of the IL-4 receptor. The use of this treatment is recommended for individuals with a blood eosinophil count ≥150/mL, and a FeNO level exceeding 25 ppb, and has demonstrated efficacy in managing both initial and final onset asthma. The efficacy of selectively targeting IL-4/IL-13 in isolation has been demonstrated to be inadequate. This phenomenon may be attributed to the fact that IL-4 expression is typically diminished in individuals with asthma. Additionally, the inhibition of IL-13 alone primarily targets bronchial wall remodeling and hyper-secretion, as opposed to eosinophil-driven exacerbations, which are frequently utilized as primary outcomes in medical trials [10]. Furthermore, it is worth noting that dupilumab has obtained approval for the therapeutic management of atopic dermatitis.

Biologics in clinical trials.

The therapeutic agents sanctioned for the management of asthma primarily focus on cytokines or immunoglobulins that are released during the activation of TH2 cells. The hypothetical and practical benefit of inhibiting these mediators, which reside at the terminus of the inflammatory cascade, lies in the potential reduction of untoward drug effects. One potential drawback, nonetheless, lies in the limited applicability of these interventions, which are exclusively suitable for a highly specific subset of individuals afflicted with severe asthma, as delineated earlier. If obstruction transpires at the commencement of the inflammatory cascade, a greater number of subsequent pathways are concurrently impacted. This purportedly enhances the efficacy of the intervention and has the potential to target a broader range of asthma endotypes.

Tezepelumab, a human IgG2λ antibody targeting thymic stromal lymphopoietin (TSLP), was administered via intravenous and subcutaneous routes during phase II clinical trials. The administration of Tezepelumab resulted in a reduction in bronchial hyperresponsiveness, FeNO levels, eosinophil count, and the frequency of exacerbations [11]. Tezepelumab demonstrated inhibitory effects on both acute and chronic allergic reactions in individuals with mild allergic asthma following inhalation of allergens, thereby indicating its potential for a broad spectrum of therapeutic effects [12].

CSJ117, an additional antibody targeting thymic stromal lymphopoietin (TSLP), is currently undergoing clinical development. Notably, it has successfully concluded phase I of the clinical trial process. CSJ117 was administered via inhalation daily over 12 weeks to individuals diagnosed with mild allergic asthma, who exhibited both an initial and final response after an inhaled allergen challenge. The administration of inhaled anti-thymic stromal lymphopoietin (TSLP) has demonstrated a notable capacity

to effectively suppress both the final and the initial allergic response when compared to a placebo, as evidenced by previous research [13].

While omalizumab, a novel monoclonal antibody, received approval for severe asthma in 2005, there is no authorized specific pharmacotherapy for the therapy of severe asthma of the "TH2-low" endotype at this point. The pathomechanisms associated with this diverse endotype remain insufficiently comprehended at present. The characterization of different types of asthma, including mixed-granulocytic, paucigranulocytic asthma, and neutrophilic, along with eosinophilic asthma, has been achieved through the quantification of granulocytes in induced sputum [14]. It has been observed that IL-17, which is secreted by TH17 cells, may serve as a crucial mediator in the context of neutrophilic asthma. This assertion is supported by the finding that IL-17 levels are elevated in individuals experiencing severe symptoms [15]. IL-17 plays a crucial role in maintaining the structural integrity of the airway epithelium through its regulatory effects on neutrophil recruitment after pathogen exposure. Nevertheless, this particular characteristic could potentially indicate that IL-17 possesses a defensive role and is not a causative factor but rather a result of asthma [16].

DISCUSSION.

In prospective times, it is plausible that distinct asthma patterns associated with genetic mutations in the IL-X pathway shall be discerned, thereby resulting in an exaggerated neutrophilic reaction to environmental pollutants and subsequent alterations in the airway. In light of the heterogeneous characteristics of asthma, the implementation of individualized biologic therapy necessitates the utilization of dependable biomarkers to assess the efficacy of treatment interventions. To attain this objective, it is imperative to direct our attention towards discernible characteristics that bear substantial influence on an individual's well-being, such as the quantification of eosinophils in sputum or the measurement of FeNO in respiratory air. Notwithstanding the existence of numerous biologic agents targeting eosinophilic asthma, a substantial proportion of patients exhibit an inadequate response to these therapeutic interventions. It is plausible that these individuals who do not exhibit a response to the treatment modalities possess distinctive physiological pathways that are not effectively addressed by existing therapeutic interventions. Asthma is a multifaceted condition characterized by various subtypes. The efficacy of personalized treatments is contingent upon their ability to effectively target the unique pathophysiological mechanisms present in each patient. No monoclonal antibodies have been approved for the 'TH2-low' subtypes at present. Tezepelumab stands as the sole compound currently undergoing phase III clinical trials, thereby suggesting a potential scope for further enhancement.

CONCLUSION.

Monoclonal antibodies (mAbs) targeting the 'TH2-high' phenotype greatly improved severe asthma treatment. For asthmatics with TH2-type immune responses, mAbs work better. These antibodies targeted IL-4, IL-5, IL-13, and TH2-high asthma IgE. Thus, many ' TH2-high' asthmatics have superior symptom control, exacerbation rates, and quality of life.

Standard mAb treatments for ' TH2-low' asthma are ineffective, making management difficult. TH2-low asthma's weaker TH2 immune response reduces mAb efficacy. Non-eosinophilic or neutrophilic inflammatory patients who failed mAbs qualify. Recent asthma research supports multi-phenotype asthma treatment despite these obstacles. Recently, TSLP monoclonal antibodies have gained popularity. Therapy for asthma targets airway inflammation, which TSLP maintains.

TSLP-targeting mAbs may lower ' TH2-low' asthmatic inflammation. Antibodies that disrupt TSLP produce airway hyperresponsiveness and eosinophilic inflammation. When standard mAbs fail, researchers target TSLP. In conclusion, monoclonal antibodies have changed severe asthma treatment, especially in the ' TH2-high' phenotype, whereas TSLP-targeting mAbs give hope for more comprehensive asthma control. Treating ' TH2-low' asthma may enhance asthmatics' lives.

LIMITATIONS.

The lack of symptom improvement noted in patients with uncontrolled asthma treated with the IL-17 receptor inhibitor brodalumab may indicate a possible leaning toward this particular conclusion. However, neither sputum neutrophils nor mediators linked to the IL-17 pathway were screened for in the study sample.

RECOMMENDATION.

Further research is needed to expand our understanding of ' TH2-low' asthma and explore additional biologic agents that may be effective in its treatment. Clinicians should consider personalized treatment approaches, including mAbs, based on the specific asthma phenotype of each patient to optimize asthma management.

LIST OF ABBREVIATIONS.

mAbs- Monoclonal antibodies
TH2- type 2 T-helper
FeNO- fractional exhaled nitric oxide
TSLP- thymic stromal lymphopoietin
GINA- Global Initiative for Asthma
IgE- immunoglobulin E
ICS- inhaled corticosteroids
IL- interleukin

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The study had no funding.

CONFLICT OF INTEREST.

The authors report no conflicts of interest in this work.

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