REVIEW ARTICLE

Clinical Management of Asthma: New Insights Overview

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Abstract

Significant advancements in asthma management have been observed in recent years. New major findings in the pathogenesis of asthma have focused on epigenetics, the innate cellular compartment, and the distinctive immune system. The accurate immunology process was complemented with innovative techniques and the use of artificial intelligence (AI). Numerous human trials and valuable evidence have highlighted asthma treatments and informed modifications in many guidelines for asthma, such as GINA, Expert Panel Report 3, and the guidelines of ERS/ATS on severe asthma, as well as the development of novel guidelines like EAACI for the use of biologicals in severe asthma. Asthma treatment has been put forward with its integration within the wider milieu of Planetary Health. Recently, progress has been meaningful regarding enhanced knowledge about the processes underlying responses/non-responses to new therapeutic approaches and asthma phenotypes. This review recapitulates current information on the international guidelines, diagnosis and therapeutic approaches for asthma management.

Keywords: *Asthma pathogenesis, asthma guidelines, precision immunology, asthma management.*

INTRODUCTION

Asthma occurs in people due to varied, multifaceted interactions of gene environment with diverse clinical phenotypes, remodelling and inflammation. Asthma phenotypes that are common include allergic/non-allergic asthma, asthma with airflow restriction, asthma related to obesity and late-onset asthma [1, 2]. The disease has impacted over 330 million people globally and is expected to surge by 2025 to over 400 million people [3, 4]. Almost 5%–10% of asthma cases suffer from severe disease; the disease exacerbations have a substantial impact related to cost and productivity burden. Following the guidelines of the European Respiratory Society (ERS) and American Thoracic Society (ATS) for severe asthma and the Global Initiative (GINA) for Asthma report, it is stated that severe asthma is the one 'that necessitates management with high dose inhaled corticosteroids (ICS) along with/ without systemic corticosteroids as second controller to avoid it to become "uncontrolled," or that remains "uncontrolled," even with the treatment' [5]. Asthma management is challenging, even though significant improvements in recent years have been observed. A group of experts has recently suggested using the term "asthma" to describe its symptoms. Also, type 2 inflammation has arisen as a crucial disease mechanism, which includes overlapping disease characteristics and their basic mechanisms or endotypes of precise IgE production; type 2-low asthma embraces numerous disease endotypes [6]. Asthma control optimally needs proper pharmacological interventions and measures for trigger circumvention that should be tailored case-wise; consistent symptoms' control, lung function conservation and identification of therapy-related adverse effects are essential. Some diverse therapeutic options for cases with difficulties in asthma control include allergen-specific immunotherapy and new targeted therapies [7].

METHODOLOGY

The literature was searched on PubMed electronically. Systematic keywords were asthma management updates and international guidelines for asthma. The full-text review articles available in the English language and presenting an updated overview of asthma management were carefully reviewed and included. All references were moved to EndNote X9, and the duplicates were removed. Through a literature search on PubMed, 255 articles were selected, of which 77 were assimilated for this review article.

ASTHMA PATHOGENESIS

Asthma is a complex morbidity with diverse phenotypes and endotypes representing varied host–environment interactions that occur from genes to the organ ultimately. They are influenced by contact with allergens, microbial pathogens and pollutants such as particulate matter and smoke [8]. Genome-wide association studies (GWAS) have been done, through which >40 areas of relationship with asthma have been identified. These susceptibility genes embrace the atopy genes, T-2 mediated inflammation and

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epithelial damage and reparation [9]. Furthermore, the studies on expression quantifiable trait loci in bronchial epithelial cells of humans detected risk alleles regulating gene expression related to epithelial function. They include IL-1RL1, IL-33, TSLP and MUC5AC, associated with epithelial damage, alarmin liberation and excessive mucus production [10]. This susceptibility supports the elementary airway inflammation being asthma's hallmark. The biomarkers to evaluate T-2 immunity facilitated inflammation due to eosinophils include blood eosinophils, IgE, exhaled fractional nitric oxide (FeNO) and sputum cytology. Sputum cell quantity can do phenotyping of asthma cases as per the granulocytic content of their sputum into eosinophilic, neutrophilic, mixed granulocytic and paucigranulocytic inflammation [11, 12]. The modifications in the airways structure entailing epithelial injury leading to goblet cell and mucous gland hyperplasia, ciliary dyskinesia and consequential mucus plugs are described as airway remodelling. Developments in semi-quantitative measurement of mucus obstruction *via* CT scan have resulted in better evaluation [13] and emphasised that mucus plugs are related to T2 eosinophilic inflammation. The non-interventional, descriptive research revealed that anti-IL-5 treatments decreased mucus plugs [14], and anti-TSLP in a placebo-based randomised investigation exhibited a decline in mucus plugging linked with baseline eosinophilic inflammation [15]. Also, sub-epithelial collagen deposition, an increased amount of myofibroblasts and fibrocytes, and smooth muscle hyperplasia and hypertrophy of the airways are present [16]. An increase in the smooth muscle mass of airways and sub-epithelial fibroblasts is the strongest predictor of airflow restriction [17]. This remodelling leads to luminal narrowing and thickening of the airway walls, which is visible *via* quantitative CT scan [18].

Increased size of the airway lumen was observed in experimental research targeting IL-13 and TSLP [19]. The increase in airway smooth muscle contraction (showing airway hyperresponsiveness) may occur in response to direct or indirect triggers; it is not dependent on the underlying inflammatory condition [20]. There is elevated mast cell infiltration into the smooth muscles of airways in asthmatics as compared to healthy individuals and cases with eosinophilic bronchitis, but this was deprived of airway hyperresponsiveness. The level of smooth muscle infiltration in airways due to mast cells is associated with the severity of airway hyperresponsiveness [21]. The mediators like histamine, PGD2 and cysteinyl leukotrienes are released by the mast cells, resulting in contraction of smooth muscles of the airways; T2 cytokines IL-4 and IL-13 are also released [20]. The smooth muscle cells of the airways are activated by IL-13 with alteration in the smooth muscle tone, airways hyperresponsiveness and bronchoconstriction. The mast cells can be activated by epithelial cells, resulting in cytokines IL-33 and TSLP (Thymic stromal lymphopoietin) that can lead to the release of cytokines fostering smooth muscle airways contraction [22]. Studies have shown that TSLP obstruction consistently leads to improved airway hyperresponsiveness following allergen, methacholine and mannitol exposures [19, 23].

International Guidelines for Asthma

Numerous guidelines for asthma management have been published; the following are some of them:

Provisional Guidelines for Asthma and COVID-19: GINA 2021

a. Mild asthma: GINA guidelines do not differentiate between purported "intermittent" and "mild persistent asthma"

b. Severe asthma is clearly defined as "uncontrolled" even with high-dose ICS, long-acting beta2 agonist, or that necessitates high-dose ICS-LABA to be controlled; this is without reference to GINA Steps

c. Explanation of subjects in research by the prescribed regimen rather than by an explicit regimen, 'Step'; severity should not be attributed to existing therapy

d. Management pathways for adults and youths:

   a. Track 1: preferred approach is low-dose ICS formoterol (as a reliever)

   b. Track 2: another approach is SABA (as a reliever), in case Track 1 is not probable or not preferred by patients without exacerbations in their current treatment

e. Treatment steps for children (6–11 years)

f. Long-acting muscarinic antagonists

g. Azithromycin in adults as an add-on

h. For biologic therapy, eligibility *is determined via* blood eosinophils [24].

Biologicals in Severe Asthma: European Academy of Allergy and Clinical Immunology (EAACI) Guidelines

a. To formulate recommendations for every biological outcome and age group, the GRADE approach is to be followed. The proposed treatment algorithm for biologicals use in the clinical setting is as follows:

b. The biological therapy is decided as per biomarkers, phenotype and outcomes, along with the joint decision with the patient to set therapy aims.

c. After 4–6 months, the patient is assessed and categorised as responder/ partial responder/ non-responder, as per pre-determined therapy aims.

d. Additional evaluation should be done for partial/ non-responder patients about local inflammation (*i.e*., induced sputum is employed as a non-invasive means) & for airway hyperresponsiveness.

e. There are many choices for persistent eosinophilic inflammation initially, with checking the compliance to asthma-related controller therapy; alternatively, to a changed dose and route of administration, aiming to another pathway and determining autoimmune biomarkers and anti-drug antibodies.

f. Non-T2 asthma options like low-dose macrolides would be suggested if eosinophilic inflammation does not exist [25].

National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group Report: 2020 Focused Updates to Asthma Management

This report discusses six significant areas:

a. Fractional Exhaled Nitric Oxide Analysis

b. Allergen Reduction Indoor

c. Inhaled Corticosteroids Intermittently

d. Long-Acting Muscarinic Antagonists

e. Immunotherapy to Treat Allergic Asthma

f. Bronchial Thermoplasty

New commendations are incorporated into the current Expert Panel Report 3 (EPR-3) asthma treatment steps illustration for assisting the clinicians to implement in patient care [26].

Severe Asthma Management: European Respiratory Society/American Thoracic Society (ERS/ATS) Guidelines

a. For severe uncontrolled eosinophilic asthma phenotypes, use anti-IL-5 and anti-IL-5Rα in adults.

b. To direct anti-IL-5 commencement in severe asthma adult cases, use the blood eosinophil cut-point, *i.e*., ≥150/μL

c. To detect the highest likelihood or response to anti-IgE therapy among adolescents or adults, consider explicit eosinophil (≥260/μL) and FeNO (≥19.5 ppb) cut-offs.

d. For severe cases of uncontrolled asthma in adolescents and adults, even with GINA step 4-5 or NAEPP step 5 treatments, use inhaled tiotropium.

e. To decrease asthma exacerbations in consistent symptomatic or uncontrolled cases on GINA step 5 or NAEPP step 5 treatments, a trial of chronic macrolide therapy is suggested regardless of asthma phenotype.

For severe eosinophilic asthma adult cases and with severe asthma (corticosteroid-dependent) despite blood eosinophil levels, anti-IL-4/13 is suggested [27].

Diagnosis of Asthma

Pulmonary Functional Imaging

It is the local quantification of lung function principally through CT scan, MRI and nuclear procedures. The distribution of parameters related to pulmonary physiology, together with ventilation, gas exchange, perfusion and biomechanics, can be charted and assessed all over the lungs noninvasively. Such information cannot be attained through conventional lung function tests measuring total lung function without a local distribution view, which is vital in asthmatics due to the mixed distribution of inflammation and remodelling. A precise, reliable and radiation-free method for severe asthma cases to evaluate bronchial wall dimensions is the use of MRI with Ultrashort Echo Time (UTE); this method has adequate spatial resolution for differentiating severe or non-severe [28].

It is suggested that mucus plugs treatment may enhance airflow in severe asthma chronic cases, which was quantified by Multidetector computed tomography (MDCT) [13]. Ventilation heterogeneity (assessed *via* 3-Helium MRI Ventilation Defect Percent or VDP), which is strongly related to assessment of airflow blockage and T2 and eosinophilic inflammation biomarkers, reveals mucus plugging as a contributor [29]. Lung ventilation variations measured by Lung clearance index, free-breathing pulmonary 1H magnetic resonance imaging (FDMRI) and inhaled-gas MRI to create VDP FDMRI VDP, produced in free-breathing asthmatic cases, were associated with static inspiratory breath-hold 3-He MRI VDP; it undervalued VDP compared to 3-He MRI VDP. FDMRI VDP can be employed for asthma assessments at facilities with no inhaled-gas MRI, though it is less sensitive than salbutamol and post-methacholine challenge [30]. Ventilation/perfusion single-photon emission computed tomography (V-P SPECT) is another technique evaluating pulmonary ventilation and perfusion to measure response to mepolizumab. The

treatment improvements can be determined with better precision through this measure with quantification [31]. In asthmatic children, hyperpolarised gas with helium (HHe-3) MRI can be used too; severe phenotype was detected by HHe-3 MRI measurements of elevated ventilation heterogeneity index and recorded areas of pulmonary eosinophilia [32]. Hyperpolarised xenon-129 MRI (129Xe-MRI) can be used as a biomarker of ventilation inhomogeneity to evaluate disease progression and treatment response in severe pediatric asthma cases [33]. Another method is "accelerated longitudinal decline in lung Quantitative CT" (qCT) to evaluate severe airway remodelling, meagre airway illness and hyperinflation and diminished local alteration in lung volumes, all of which can be related to asthma exacerbations and further decrease in lung function [34].

Recent Therapeutic Approaches

Asthma Management with SMART Approach

"The Global Initiative for Asthma and the National Asthma Education and Prevention Program Coordinating Committee" highly recommended in steps 3 and 4 regarding asthma therapy to use an inhaler having the blend of an inhaled corticosteroid (ICS) and a long-acting bronchodilator (formoterol) as maintenance and rapid relief treatment (SMART or MART); there is provision of practical information to implement SMART in evidence-based clinical practice. With the SMART approach, the ICS-formoterol combination offers rapid asthma relief akin to that of short-acting bronchodilators like albuterol, with overall lesser ICS exposure and risk mitigation for severe asthma exacerbations. The SMART clinical research was mostly conducted in cases of ≥12 years of age, with one inhalation 1-2 times daily (step 3) and two inhalations 2 times daily (step 4) of budesonide-formoterol (delivered dose = 160/4.5 μg). The patients inhale additional budesonide-formoterol 160/4.5 μg for steps 3 and 4, *i.e*., one inhalation for symptom relief as per need, for a maximum of 12 inhalations delivering 54 μg formoterol in any single day. The safety and efficacy of budesonide-formoterol and beclometasone-formoterol have been established in the SMART approach, but not with other ICS-long-acting bronchodilator blends. The SMART schedule should be individualised with a vigilant elucidation of its part in self-management. The availability of the SMART regimen and its cost to patients are related to the recommended dose and the payer contracts [35]. Once good control is achieved, defined by measuring symptoms and exacerbations, the regimen should be stepped down to achieve the minimum effective ICS dose; each decrease should be observed as a trial, and the patient should be educated to resume their former dose in case of symptoms worsening [36].

Precision Medicine Approach for Asthma

Biological Markers

Biomarkers or biological markers are the quantifiable indicators relating to an endotype with a phenotype. It is to be noted that the existing biomarkers are not accurate in the selection of explicit asthma endotypes responding to a targeted therapy, *e.g*., blood eosinophilia forecasts treatment response to the existing medications in severe asthma (anti-IL-4/IL-13, anti-IL-5 and anti-IgE) [37]. Additionally, T2 airway inflammation molecular markers do not differentiate between eosinophilic, chronic obstructive pulmonary disease (COPD) and eosinophilic asthma, although the connection between eosinophilia and T2 markers looks infirm in COPD as compared to severe asthma [38]. Moreover, the biomarkers are dynamic, fluctuate temporally, reflecting adaptive ability to resist external threats; this aspect can be covered by the longitudinal studies, but repeated sampling is challenging, thereby restricting their usage. At present, the feasibility of using and the cost of determining samples are the most prominent impediments to biomarker use. Point-of-care tests, which are rapid, easily manageable and cost-effective, are in process. The initiation of such methods, along with advances into biomarker combination approaches, may possibly generate robust information for improving the detection and management of allergic illnesses. When frequent sampling is not the main burden to patients, the electronic nose (eNose) is used to measure exhaled breath volatile organic compounds, having high potential for diagnosis and phenotyping of non-invasive asthma. eNose profiles have been demonstrated as notable between pre-viral and post-viral challenge stages in asthmatic and healthy control groups distinctly [39].

The basophil activation test (BAT) can be an exciting means for severe eosinophilic asthma patient selection, for a biological marker, such as activated basophils, particularly those expressing CD125, were contrariwise linked to the efficacy of anti-IL-5/IL-5Rα drugs [40]. In young children, the upper airway immune mediator levels were studied amid asthma-like episodes in relation to their capacity in predicting azithromycin response. It was noted that high CCL22 levels and low TNF-α and IL-10 levels projected improved therapy response [41]. In African American children, noteworthy variances in nasal epithelial DNA methylation were seen between

non-severe and severe asthmatics, a subcategory of which may be beneficial for the prediction of asthma severity [42]. In severe asthmatics, sputum TNFR1 and TNFR2 were elevated and were related to growing age, decreased lung function and poor asthma control. Serum TNFR1 level was elevated too in severe asthma, and sputum, along with serum TNFR2, were elevated in recurrent exacerbations [43].

Advancements have been seen in the prediction of future risk, too. As per the short and midterm data, rhinovirus (RV) infection is suggested to be a significant clinical marker of unstable asthma in preschool children. Vitamin D supplementation has also been hypothesised to have an anti-rhinovirus effect [44]. A study was conducted in a particular set of children with a history of early wheeze. It was found that in their infancy, ASM thickness and mast cell infiltration were related to exercise-induced bronchoconstriction and in school age, wheezing incidents required hospitalisations, whereas infancy, bronchial eosinophils were related to elevated airway hyperresponsiveness to methacholine in school life [45]; early identification or forecast of asthma eruption due to viruses would permit the treatment timely. eNose variations were noted by research to increase faster after a rhinovirus-16 challenge, distinctly defining adult healthy and asthma cases [46]. There have been findings of genetic variants in the interleukin 1 receptor-like 1 (*IL1RL1)* gene among children linked with susceptibility to asthma episodes [47]. Furthermore, delayed exacerbation resolution due to infections was found to be related to a defective TLR2 and TLR4 upregulation in neutrophils [48].

For asthma exacerbation diagnosis, activated peripheral Th2 cells can be a biomarker [49]. For more precise risk estimation of ryegrass pollen-associated epidemic thunderstorm asthma (ETSA), allergen sensitisation field characterisation, inclusive of the component-resolved detection along with clinical characteristics, can be important. It is revealed that Lol p 5 sensitisation, excluding Lol p 1, might be accountable for triggering ETSA [50]. Further biomarkers were found to be associated with asthma comorbidities. In all kinds of comorbidities for asthma, rhinitis and dermatitis, 8 genes were consistently found to be overexpressed, *e.g*., "CLC, EMR4P, IL-5RA, FRRS1, HRH4, SLC29A1, SIGLEC8 and IL1RL1". Eosinophil-related immune response and signal transduction were prominent in the comorbid conditions. In comorbid ailments, IL-5/JAK/STAT and IL-33/ST2/IRAK/TRAF were detected as main signalling pathways through protein-protein interaction network analyses [51].

Omics/AI Models

By combining the current data through various omics sources, new insights regarding steroid responsiveness mechanisms can be provided. Through this method, a potentially new locus for ICS response was detected in asthma cases as latent TGF-beta binding proteins (LTBP)1, which is a family member of latent-transforming growth factor-beta binding proteins [52]. Two enriched clusters were generated by application of cytometry and machine learning (ML) to BAL cells from corticosteroid-resistant asthma: (i) IL-4+ innate immune cells and (ii) IFN-γ+ T cells, together with tissue-resident memory cells. The signs of mitosis and IL-7 signalling in "CD206-FcεRI+CD127+IL-4+ innate cells" in the first group and the T cell adaptive immune responses in the other were seen *via* immune cell association, developed by the Exploratory Matrices (ICLite) algorithm [53].

To detect disease subtypes, "Merged Affinity Network Association Clustering (MANAclust)" is an automated, coding-free pipeline that enables the incorporation of numeric and categorical data for unsupervised clustering across clinical and multi-omic profiles. Clinically and molecularly discrete clusters were detected by MANAclust, together with heterogeneous sets of 'healthy controls' and viral and allergy-related subgroups of asthma cases. It further exhibited that cases with similar signs and symptoms had dissimilar molecular profiles [54].

Biological Therapies

Biological treatment additionally should be considered for severe asthma cases with recurrent exacerbations and inadequate symptom control or those who are OCS-dependent [3]. The existing biologics can target eosinophilic T2-high severe asthma successfully. Aiming at the epithelial-derived cytokines has established assistance to those with eosinophilic T2high and non-eosinophilic T2low asthma, despite the unsuccessful T17, IL-23, and anti-neutrophil targeted treatments. Randomised controlled trials to compare these biologicals directly for severe asthma are unavailable, thus lacking any evidence for clinical decision-making. The suitability for biological treatment is reliant on the licensing criteria, affordability and local payer criteria that differ globally. Eligibility comprises age, the quantity of exacerbations in the previous year, consistent OCS use, asthma control, pulmonary function, biomarkers like blood eosinophil count, quality of life, comorbidities and cost. There should always be a consideration of patient preference

that can be more updated by frequency of dosage and administration route [12].

Some biological therapies are discussed as follows:

Omalizumab (Anti-IgE): It is administered in individuals≥ 6 years of age by subcutaneous route, 75–600 mg every 2 or 4 weeks, based on weight and total IgE. GINA eligibility criteria are: "severe asthma with severe exacerbations within the previous year, inhaled allergens sensitisation, total serum IgE and weight within local dosing range, blood eosinophils ≥260 cells/μL, FeNO ≥20 ppb will be the predictors of good response".

Mepolizumab (IL-5): It is administered in individuals≥12 years of age subcutaneously, 100 mg every 4 weeks and in individuals 6–11 years of age, given 40 mg every 4 weeks. GINA eligibility criteria are: "severe asthma with severe exacerbations within the previous year, locally specified blood eosinophil ≥150 cells/μL or ≥300 cells/μL; higher blood eosinophils, greater quantity of severe exacerbations in the former year, nasal polyposis, maintenance of OCS at baseline will be predictors of good response".

Reslizumab (IL-5): It is administered in individuals≥18 years of age, 3 mg/kg every 4 weeks. GINA eligibility criteria are: "severe asthma with severe exacerbations within the previous year, locally specified blood eosinophil ≥150 cells/μL or ≥300 cells/μL; adult-onset asthma will be a predictor of good response".

Benralizumab (IL-5Rα): It is administered in individuals≥18 years of age subcutaneously, 30 mg every 4 weeks for the initial 3 doses, then 30 mg every 8 weeks. GINA eligibility criteria are: "severe asthma with severe exacerbations within previous year, locally specified blood eosinophil ≥150 cells/μL or ≥300 cells/μL; higher blood eosinophils, greater number of severe exacerbations in the former year, nasal polyposis, baseline OCS maintenance, meager lung function FEV1 <65% will be predictors of good response".

Dupilumab (IL-4Rα): It is given in ≥12 years of age subcutaneously, 200 mg or 300 mg every 2 weeks (OCS dependent or multimorbidities). GINA eligibility criteria are: "severe asthma with severe exacerbations within the previous year, blood eosinophil ≥150 cells/μL and ≤1500 cells/μL, or FeNO ≥25 ppb, or OCS maintenance; higher blood eosinophils and FeNO will be the predictors of good response".

Tezepelumab (TSLP): It is administered in individuals≥12 years of age subcutaneously, 210 mg every 4 weeks. GINA eligibility criteria are: "severe asthma with severe exacerbations within the previous year; higher blood eosinophils and higher FeNO will be predictors of good response, while some advantage to T2 low asthma cases".

All the licensed biologicals, *i.e*., reslizumab, omalizumab, benralizumab, dupilumab, mepolizumab and tezepelumab, are recommended as an adjunct treatment for severe asthma cases with recurrent exacerbations and T2 inflammation signs. For the cases without T2 airway inflammation, Tezepelumab therapy is also recommended [3]. Also, biologicals are suggested to permit OCS step-down to diminish further risk of corticosteroid-related illness [21].

Immunotherapy

In certain allergic asthma cases, immunotherapy can be important. There is subcutaneous or sublingual administration (SLIT) of an exogenous aeroallergen to which an individual has shown sensitisation so as to mitigate the IgE-mediated allergic responses related to asthma and rhinitis [26]. Registered treatments that have shown efficacy in asthmatics in Australia are house dust mite and grass pollen SLIT [55], with chosen therapy often directed by an allergy expert [26]. Immunotherapy can deteriorate asthma symptoms, so it should be done under expert supervision [56].

Education for Self-Management

Irrespective of asthma severity, all the patients should have an individualised 'Asthma Action Plan', a document detailing symptoms indicating deterioration, control or an exacerbation and their management as part of education for self-management. The addition of peak flow values can be supportive in some cases, such as poor perceivers of symptoms. It was found that the patients with self-management education were hospitalised 36% less frequently than those without it [56, 57].

New Asthma Clinical Trials

The adherence to long-term therapies can be achieved by simple dosing schedules, as reported in clinical trials that involve various therapeutic agents used in the management of asthma exacerbations (**Table 1**). Budesonide/formoterol administration as per need attains better control and a lesser exacerbation as compared to as per need administration of terbutaline, while exposing mild asthma patients to a reduced amount of ICS than fixed dose budesonide treatment [54, 58]. This method reduces short-term exacerbations in mild asthma adolescents who are at risk of developing severe asthma [59, 60]. The PALLADIUM trial exhibited similar enhancement of pulmonary function amid once per day mometasone/

Table 1: Summary of clinical trials involving various therapeutic agents used in the management of asthma exacerbations.

Treatment/Trial	Patient population	Comparison/Design	Outcome(s)	Ref.
Budesonide/formoterol (as-needed)	Mild asthma patients	Compared to as-needed terbutaline and fixed-dose budesonide	Better control, fewer exacerbations, lower ICS exposure	[54, 58]
Budesonide/formoterol (as-needed) in teens	Adolescents with mild asthma are at risk of severe progression	Strategy focused on reducing short-term exacerbations	Reduction in short-term exacerbations	[59, 60]
PALLADIUM trial	General asthma population	Mometasone/indacaterol once daily *vs*. fluticasone/salmeterol twice daily	Similar improvement in pulmonary function	[61]
Eicosanoids (PGs & LTs)	N/A	Mechanistic insight	Known mediators of airway inflammation and bronchoconstriction	[62]
Fevipiprant	Patients ≥12 years with moderate-to-severe asthma	Step-on oral therapy *vs*. standard care	No significant reduction in exacerbations	[63]
Triple therapy (beclomethasone/formoterol/glycopyrronium)	Adults with moderate-to-severe uncontrolled asthma	Compared to beclomethasone/formoterol only	Improved lung function; reduced exacerbations, especially with high reversibility	[64]
CAPTAIN trial	Adults with uncontrolled asthma	Fluticasone/umeclidinium/vilanterol *vs*. fluticasone/vilanterol	Improved pulmonary function	[65]
Tiotropium	Mild asthma with low sputum eosinophilia	Compared to ICS	Equally effective	[66]
Tezepelumab	Moderate-to-severe uncontrolled asthma	Anti-TSLP monoclonal antibody	Reduced exacerbations, improved lung function, asthma control, and quality of life across phenotypes	[67, 68]
Tezepelumab (seasonal/chronic effects)	Broad asthma population	Comparison to placebo	Reduced exacerbations year-round; effective with or without chronic rhinosinusitis	[69, 70]
Tezepelumab (mechanistic studies)	Moderate/severe asthma patients	Compared to placebo, assessed *via* AHR and biopsies	Decreased AHR (mannitol), reduced airway inflammation	[23]
Ongoing Tezepelumab trials	Severe asthma patients	Evaluating OCS reduction, airway inflammation, and long-term safety	Trials in progress	[71-73]
Astegolimab	Adults with severe asthma	Anti-ST2 (IL-33 receptor) therapy	Reduced exacerbations regardless of eosinophil levels	[74]
QUEST (dupilumab efficacy in adolescents)	Adolescents (12–17 yrs) *vs*. Adults (≥18 yrs)	Post hoc analysis	Improved pulmonary function, reduced T2 biomarkers	[75]
Dupilumab in T2-high asthma	High-dose ICS patients with T2 asthma	Post hoc analysis	Reduced severe exacerbations, improved asthma control and lung function	[76]
ANDHI trial (benralizumab + nasal polyps)	Adults with eosinophilic asthma + nasal polyps	High-dose ICS + add-on therapy *vs*. benralizumab	Clinically significant improvement in SNOT-22 scores	[77]

indacaterol and twice per day fluticasone/salmeterol administration [61]. The most researched eicosanoids are prostaglandins and leukotrienes; they are well-known inducers of the pathophysiology of airways, together with bronchoconstriction and inflammation [62]. Fevipiprant inhibits PGD2-mediated ILC2 and Th2-cell activation and is a selective PD-2 antagonist. In a couple of clinical trials, no decrease was seen in moderate-to-severe exacerbations in ≥12 years of asthma cases administered with step-on fevipiprant orally in comparison to the standardised care [63]. According to GINA step 5, LAMAs (long-acting

muscarinic antagonists) are suggested as step-on controllers. Two clinical trials studied the effects of triple therapy (*i.e*., beclomethasone/formoterol/glycopyrronium) in adult asthmatics in a single device with moderate-severe uncontrolled asthma; cases with this triple therapy attained considerably enhanced pulmonary function than those administered with beclomethasone/formoterol only. As indicated by post hoc analysis, the triple regimen diminished the exacerbations, particularly in cases with greater reversibility at baseline [64]. The CAPTAIN trial also established that fluticasone/umeclidinium/vilanterol enhanced pulmonary function in uncontrolled adult asthmatics in comparison to fluticasone/vilanterol administration [65]. For treatment of mild asthma with diminutive sputum eosinophilia, tiotropium has proven lately to be as effective as ICS [66].

An anti-TSLP monoclonal antibody called Tezepelumab displayed a decline in the exacerbations and enhancement in the pulmonary function, asthma control and quality of life in moderate to severe uncontrolled asthma cases of diverse phenotypes [67, 68]. This monoclonal antibody decreased exacerbation rates across all seasons [69] and in cases with/ without chronic rhinosinusitis [70]. In comparison to placebo, Tezepelumab also reduced the AHR assessed by mannitol and airway inflammation evaluated in bronchial biopsies [23]. Three more clinical trials are running to measure the capacity of tezepelumab to diminish OCS administration [71] and airway inflammation [72], and to examine its enduring safety in severe asthma cases [73]. Astegolimab targets ST2 (IL-33 receptor) and reduces exacerbations irrespective of blood eosinophils in severe asthma adult cases [74]. QUEST post hoc analyses measured dupilumab efficacy in adolescent cases (12–17 years of age) and compared with adult cases (aged ≥18 years). Dupilumab enhanced the pulmonary function and decreased T2 biomarker levels [75]. In one more post hoc test, dupilumab substantially decreased severe exacerbations and enhanced pulmonary function and asthma control in a T2 asthma subset, administered with high doses of ICS [76]. In the "Sino-Nasal Outcome Test-22 (SNOT-22)" on adults with (ANDHI trial) subsequent treatment with benralizumab, a clinically significant improvement was observed in adult cases of severe asthma (eosinophilic) and chronic rhinosinusitis with nasal polyps, who had ≥2 previous-year exacerbations in spite of high dose ICS with an added controller medication [77].

CONCLUSION

Asthma is a complex morbid condition necessitating optimum management through knowledge regarding diverse immune pathway drivers, stepwise addition/deletion of medicines individualised for patients and their symptoms. Asthma phenotyping and endotyping through biomarkers and the advancements in the field of biologicals targeting precise immune pathways have led to substantial progress in the control of severe illness. Noteworthy amendments in treatment guidelines of asthma have taken place in recent years, with a more individualised, rational approach to disease management. Even with the well-identified heterogeneity in asthma disease, there are numerous mechanisms and treatable traits like bronchoconstriction, which are common in all the phenotypes of asthma. Thus, the precise management of asthma cases necessitates a suitable equilibrium between guideline-based severity-customised therapy and precision medicine-based customised methods.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

Mubasshir Saleem: Conceptualisation, Supervision, Drafting of the initial manuscript.

Humaira Mehboob: Literature search, Data curation, Drafting of the initial manuscript.

Nausheen Ameen Lakhani: Literature search, Critical review and editing.

Sana Shahid: Manuscript review, Editing, Project administration.

Novera Haider: Manuscript review and critical editing.

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