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Review Article

Aerosol Biologics for the Treatment of Eosinophilic Asthma

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Abstract

Asthma is a heterogeneous chronic airway disease comprising of distinct phenotypes characterized by different immunopathophysiologic pathways, clinical features, disease severity, and response to treatment. The phenotypes of asthma include eosinophilic, neutrophilic, mixed cellularity, and paucigranulocytic asthma. Eosinophilic asthma is principally a T helper type 2 (Th2)-mediated airway disease. However, several other immune and structural cells secrete the cytokines implicated in the pathogenesis of eosinophilic asthma. Innate type 2 lymphoid cells, mast cells, basophils, and eosinophils secrete Th2 cytokines, such as interleukin-4 (IL-4), IL-13, and IL-5. Additionally, airway epithelial cells produce alarmin cytokines, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). Alarmins are the key initiators of allergic inflammation at the sentinel mucosal surfaces. Innovative biotherapeutic research has led to the discovery of monoclonal antibodies which target and inhibit the immunopathological effects of the cytokines involved in the pathogenesis of eosinophilic asthma. Parenteral biologics targeting the inciting interleukins, include mepolizumab and reslizumab (anti-IL-5), benralizumab (anti-IL-5Rα), dupilumab (anti-4Rα), and tezelizumab (anti-TSLP). They have been shown to significantly reduce annualized exacerbation rates, improve asthma control, lung function, and quality of life. Currently, there are no pulmonary delivered aerosol biologics for topical treatment of asthma. CSJ117 is a potent neutralizing antibody Fab fragment against TSLP, formulated as a PulmoSol TM engineered powder, and is delivered to the lungs by a dry powder inhaler. Phase 2 placebo-controlled clinical trial evaluated the efficacy and safety of CSJ117. CSJ117 delivered as an inhaler attenuated the late asthmatic response (LAR), and the early asthmatic response (EAR) after allergen inhalation challenge (AIC) at day 84 of treatment. The maximum decrease in FVE1 from pre-AIC were significantly lower in the CSJ117 group compared to placebo (P = 029), during LAR. CSJ117 also significantly reduced fractional exhaled nitric oxide before AIC at day 83; and significantly reduced the allergen-induced increase in % sputum eosinophil count. Pulmonary delivery of biologics directly to the airway mucosal surface has several advantages over parenteral routes, particularly in treating airway diseases such as asthma. Inhaler delivered biologics, such as CSJ117 are innovative and attractive methods of future precision treatment of asthma, and other respiratory diseases.

Keywords: eosinophilic asthma; interleukins; biologics; tezepelumab; CSJ117

Introduction

Asthma is a significant public health, and socio-economical problem affecting more than 358 million individuals worldwide [1]. It is a heterogeneous chronic airway disease encompassing distinct phenotypes characterized by different immunopathophysiological pathways, clinical features, disease severity, physiology, and response to treatment. The phenotypes of asthma include eosinophilic, neutrophilic, mixed cellularity, and paucigranulocytic asthma. Eosinophilic asthma is principally a T helper type 2 (Th2)-mediated disease. However, several other immune, such as innate type 2 lymphoid cells (ILC2s), mast cells, basophils, and eosinophils; and structural cells, including fibroblasts, myofibroblasts, and airway smooth muscle cells also secrete the cytokines, and chemokines implicated in the pathogenesis of eosinophilic asthma. Dysfunctional and injured airway epithelial cells exude a special type of cytokines termed alarmins, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). Alarmins are the key initiators of allergic eosinophilic inflammation at the sentinel mucosal surfaces. Because there are several types of immune, and structural cells secreting cytokines promoting eosinophilic inflammation, eosinophilic asthma is also termed as Th2-high asthma, in contrast to Th2-low neutrophilic, and paucigranulocytic asthma.

Despite national guidelines [1-3], and innovative therapies, such as single dual inhaler or single triple inhaler therapy [4-7], about 3.6-10% of the patients with asthma are unresponsive to the standard of care therapy [8-

10]. Precise understanding of the pathophysiological mechanisms, and pathways involved in the pathogenesis of asthma has led to the innovate discovery of biologics for add-on treatment of severe, uncontrolled eosinophilic asthma.

A repertoire of biologics are currently available for the treatment of severe, uncontrolled eosinophilic asthma [11-15]. Parenteral administered biologics targeting the inciting interleukins in the pathogenesis of asthma, include omalizumab (anti-IgE), mepolizumab and reslizumab (anti-IL-5), benralizumab (anti-IL-5Rα), dupilumab (anti-4Rα), and tezelizumab (anti-TSLP). However, monoclonal antibodies (mAb) are less effective in the treatment of other phenotypes of asthma with low blood eosinophil counts, and low fractional exhaled nitric oxide (FeNO) levels, such as neutrophilic, and paucigranulocytic asthma [16-19]. Moreover, omalizumab [20], mepolizumab and benralizumab [21], and dupilumab [22, 23] therapies reduce exacerbations by about 50%, and are unable to eliminate exacerbations completely. Discontinuation of the biologics may result in poor asthma control, and even worse symptoms, and frequent exacerbations. Thus, there is still unmet need to explore for novel biologics capable of treating most of the phenotypes of asthma, and to prevent airway remodeling, and fixed severe airflow limitation. (Table 1) depicts the dosages of the approved biologics for the treatment of severe eosinophilic asthma.

Biologic	Dosage	Efficacy
Omalizumab*	75-375 mg SC Q 2/4 wk	Reduces exacerbations (47-53%)
Mepolizumab*	100 mg SC Q 4 wk	Reduces exacerbations (50-60%)
Reslizumab	3 mg/kg IV Q 4 wk	Reduces exacerbations (34-75%)
Benralizumab*	30 mg SC Q 8 wk	Reduces exacerbations (25-60%)
Dupilumab*	300 mg SC Q 2 wk	Reduces exacerbations (60-80%)
Tezepelumab*	210 mg SC Q 4 wk	Reduces exacerbations (41-56%)

Abbreviations: IV, intravenous, given over 25-50 min; SC, subcutaneous, Q, every; wk, weeks. * Approved for childhood asthma. Pediatric dosages depend on age and body weight of the child or adolescent.

Table 1: Dosages of approved biologics by the Food and Drug Administration for the treatment of severe asthma

Results

Airway epithelial cells play a key role in the regulation of tissue homeostasis by producing and secreting several proteins, such as antioxidants, lipid mediators, cytokines, chemokines, and growth factors [24, 25]. Damaged, and dysfunctional epithelium produce large quantities of cytokines, and growth factors that interact with the underlying mesenchymal cells, including fibroblasts, and myofiblobasts to induce epithelial-mesenchymal transition (EMT), promote airway remodeling [26-28], resulting in persistent airway obstruction [26].

The epithelial-derived cytokines (also termed alarmins), such as interleukin-25 (IL-25) [29-31], IL-33 [31-34], and thymic stromal lymphopoietin (TSLP) [31,35-38] play an initiating key role in the pathogenesis of eosinophilic asthma. Alarmin cytokine secretion can be aroused by respiratory viral, bacterial, and fungal infections, allergens, proteases, chemical irritants, mechanical injury, and cytokines, such as TNF-α, IL-1β [24,29]. Epithelial-derived cytokines secretion during viral respiratory infections is the major trigger of asthma exacerbations, particularly in children [39,40].

Biologics targeting alarmin cytokines have a potential to prevent, and efficaciously treat asthma, and exacerbations [41-45]. Inhibiting upstream alarmin cytokines by specific monoclonal antibodies is a very effective strategy capable of interfering with the downstream inflammatory cascades resulting in eosinophilic asthma [41,46]. Current biologics are not disease modifying, and discontinuing treatment with these biologics result in return of the severity of asthma to pre-treatment levels, or even worsening of asthma control [47,48]. Blocking alarmins, has the potential to inhibit EMT, airway hyperresponsiveness, and remodeling, thus preventing decline in lung function, and persistent severe eosinophilic asthma [42].

Currently, there are no biologics targeting IL-25, and IL-33 approved for the treatment of eosinophilic asthma. Itepekimab is a human IgG4P monoclonal antibody targeting IL-33. Wechsler et al. [49] have shown that a single subcutaneous injection of itepekimab 300 mg reduces exacerbations, and improve asthma control, lung function (FEV1), and health-related quality of life (HLQoL). The efficacy of itepekimab was almost similar to that achieved by dupilumab, although the outcomes were slightly less. However, dual itepekimab plus dupilumab treatment did not result in any clinical and statistical improvement in asthma control, and lung function.

Tezepelumab is a first-in class fully-human IgG2ʎ monoclonal antibody that binds to TSLP, thus blocking its interaction with the TSLP heterodimeric receptor, TSLPR, henceforth inhibiting multiple downstream inflammatory pathways [50,51]. Tezepelumab administered as add-on therapy has been shown to be efficacious, safe, and well tolerated by patients with severe uncontrolled asthma, regardless of the phenotype of asthma. Several clinical trials have documented that tezepelumab significantly reduces exacerbations by about 71%, and improve asthma control, lung function [52,53], and HLQoL in patients with severe, uncontrolled asthma [52]. Subgroup analysis of the PATHWAY study revealed that the reductions in annualized asthma exacerbation rates (AAER) were significant irrespective of patient phenotype, as assessed by blood eosinophil count (< 150 cells/μL), ≥ 150 cells/μL, < 300 cell/μL or ≥ 300 cells/μL), and FeNO, and serum IgE [53]. This denotes that tezepelumab is equally effective in patients with different phenotypes of asthma [53].

Pham et al. [54] re-analysis of the PATHWAY data showed that tezepelumab reduced blood eosinophil count, serum IgE, and FeNO levels; and Th2 cytokines, including IL-5, and IL-13 in patients with severe, uncontrolled asthma. Based on the findings from the PATHWAY studies, tezepelumab was granted Breakthrough Therapy Designation by the US Food and Drug Administration (FDA) in 2019 for patients with severe asthma without an eosinophilic phenotype, who were receiving ICS/LABA with or without OCS, and additional asthma controllers [55].

Phase III NAVIGATOR multicentre, randomized, double-blind, placebo-controlled trial investigated the efficacy and safety of tezepelumab in 1061 patients aged 12 to 80 years with severe, uncontrolled asthma [56]. Tezepelumab significantly reduced the annualized asthma exacerbation rate by more than half in this broad group of patients ($P < 0.001$). The AAER average was 0.9 in the 529 patients who received tezepelumab versus 2.10 for the 532 patients who received placebo in the 52 week trial. Tezepelumab also significantly improved lung function. Pre-bronchodilator FEV1 improved from baseline by about 0.23 L on average with tezepelumab, and by a mean of 0.09 L in patients who received placebo ($P < 0.001$). Furthermore, tezepelumab treatment reduced the rate of emergency department visits by fivefold, and hospitalization by 85%. Notably, there was significant improvement in the Asthma Control

Questionnaire-6 (ACQ-6), and the Asthma Quality of Life Questionnaire (AQLQ) scores [56]. This shows that tezepelumab is efficacious and safe for the treatment of adolescents and adults with severe, uncontrolled asthma.

Post-hoc analysis of phase 2b PATHWAY multicentre, randomized, double-blind, placebo-controlled study of 555 patients aged 18-75 years with severe, uncontrolled asthma with or without nasal polyps (NP) revealed that tezepelumab reduced AAER in both groups of patients [57]. Patients who received placebo with asthma and NP, and asthma without NP had higher AAER compared to those treated with tezepelumab [56]. The AAER was reduced to a similar extent in both groups of patients with asthma and NP, and asthma without NP who received tezepelumab 210 mg. The reduction in AAER for patients with asthma and NP was 75%, and the reduction in AAER was 73% in patients with asthma without NP. In both groups of patients who received placebo, patients experienced one to three more exacerbations than in the tezepelumab 210 mg group. Furthermore, treatment with tezepelumab 210 mg resulted in decrease in blood eosinophil counts, and FeNO levels compared to placebo [57].

Exploratory analysis of the NAVIGATOR phase III trial has demonstrated that tezepelumab reduced exacerbations, and improved lung function; and nasal symptoms in patients with severe, uncontrolled asthma with nasal polyps [58]. Tezepelumab reduced AAER by 86% in patients with asthma and nasal polyposis, and by 52% in patients with asthma without nasal polyposis over 52 weeks, compared to placebo. Tezepelumab improved lung function at week 52 in both groups of patients with an increase in pre-bronchodilator FEV1 of 0.20 L in the patients with asthma and NP, and 0.13 L in patients with asthma without NP. Concomitantly, tezepelumab significantly improved symptoms of nasal polyps at week 52. It significantly reduced the SinoNasal Outcome Test (SNOT-22, [59]) scores in patients with asthma and nasal polyps by 9.6 points versus placebo. The adjusted mean scores reduction from baseline for tezepelumab was 20.10 points, and for placebo was 10.55 points. The baseline mean (± sd) SNOT-22 scores for tezepelumab was 49.4 ± 21.5, and for placebo was 47.8 ± 19.0 [56]. Thus, demonstrating that tezepelumab may also be effective in the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) [58]. Tezepelumab is in phase 3 clinical trials for the treatment of CRSwNP.

The results from the NAVIGATOR trial exploratory analysis are exciting [58]. Patients with eosinophilic asthma and comorbid chronic rhinosinusitis with nasal polyps have more severe united airway disease than patients with eosinophilic asthma or CRSwNP alone [57,60]. Asthmatic patients with CRSwNP experience frequent exacerbations, hospitalization, emergency department visits; and have poor lung function, and HLQoL [61,62]. On the other hand, patients with CRSwNP and asthma have persistent severe nasal obstruction, hyposmia, sleep disturbance, anxiety, and depression, and worse HLQoL [63-65]. They are often corticosteroid dependent, and require frequent functional endoscopic nasal surgery for nasal polyps [66,67].

Treatment of severe eosinophilic asthma with comorbid CRSwNP is challenging. Such patients require a universal targeted therapy, such as biologics, and in particular biologics delivered directly to the nasal airways, and tracheobronchial tree. Currently, there are no approved intranasal or inhaler biologics for the treatment of eosinophilic asthma, and CRSwNP. Noteworthy, dupilumab [68], and omalizumab [69] which are administered subcutaneously are approved for the treatment of both eosinophilic asthma, and CRSwNP.

Discussion

Pulmonary Delivery of Aerosol Biologics

Biological drugs (synonymous known as biologics) are a diverse group of therapeutic agents which are large and complex molecules produced through sophisticated biotechnology [70, 72]. The biologics currently used to treat severe asthma are monoclonal antibodies, and antibody fragments, which are administered subcutaneously, or intravenously (reslizumab). Injection of drugs is painful and inconvenient, especially when the drugs are for the treatment of chronic diseases, such as asthma, and alpha-1 antitrypsin deficiency [73, 74]. Moreover, 10% of the patients worldwide suffer from needle phobia leading to poor compliance [75]. Pulmonary delivery of biologics to the lungs improve pharmacokinetics, and toxicity profiles of proteins. It is a non-invasive route, and allows for self-administration, which could improve patient compliance [76].

Pulmonary delivery of biologics is an attractive non-invasive route of administration for the treatment of respiratory diseases [76-79], such as asthma [80-84], cystic fibrosis [85, 86], alpha-1 antitrypsin deficiency (AATP) [87,88], pulmonary alveolar proteinosis (PAP) [89,90], lung cancer [91,92], and SARS-CoV-2 [93-95]. Pulmonary delivery of biologics is also an alternative route for administering biologics for the treatment of non-respiratory systemic diseases, including diabetes mellitus [96-98], anaemia [99], and multiple sclerosis [100]. The development of inhalation biologics, and design of methods of inhalation technology are outside the scope of this manuscript, but excellent information can be found in references [76-79]. Table 2 shows preclinical trials of aerosol biologics for the treatment of respiratory diseases, and non-respiratory systemic diseases.

Alpha-1 anti-trypsin deficiency (AATP)
Pulmonary alveolar proteinosis (PAP)
Cystic fibrosis
Bronchiectasis
Bronchiolitis obliterans organizing pneumonia (BOOP)
Asthma
Chronic obstructive pulmonary disease (COPD)
Acute aplastic bronchitis
Pulmonary hypertension
Respiratory viral infections (RSV, Parainfluenza)
Pneumonia (Pseudomonas aeroginosa)
Tuberculosis
Non-tuberculous mycobacterial infection
Acute lung injury (ALI)
Acute respiratory distress syndrome (ARDS)
Respiratory viral infections (RSV, influenza)
SARS-CoV-2
Lung cancer, lung metastasis

Diabetes mellitus
Multiple sclerosis
Anaemia
Infertility

Table 2: Preclinical trials of aerosol biologics in respiratory diseases, and non-respiratory systemic diseases

The large surface area, and the extensive vascularization of the airways, and lungs enable rapid absorption, and fast onset of action of drugs delivered to the lungs [101]. Pulmonary delivery also offers the advantage of delivering biologics at high concentration in the lungs, and directly to inflammatory cells, and has the potential to achieve high blood levels of the biologics. Additionally, there is a lower level of proteolytic enzymatic activity in the lung, and minimal first-pass metabolism [76], hence higher concentrations of the biologics in the airways, and lung parenchyma.

However, despite the beneficial effects of pulmonary delivery of biologics, it requires innovative biotechnology to develop biologics, and inhaler devices to propel the biologics to the tracheobronchial tree, and lung parenchyma [76-79]. Furthermore, there are anatomical, physiological, and immunological factors that affect the pharmacodynamics, and biotherapeutic efficacy, and safety of inhaled biologics [102]. The other obstacle is the formulation of biologics for delivery into the lungs [78,79, 103]. Three methods have been applied to modify the structure, aerodynamic diameter (Dae), shape, hydroscopicity, and density of biologics to enhance their absorption through the mucociliary blanket, pharmacokinetics, and bioavailability [104,105]. They include antibody fragment development [106,107], Fc engineering [108,109], and pegylation [110,111]. Pegylation protects proteins from renal clearance and proteolytic degradation, thus prolongs protein local residence time, and bioavailability in the body [110]. Pegylation has been shown to be an effective method for extending the retention time of biologics in the lung, such as human alpha-1 proteinase inhibitor (α1-PI) [112], IFN-α [113], and antibody fragments [114,115].

The type of inhaler has critical importance for the delivery of biologics, because 75% of inhaled protein formulations in clinical research are produced as liquids [76]. There are four main types of inhalers for the delivery of orally inhaled proteins, peptides, and cytokines, such as pressure metered dose inhalers (PMDI), dry powder inhalers (DPI), soft mist inhalers (SMI), and nebulizers [77,79,116-120].

Most biologics in clinical trial for the treatment of asthma have been delivered to the lung by DPIs. However, SMIs are novel multidose propellant-free, handheld inhalers, and are more suitable for delivery of biologics than pMDI [79]. The most experience of pulmonary delivery of biologics with DPIs has been the Exubera® and Technosphere® insulin (Afrezza®), for the treatment of diabetes mellitus [121]. Currently, three DPIs have been utilized in clinical trials for the delivery of biologics to the lungs. They include the F1P for administration of the anti-IL-13 monoclonal antibody fragment VR942 (Abrezekimab) [102]; Cyclohaler® (single dose, PB Pharma GmbH, Meerbusch, German) for the administration of DAS181 (Fludase®) [122]; and Concept1 (single dose, Norvatis, Basel, Switzerland) (NCT4410523) for administration of the anti-thymic stromal lymphopoietin monoclonal antibody Fab fragment CSJ117 [84,123]. Biotechnological modification of proteins and peptides, and proper inhaler devices can be successfully used to deliver biologics which are effective, and immunologically safe for the treatment of airway diseases, pulmonary diseases, and systemic diseases.

The precise mechanism by which mAb, and antibody fragments exert their immunotherapeutic effects is by inhibiting surface receptors on immune and inflammatory, and immune cells, thus preventing these cells from secreting cytokines, chemokines, and adhesion molecules. Several mAb, and antibody fragments are currently in preclinical and clinical trials for the treatment of eosinophilic asthma [81-83,120,122-126], and neutrophilic asthma [127]. However, CSJ117 has demonstrated very encouraging and promising results.

Csj117 Dpi for the Treatment of Eosinophilic Asthma

CSJ117 is a potent neutralizing antibody Fab fragment against TSLP. It is formulated as a PulmoSol ™ engineered powder in hard capsules for delivery to the lungs by a dry powder inhale (DPI). Phase 2 double-blind, placebo-controlled clinical trial evaluated the efficacy and safety of CSJ117 on the late asthmatic response (LAR), the early asthmatic response (EAR), and biomarkers of eosinophilic asthma after allergen inhalation challenge (AIC) [84,128]. CSJ117 significantly attenuated the LAR and EAR at day 84 of treatment. The maximum decrease in FVE1 from pre-AIC were significantly lower in the CSJ117 group compared to placebo (P = 029), during LAR. CSJ117 also significantly reduced fractional exhaled nitric oxide before AIC at day 83; and significantly reduced the allergen-induced increase in % sputum eosinophil count [84]. This study demonstrates the potential of inhaled biologics, particularly those targeting the alarmin cytokines in the treatment and prevention of eosinophilic asthma. Aerosol CSJ117 by acting topically and blocking the immunopathological effects of TSLP may become the precise asthmatic drug delivery in the nearby future.

Conclusion

Eosinophilic asthma is principally a Th2-mediated airway disease. Th2 lymphocytes, ILCs, mast cells, and eosinophils secrete inflammatory cytokines, such as IL-4, IL-13, and IL-5 which promote airway inflammation, AHR, and remodeling. Additionally, dysfunctional epithelial cells exude alarmin cytokines, including IL-25, IL-33, and TSLP which further amplifies the inflammatory cascade, and airway remodeling. Patients with eosinophilic asthma respond favourably to targeted mAb, such as omalizumab, mepolizumab, dupilumab, and tezepelumab. However, biologics do not modify progressive airway remodeling which is responsible for severe asthma. Conventionally, asthma is best treated with locally-acting aerosol inhalers, such as LABA, ICS, and single triple inhaler therapy. Currently, there are no aerosol biologics for the treatment of asthma. CSJ117 is a potent neutralizing antibody Fab fragment against TSLP, formulated as a PulmoSol ™ engineered powder, and is delivered to the lungs by a dry powder inhaler. CSJ117 delivered as an inhaler has been shown to attenuate the late asthmatic response, and the early asthmatic response after allergen inhalation challenge at day 84 of the treatment. CSJ11 significantly improved pre-AIC lung function (FEV1) compared to placebo. Additionally, CSJ117 significantly decreased inflammatory biomarkers of eosinophilc asthma, such as allergen-induced increase in % sputum eosinophil count, and FeNO. Pulmonary delivery of aerosol biologics to the lungs is a precise targeted route of drug administration to treat patients with eosinophilic asthma.

Conflict of interest:

The author declares that the publication was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

AAER: Annualized asthma exacerbation rates

AATP: Alpha-1 anti-trypsin deficiency
ACQ-6: Asthma Control Questionnaire-6
AHR: Airway hyperresponsiveness
AIC: Allergen inhalation challenge
ALI: Acute lung injury
AQLQ: Asthma Quality of Life Questionnaire
ARDS: Acute respiratory distress syndrome
BOOP: Bronchiolitis obliterans organizing pneumonia
COPD: Chronic obstructive pulmonary disease
COVID-19: Coronavirus Disease 19
CRSwNP: Chronic rhinosinusitis with nasal polyps
Dae: Aerodynamic diameter
DPI: Dry powder inhaler
AER: Early asthmatic response
EMT: Epithelial-mesenchymal transition
FeNO: Fractional exhaled nitric oxide
FEV1: forced expired volume in one second
HLQoL: Health-related quality of life
ICS: Inhaled Corticosteroid
IgE: Immunoglobulin E
IL: Interleukin
ILCs: Innate type 2 lymphoid cells
LABA: Long-acting beta-2 agonist
LAR: Late asthmatic response
mAb: monoclonal antibody
OCS: Oral Corticosteroid
PAP: Pulmonary alveolar proteinosis
PMDI: Pressure metered dose inhaler
RSV: Respiratory syncytial virus
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
SNOT-22: SinoNasal Outcome Test 22
Th2: T helper type 2 lymphocytes
TNF-α: Tumor necrosis factor-α
TSLP, thymic stromal lymphopoietin

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