Emerging Treatment Options in Severe Asthma

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Abstract: Asthma is a heterogeneous chronic inflammatory airways disease that affects more than 325 million people worldwide. Of these, approximately 10% have severe asthma that is refractory to commonly available treatments. In the past 15 years, there have been substantial advances in the understanding of asthma pathophysiology that have allowed for the development of targeted biological treatments such as omalizumab and mepolizumab in patients with severe asthma. On the horizon, several new classes of asthma treatments, specifically biological modulators of interleukin-4 (IL)-4, IL-5, IL-13, IL-33, and thymic stromal lymphopoietin (TSLP), are in both early and late phases of development or going through regulatory approval. Successes have also been met with failures, namely in targeting IL-17 and neutrophil-high asthma. This likely reflects knowledge gaps in the pathophysiology of non-eosinophilic and corticosteroid insensitive asthma. New treatment options are vital to patients with severe asthma who fall outside the indications for new biologic therapies or for those that have failed to respond. This review article shall be limited to a discussion on available and emerging biological treatment options in severe asthma and bronchial thermoplasty.

Keywords: Asthma, biologics, bronchial thermoplasty, monoclonal antibodies, novel agents, severe asthma.

1. INTRODUCTION

Asthma is a heterogeneous airways disease characterized by inflammation causing intermittent cough, wheezing, and shortness of breath. It is associated with significant morbidity, mortality, and costs to the healthcare system. Severe asthma represents up to 10% of patients with asthma; yet it contributes to approximately 50% of all asthma-related costs [1]. Recent epidemiological studies demonstrate that the incidence of asthma is rising and health care costs (especially when associated with novel biological agents) are increasing [2]. The mainstays of asthma treatment are inhaled corticosteroids (ICS) and Long-Acting Beta-Agonists (LABA). The leukotriene receptor antagonists, and Long-Acting Anti-Muscarinic Antagonists (LAMA), tiotropium bromide are the next recommended steps in attaining control [3-7]. The last two decades have seen significant developments in our understanding of the pathophysiology and complex biology underpinning asthma.

Asthma is a disease with multifactorial etiology. Most treatments are directed at “Th2-high” inflammation, but there remains a significant subset of patients whose disease is mediated through “non-Th2 high” mechanisms and this subset tends to have a less pronounced response to ICS [8, 9]. Fig. (1) (below) highlights the many potential targets for treatment in allergic and non-allergic eosinophilic asthma.

An endotype is a subtype of a condition defined by a distinct functional and pathophysiological mechanism. For simplicity (when discussing available treatments), asthma can be thought of as two distinct endotypes: a Th2 high endotype (eosinophilic) and Th2 low endotype (neutrophilic, pauci-granulocytic), though this does ignore other emerging endotypes (to which no universal consensus exists) [10].

T-helper (Th) cells are a type of T cells that play a key role in orchestrating the immune system. Depending on their microenvironment, immature Th0 cells mature to become one of a number of subsets including Th1, Th2, Th17. T-helper 1 cells are the host immunity effectors against intracellular bacteria and protozoa. They are triggered by interleukin (IL)-12 and their effector cytokines are interferon (IFN) γ and IL-2 [11]. T-helper 2 cells are the host immunity effectors against extracellular parasites including helminths and are involved in atopy and allergy. They are triggered by IL-4 and IL-2, and their effector cytokines are IL-4, IL-5, IL-9, IL-10, IL-13 and IL-25. The main effector cells are eosinophils, basophils, and mast cells as well as B cells (influencing B cell type class switching to immunoglobulin E (IgE) producing B cells), and IL-4/IL-5 CD4 T cells [12].

Asthma endotypes play a significant role in treatment decisions and this has been reflected in the 2017 Global Initiative for Asthma (GINA) strategy document [13]. International asthma guidelines now reflect that the standard “one size fits all” approach to severe asthma is no longer appropriate, and where possible, a personalized approach should be taken (characteristics including age of diagnosis, atopy, blood tests such as IgE and blood eosinophil count, and body mass index for example). However, selection of
candidates for therapy based on these characteristics are of limited value as it does not provide insight into the underlying pathophysiological mechanism.

This article will review the pathophysiology underpinning novel biologic treatments of severe asthma including targeting IgE, IL-4, IL-5 and IL-13 (typically associated with Th2 high asthma), IL-17 (typically a non-Th2 related cytokine), IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) (the epithelial alarmins). The review shall also discuss prostaglandin D2 inhibitors and Bronchial Thermoplasty (BT). Table 1 summarizes several recent clinical trials for treatment of severe asthma; some of these therapies are now approved for clinical use.

2. ANTI-IMMUNOGLOBULIN E THERAPIES

Immunoglobulin-E is recognized as a key player in the pathophysiology of allergic asthma, playing a central role in acute allergic reactions and chronic inflammatory allergic diseases. In sensitized individuals, exposure to specific allergen(s) can bind to the high-affinity IgE receptor, FceRI, expressed on mast cells, dendritic cells, monocytes, eosinophils and basophils [14, 15]. The cross-linking of receptor-bound IgE triggers the activation of these cells [16], leading to the production and release of various pro-inflammatory Th2 cytokines such as IL-3, IL-4, IL-5, IL-13, chemokine ligand-5, and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) and several lipid mediators [17].

Binding of IgE promotes positive feedback to mast cells and basophils, enhancing sensitization, survival and proliferation [16]. Allergen cross-linking of adjacent surface IgE molecules on mast cells and basophils triggers the release of preformed mediators contained in intracytoplasmic granules within seconds or minutes, such as histamine and tryptase, leading to local vasodilation, edema, local neurogenic stimulation and mucus secretion. This results in clinical manifestations of a type 1 hypersensitivity reaction, the most extreme example being anaphylaxis [18]. A proportion of asthmatics show late response between 3 to 10 hours after antigen challenge when their forced expiratory volume 1 second (FEV1) decreased by 15% or more [19]. This late response is characterized by tissue eosinophilia, and mucosal hyperreactivity to both allergic and non-allergic triggers that can last for days or even weeks after a single allergen challenge [19]. Thus, targeting IgE in persons with severe allergic asthma is thus very attractive. Omalizumab is a humanized IgG1k monoclonal antibody (mAb) that binds human IgE and is the only anti-IgE therapy currently available.

Early anti-IgE mAb studies in healthy asthmatic subjects demonstrated an increase in the dose of allergen required to
Table 1. Recent trials in the treatment of severe asthma.

<table>
<thead>
<tr>
<th>Medication/Treatment</th>
<th>Route</th>
<th>Mechanism, Targeted Cytokine</th>
<th>Effects</th>
<th>Pivotal Studies</th>
</tr>
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<tbody>
<tr>
<td>Omalizumab*</td>
<td>S/C</td>
<td>Humanized IgG1k mAb against human IgE</td>
<td>Decreased asthma exacerbations and ED visits. Improved PEF and asthma symptoms.</td>
<td>INNOVATE [26], EXTRA [27] EXPECT [31]</td>
</tr>
<tr>
<td>Mepolizumab*</td>
<td>S/C</td>
<td>Humanized IgG mAb against IL-5</td>
<td>Reduction in asthma exacerbations, sputum and peripheral eosinophilia, and oral glucocorticoid maintenance dose.</td>
<td>DREAM [56], MENSA [57], SIRIUS [58], COSMOS [59]</td>
</tr>
<tr>
<td>Reslizumab*</td>
<td>IV</td>
<td>Humanized IgG mAb against IL-5</td>
<td>Reduction in asthma exacerbations and eosinophilia, increase in time to first exacerbation, improved asthma control and FEV1.</td>
<td>BREATHE [64, 68]</td>
</tr>
<tr>
<td>Benralizumab*</td>
<td>S/C</td>
<td>Humanized IgG1k mAb against IL-5R α chain</td>
<td>Reduction in asthma exacerbations, improved pre-bronchodilator FEV1 and time to first asthma exacerbation.</td>
<td>SIROCCO [77], CALIMA [78]</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>SC</td>
<td>Fully human IgG4 mAb against IL-4R α, blocking IL-4 and IL-13 signaling</td>
<td>Reduction in annualized asthma exacerbation rates, improved FEV1.</td>
<td>[90]</td>
</tr>
<tr>
<td>Tezepelumab</td>
<td>SC</td>
<td>Human mAb against TSLP</td>
<td>Reduction in annualized asthma exacerbation rates, improved pre-bronchodilator FEV1</td>
<td>[119]</td>
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<tr>
<td>Fevipiprant</td>
<td>PO</td>
<td>CRTH2 receptor antagonist</td>
<td>Reduction in sputum eosinophilia, improvement in FEV1</td>
<td>[136]</td>
</tr>
<tr>
<td>Bronchial Thermoplasty</td>
<td>Bronchoscopy using RF energy</td>
<td>Airway remodeling by ASM, ECM</td>
<td>Reduction in asthma exacerbations, ED visits, work/school absenteeism. Improved morning PEF, symptom control, symptom free days.</td>
<td>AIR [142], RISA [143], AIR2 [144]</td>
</tr>
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</table>

Summary of current advanced therapies in severe asthma, observed effects, and pivotal trials for reference. * = clinically approved for use in USA, Canada, European Union, Japan. ** = clinically approved in specialist centers (usually part of research studies). Abbreviations: ASM = airway smooth muscle; CRTH2 = chemoattractant receptor Th2; ECM = extracellular matrix; FEV1 = forced expiratory volume in 1 second; IL = interleukin; mAb = monoclonal antibody; PEF = peak expiratory flow; RF = radiofrequency; SC = subcutaneous; TSLP = thymic stromal lymphopoietin.

invoke an early asthma response and reduced the fall in FEV1 in both early and late phases in the allergen challenge model of mild asthmatics [20]. Subsequent randomized controlled trials showed a reduction in asthma exacerbations, Emergency Department (ED) visits, hospitalizations, and use of oral corticosteroids in patients with moderate-severe asthma using omalizumab as an add-on therapy [21-23]. Omalizumab improves the quality of life as measured by the Asthma Quality of Life Questionnaire (AQLQ) and the Rhinitis Quality of Life Questionnaire, and by reducing or discontinuing corticosteroid, reduces or eliminates steroid related side effects [24, 25]. The INNOVATE study demonstrated that the addition of omalizumab reduced asthma exacerbations and ED visits over a 48 week period [26, 27]. The long-term benefits of omalizumab have been systematically reviewed that showed a sustained benefit for many years on treatment [28].

A review of the tolerability of omalizumab from clinical trials and post-marketing data demonstrated a placebo-like safety profile that is reassuring [29, 30]. The EXPECT trial showed that omalizumab is safe in all trimesters in pregnancy [31]. However, there is a Food and Drug Administration (FDA) boxed warning for anaphylactic reactions, cardiovascular events, and transient ischemic attacks. EXCELS was a post-marketing observational cohort requested by the FDA (5007 patients) that found a higher incidence rate of cardiovascular and cerebrovascular events in the omalizumab versus the non-omalizumab cohort. The authors concluded that it was likely that differences in asthma severity between cohorts contributed to this imbalance, but some increase in risk could not be excluded [32].

Omalizumab is approved for patients aged 6 years and older with moderate to severe asthma, an IgE level of 30 to 700 IU/mL, incomplete symptom control with inhaled corticosteroids, and allergic sensitization demonstrated by skin prick or in vitro testing. The dosing is weight based (0.016mg/kg) ranging from 150mg to a maximum 375mg subcutaneously (S/C) every 2 or 4 weeks.

Finally, the length of treatment is an important consideration. Indefinite use improves symptoms and reduces exacerbation rates. These effects can persist for 3 years after discontinuation of therapy, suggesting that it affects the disease’s natural history and reduces morbidity [33, 34]. However, approximately 55% of patients who discontinue omalizumab do experience a loss of asthma control. When resumed, the majority of patients (80%) re-achieve a good clinical response [35]. In a small 49 patient study, 60% of those who discontinued omalizumab continued to have a significant clinical benefit for 4 years [36]. To date, it is not known which subgroup of patients
who respond to omalizumab can discontinue it and after what length of treatment.

3. ANTI-IL5 THERAPIES

Interleukin-5 (IL-5) is a 134-amino acid protein that forms a 52 kiloDalton (kDa) homodimer. It is similar to GM-CSF and IL-3. Interleukin-5 stimulates B cell maturation and the differentiation of eosinophil precursors [37]. Interleukin-5 exerts its effects via the IL-5 receptor (IL-5R), which is comprised of two subunits: the α subunit, expressed exclusively on eosinophils and basophils, and the β subunit, found on most leukocytes [38]. It is vital for the development, maturation, migration and activation of eosinophils from CD34+ hematopoietic progenitor cells in the bone marrow. It enhances the release of inflammatory mediators such as major basic protein and leukotrienes from eosinophils and increases eosinophil survival in tissue [39]. Eosinophils cause tissue damage by degranulating and releasing multiple inflammatory peptides and reactive oxygen species (ROS) and cysteinyl leukotrienes (cLT) [39].

Interleukin-5 is produced by several cells including CD4+ type 2 cells, CD8+ type 2 cells, CD34+ hematopoietic progenitor cells, eosinophils, basophils, mast cells, and innate lymphoid cells type 2 (ILC2s) [40-43]. Concentrations of IL-5 are significantly higher in asthmatic airways compared to normal healthy controls and this is associated with disease severity, airway eosinophilia and remodeling [44, 45]. These characteristics make it a very attractive target in the severe eosinophilic asthmatic population. Among anti-IL5 biologics, mepolizumab and reslizumab target the IL-5 ligand and benralizumab targets IL-5Rα. They are all currently available in Canada.

4. MEPOLIZUMAB

Mepolizumab is a humanized monoclonal N-glycosylated IgG1/k antibody that binds the α-chain of IL-5, preventing its association with the α subunit of its receptor, IL-5R, on eosinophils [46]. Its development was initially abandoned due to ineffectiveness in mild to moderate asthma [47], but re-established its relevance in later studies when it was shown to reduce sputum and peripheral eosinophilia in severe eosinophilic asthma subjects [48, 49]. Studies have demonstrated mepolizumab reduces blood eosinophilia by 50% within 24 hours of dose administration, with a maximum reduction of up to 85% [50, 51]. Similarly, airway eosinophilia is decreased by up to 79% [52]. In Canada, mepolizumab is approved for use in severe eosinophilic asthma patients that required two or more doses of systemic corticosteroids in the last 12 months. Blood eosinophilia above 150 cells/µl at treatment initiation or 300 cells/µl in the last 12 months is also required. Some commentators have expressed concern that the level of 150 cells/µL is too low and could affect the clinical benefit of mepolizumab in patients with borderline blood eosinophil counts [50, 53, 54]. Indeed, in a subgroup analysis of "Mepolizumab Treatment in subjects with Severe Eosinophilic Asthma", the trial showed better results in subjects with blood eosinophils >500 cells/µl than those with lower blood eosinophil counts [55]. In the United Kingdom, the requirement is more stringent as the National Institute for Health and Care Excellence (NICE) requires the patients to have had four exacerbations requiring oral corticosteroids (or continuous corticosteroids >5mg/day for >6 months) and blood eosinophil count of 300 cells/µl at initiation of treatment.

Anti-mepolizumab antibodies have been detected in approximately 6% of patients but neutralizing antibodies have only been detected in one patient [56, 57]. Mepolizumab was the first anti-IL-5 mAb to become commercially available and is given as a 100mg S/C injection every four weeks; its dosing is not weight based, unlike Reslizumab.

Several pivotal mepolizumab trials have been conducted, including the ‘Dose Ranging Efficacy and Safety with Mepolizumab’ in severe asthma (DREAM) study [56], ‘Mepolizumab as an Adjunctive Therapy in Patients with Severe Asthma’ (MENSA) study (assessing exacerbation reduction) [57], ‘Steroid Reduction with Mepolizumab Study’ (SIRIUS) (assessing oral corticosteroid reduction) [58], and the subsequent 52 weeks extension following MENSA and SIRIUS open-label efficacy and safety study, COSMOS [59]. In these studies, mepolizumab in IV and S/C formulations decreased clinically significant exacerbations by 50% compared to placebo. Mepolizumab also allows for a significant decrease in the maintenance dose of oral glucocorticoids required in severe eosinophilic asthma subjects [58].

Mepolizumab has also been trialed for other diseases such as eosinophilic granulomatosis with polyangiitis (EGPA) and eosinophilic esophagitis [60]. A recent phase III trial of patients with relapsing or refractory EGPA evaluating S/C mepolizumab in addition to standard of care (oral corticosteroids) resulted in significantly more weeks of remission and a higher proportion of participants in remission (53%) than did placebo (19%), allowing for reduced glucocorticoid use [61]. Of note, the dose used was 300mg S/C monthly which is three times the dose administered in severe eosinophilic asthma.

Safety data for mepolizumab has been very favorable. Large phase III trials including DREAM, MENSA, SIRIUS, and COSMOS have demonstrated that it is well tolerated at all doses with very few adverse effects, suggesting both short and long-term safety [56-59]. Death related to mepolizumab has not been reported in these trials. The most common reported adverse event was headache and was similar in incidence to placebo. The FDA lists hypersensitivity, opportunistic infections (specifically Herpes zoster), and parasitic infections as precautions when administering mepolizumab. The role of IL-5 and eosinophils in tumor surveillance is poorly characterized. However, there is no evidence of defective tumor surveillance in IL-5–deficient or eosinophil-deficient mice. Its safety and effectiveness were recently reviewed and pregnancy and other post-marketing data expected to arrive in the next 5 years [62].

5. RESLIZUMAB

Unlike mepolizumab and benralizumab (both IgG1 humanized mAbs), reslizumab is an IgG4/k humanized mAb that binds to IL-5 with high affinity. Its concentration peaks shortly after the IV infusion, with a half-life of approximately 24 days [63]. Reslizumab significantly
reduces eosinophil counts in sputum and blood as soon as after the first dose of therapy and this effect can be seen up to approximately 120 days after the last reslizumab dose [64-67]. Similar to mepolizumab, anti-reslizumab antibodies have been detected in a small subset of patients (approximately 5%) in these studies, but their presence does not appear to affect the pharmacodynamics, efficacy, or safety.

The BREATH program was a series of three phase 3 randomized, double-blind, placebo-controlled clinical trials over 16 weeks [68] to assess lung function or 52 weeks [64] to assess asthma exacerbations. Reslizumab significantly reduces asthma exacerbations by up to 59% and an increased time to first exacerbation [64]. The FEV1 improved in all studies, and this effect was maintained for at least 2 years, as seen in an open-label extension study [69]. Notably, all subjects had a blood eosinophil count of at least 400 cells/μl at enrolment, unlike the mepolizumab trials. Reslizumab is given as IV infusion and is weight-based (3mg/kg), in contrast to both mepolizumab and benralizumab.

The BREATH program demonstrated significant improvements in the quality of life as measured by the Asthma Control Questionnaire (ACQ) and AQLQ, reduced rescue inhaler use, and a significant reduction in peripheral eosinophilia that were maintained throughout the trials [64, 68]. Interestingly, it appears that adults with late-onset asthma (age of onset ≥40 years) have greater reductions in asthma exacerbations than individuals with early-onset asthma [70]. Additionally, patients with chronic sinusitis with nasal polyps compared to those without nasal polyps experience fewer asthma exacerbations [71]. Reslizumab is indicated as an add-on maintenance therapy for uncontrolled severe asthma with an eosinophilic phenotype.

The most common adverse effect was headache with a 2% overall incidence. According to the FDA reslizumab factsheet in placebo-controlled clinical studies, 6 out of 1028 patients (0.6%) receiving 3 mg/kg reslizumab had at least 1 malignant neoplasm reported compared to 2 out of 730 patients (0.3%) in the placebo group [72]. There is a reported anaphylaxis rate of 0.19-0.3% (usually developing within 20 minutes) leading to a boxed warning in the United States [63]. Increases in creatinine phosphokinase (CPK) were seen with reslizumab compared to placebo (0.58 vs. 0.21%). Elevations in blood CPK with reslizumab were asymptomatic, transient and were not a cause of therapy discontinuation. There are currently no post-marketing data published and further studies are required to establish its long-term safety.

6. BENRALIZUMAB

Benralizumab is a humanized afucosylated IgGk1 mAb that binds to the IL-5R α chain, thereby blocking downstream effects of IL-5 signaling. The afucosylated IgGk mAb is characterized by a high-binding affinity for the FcyRIIA region and thus enhance antibody-dependent cell-mediated cytotoxicity (ADCC) activity. An early study of IV benralizumab in mild atopic asthma reduced blood eosinophilia to undetectable levels within 24-48 hours [73]. Benralizumab has a half-life of approximately 18 days [74]. It significantly decreases eosinophils in the mucosa, sputum, and blood [75]. Phase II studies demonstrated a reduction in overall exacerbation rates by 49% as well as exacerbations requiring hospitalization by 60% [76].

CALIMA and SIROCCO (named after indigenous winds!), were pivotal multicenter international randomized, double-blind, placebo-controlled trials enrolling patients with uncontrolled asthma while on ICS/LABA combination therapy [77, 78]. Both trials compared S/C benralizumab given every 4 or 8 weeks against placebo. CALIMA demonstrated a significant improvement in asthma exacerbations, pre-bronchodilator FEV1, and time to next asthma exacerbation compared to placebo [78]. Similarly, in SIROCCO, both dosing schedules significantly reduced annual exacerbation rates and were associated with a significant pre-bronchodilator FEV1 improvement [77]. Several benralizumab studies are currently being conducted including: the effectiveness of benralizumab in patients with uncontrolled asthma with eosinophilic inflammation (SOLANA), the safety extension study on adults and adolescents (MELTEM), and the recently completed assessment of the appropriateness for home administration with an auto-injector (GRECO).

During CALIMA and SIROCCO, benralizumab demonstrated a placebo-like safety profile, the most common adverse events were nasopharyngitis, headache, and worsening of asthma control [77, 78]. These studies have demonstrated short-term tolerability and safety, but further data are needed to establish its long-term safety. One attraction that benralizumab offers is an S/C route and is every 8 weeks (after 3 initiating doses in a 28-day period) as opposed to other anti-IL5 therapies which are administered every 4 weeks. Overall, treatment-emergent anti-drug antibody response developed in 13% of patients taking benralizumab during the 48 and 56-week trial periods which is higher than either mepolizumab or reslizumab. About 12% of patients developed drug neutralizing antibodies. Patients with high anti-benralizumab antibody titers were associated with increased clearance of benralizumab and blood eosinophil levels compared to antibody negative patients. Notably, there was no evidence of any association between anti-benralizumab antibodies and efficacy or safety.

7. ANTI-IL4/13 THERAPIES

Interleukin-4 and IL-13 are pleiotropic cytokines that are released by a variety of different cell types, including epithelial cells, eosinophils, basophils and mast cells, and have a broad range of overlapping biological functions, particularly in relation to allergic diseases [79-81].

Both IL-4 and IL-13 signal through the shared type-II IL-4 receptor, a heterodimer consisting of IL-4 receptor a (IL-4Ra) and IL-13 receptor a 1 (IL- 13Ra1) [82]. Receptor binding, in turn, activates the JAK/STAT signaling cascade, leading to the transcription of genes required for T-cell function, immunoglobulin class switching to IgE and antigen presentation by B cells [83]. Dysregulation of IL-4 and IL-13 signaling is thought to contribute to the pathophysiology of inflammatory and allergic diseases, such as asthma and Atopic Dermatitis (AD). They induce B cells to generate allergen-specific IgE and augment goblet cell metaplasia, participating in the inflammatory response [84]. Initial
results with IL-4 inhibition using altrakincept and pascolizumab were promising; however, subsequent clinical studies have been disappointing and there are currently no further studies planned [85-87].

Dupilumab is a fully human IgG4 monoclonal antibody against the IL-4Rα subunit, leading to the inhibition of IL-4 and IL-13 signaling. It has been approved for the treatment of moderate to severe atopic dermatitis without relief using topical therapies [88]. A phase IIa trial demonstrated that once weekly dupilumab significantly reduced asthma exacerbations by 87% with improvements in lung function in moderate to severe asthmatics [89]. Interestingly, these effects were maintained even when background therapies were withdrawn (though an unlikely event in clinical practice). In a subsequent phase IIb trial, dupilumab was administered every 2 or 4 weeks and showed a significant improvement in FEV1. There was also a significant reduction in the annualized exacerbation rates by 70% in the overall population [90]. The most common adverse effects during these trials were nasopharyngitis, upper respiratory tract infection, and injection site reaction. No anaphylaxis was reported during this study.

Ongoing trials for asthmatics ≥12 years old currently are the phase III studies QUEST (52-week double-blind placebo-controlled trial for persistent asthma), VENTURE (randomized double-blind placebo controlled trial evaluating the reduction of oral corticosteroid use in steroid-dependent asthma) and the phase II/III study TRAVERSE (1 year open-label study evaluating safety and tolerability in patients from a previous dupilumab trial). Dupilumab is currently only approved in Canada for atopic dermatitis.

8. EPITHELIAL DERIVED CYTOKINES

The airway epithelium is exposed to multiple potential allergens and infectious agents. The interaction between the airway epithelium and the inhaled environment is paramount to understanding the pathobiology of asthma. Several studies have identified an important role of airway epithelial-derived cytokines, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) in asthma pathogenesis [91]. These cytokines have been described as epithelial-derived alarmins that activate the innate and humoral arms of the immune system in the presence of actual or perceived damage. Each of these three epithelial-derived alarmins has been implicated in the pathobiology of inhaled allergen-induced airway responses. The best evidence to date exists for TSLP, in that a human mAb, which binds TSLP and prevents engagement with its receptor, significantly reduces airway inflammation in patients with allergic asthma and attenuates allergen-induced airway responses.

9. EPITHELIAL-DERIVED IL-25

Interleukin-25, also known as IL-17E, is part of the IL-17 family of cytokines, and is expressed by airway epithelial cells, basophils, eosinophils, activated mast cells, and Th2 polarized cells [92, 93]. Several cells types have been identified to express the IL-25 receptor (IL-25R): airway smooth muscle (ASM), airway epithelial cells, mast cells, fibroblasts, eosinophils, and invariant natural killer T cells [92, 94]. Interleukin-25 is constitutively expressed in epithelial cells and is released upon exposure to proteases, such as trypsin, papain and allergen proteases present in house dust mite (HDM) extract [95].

In mouse models, IL-25 inhibition using a mouse generated mAb against recombinant IL-25 led to a significant reduction in IL-5 and IL-13 production, serum IgE levels, eosinophil infiltration, and significantly reduced airway hyperresponsiveness (AHR) [96]. Humans with high levels of IL-25 messenger RNA from airway brushings were found to be highly allergic with evidence of eosinophil activation, increased levels of IL-13, and greater methacholine airway responsiveness compared to the low IL-25 levels subgroup and those without asthma [97]. Interleukin-25 is an effector of AHR as it enhances methacholine-induced smooth muscle contraction in bronchial rings of asthmatics when compared to normal controls [98]. Brodalumab is a human mAb that binds to the IL-17A receptor, thereby blocking the action of IL-17A, IL-17F, IL-17A/F heterodimer, and IL-25. It has been shown to improve symptoms as scored by ACQ but there is no effect on lung function in moderate-to-severe asthmatics [99].

New, targeted studies of the particular sub-group are certainly warranted. Such studies may also clarify whether the postulated beneficial effect of the anti-IL-17A receptor antibody in highly reversible asthma relates to an impact on neutrophil recruitment or other mechanisms. With a better understanding of biomarkers and relevant targeting, anti-IL-17 mAbs may still have a role in severe asthma.

10. EPITHELIAL DERIVED IL-33

Inteleukin-33 was originally identified as a nuclear factor of high endothelial venules (termed NF-HEV) [100]. It is the ligand for the previously known orphan receptor suppression of tumorigenicity 2 (ST2) that had already been associated with allergic disease [101]. It is part of the IL-1-superfamily of cytokines. Epithelial cells from tissues exposed to the external environment, such as eyes, skin, intestine, airways, lymphoid organs, keratinocytes, smooth muscle cells, and human endothelial cells produce IL-33 [102-104]. Inteleukin-33 stimulates the production of IL-4, IL-5, and IL-13 by Th2 cells, eosinophils, ILC2 cells, mast cells, and basophils [105]. It has emerged as one of the major alarm signals that is released either from damaged airway epithelial cells, or from mast cells that perceive danger.

Inteleukin-33 and ST2 are expressed at higher levels in other allergic diseases such as rhinosinusitis, and its levels correlate to the severity of asthma [106-108]. The ST2 receptor is found in either the more abundant transmembrane ST2L form or in the cytoplasm as the soluble sST2 form, which acts as a decoy by binding and neutralizing IL-33 [109]. Inteleukin-33 is a more potent activator of eosinophils than IL-5 at triggering degranulation and superoxide release from human eosinophils [110]. A mAb targeting IL-33 in mouse models have demonstrated reduced airway inflammation and remodeling in IgE mediated airway inflammation [111]. These features of IL-33 make it an attractive target in treating asthma and may be a useful biomarker. There are murine studies demonstrating effectiveness using soluble receptors. AMG 282, an anti-IL-33 mAb, is in an early phase of development by Genentech.
Lastly, there is an emerging role for soluble ST2, an IL-33 decoy receptor, in the inhibition of IL-33 signaling, and may serve as an important biomarker in asthma [112].

11. EPITHELIAL DERIVED TSLP

Thymic stromal lymphopoietin is a member of the IL-2 cytokine family and binds to a high affinity receptor complex consisting of TSLP receptor (TSLPR) and IL-7Rα subunit. Serum TSLP levels are higher in patients with asthma compared to normal healthy controls and patients with COPD [113]. These receptors are expressed by a variety of cell types: myeloid dendritic cells (DC), CD4 and CD8 positive T cells, regulatory T cells, B cells, mast cells, natural killer T-cells, monocytes, CD34 positive progenitor cells, eosinophils, basophils, ASM, and bronchial epithelial cells [114, 115] The highest levels of TSLP have been observed in the bronchial and skin epithelial cells. It is also found in fibroblasts, ASM, endothelial cells, mast cells, macrophages and monocytes, granulocytes, and DCs [114]. Severe asthmatics express a higher level of TSLP in the airway mucosa and have a lower FEV1 when compared to healthy controls [116]. Thymic stromal lymphopoietin also correlates with AHR and serum IgE levels [117].

The beneficial effects from the blockade of TSLP in humans was first observed in a small randomized, double blind, placebo-controlled study in subjects with mild allergic asthma, receiving 3 monthly doses of AMG 157, or tezepelumab, a human mAb targeted against TSLP. The tezepelumab group had significantly attenuated responses to allergic stimuli, measured by a decline in FEV1, blood and sputum eosinophils, and fraction of excreted nitric oxide (FeNO) when compared to the placebo group [118]. Tezepelumab significantly reduces the annualized asthma exacerbation rate and is associated with a higher pre-bronchodilator FEV1 in moderate to severe asthmatics [119]. This effect was observed in all groups, although it was most pronounced in patients with a higher eosinophil count. After baseline, positive antidrug antibodies were noted in 13 of 148 patients (8.8%) in the placebo group, 7 of 144 patients (4.9%) in the low-dose tezepelumab group, 1 of 140 patients (0.7%) in the medium-dose group, and 3 of 142 patients (2.1%) in the high-dose group [119]. No neutralizing antibodies were detected. Larger clinical studies are required before its clinical use can be approved.

12. NEUTROPHILIC ASTHMA

A landmark study in 1999 defined two distinct inflammatory endotypes of severe, corticosteroid-dependent asthma based on the presence or absence of eosinophils in endobronchial biopsy and lavage [9]. Since then, Th2-high and Th2-low have remained the most well recognized and described endotypes of severe asthma. The Th2-high endotype is characterized by the presence of eosinophilic airway inflammation, while the Th2-low endotype is usually characterized by neutrophilic or paucigranulocytic airway inflammation. Subjects with higher sputum neutrophils (i.e. Th2-low) responded poorly to inhaled corticosteroids compared to those without sputum neutrophilia, and correlated to disease severity [120, 121].

To date, there are no approved therapies for the treatment of neutrophilic asthma. Two potential therapeutic targets involved in neutrophil migration exist: the CXC chemokine receptor 2 (CXCR2), a large G-protein coupled receptor, and leukotriene B4 (LTB4), a lipid mediator produced from arachidonic acid.

CXC chemokine receptor 2 inhibition significantly reduces sputum neutrophils after a lipopolysaccharide challenge in healthy volunteers [122]. Its inhibition demonstrated a 36% reduction in sputum neutrophils, with a mean reduction in blood neutrophils by 14%, and fewer mild exacerbations [123]. However, no improvement in lung function was observed. In a larger randomised, double blind, placebo controlled dose finding trial, there was no dose of AZD5069 that was able to reduce the rate of severe asthma exacerbations despite reducing sputum neutrophilia [124]. This lack of clinical efficacy raises the importance of CXCR2-mediated neutrophil migration in severe asthma.

There may be some therapeutic benefit with LTB4 inhibition in asthma associated with aspirin sensitivity and nasal polyps, but additional research and data are required to investigate this particular endotype and further understand the pathobiology behind neutrophilic asthma [125].

Interleukin-17 may be an important player in steroid resistant asthma as it produces a robust neutrophilic response and its concentration has been associated with expression of airway polymorphonuclear cells. Importantly, a strong relationship between the expression of IL-17 and asthma severity has been shown [121]. Neutrophilic and paucigranulocytic asthma may in fact be two distinct phenotypes in steroid resistant asthma. This is particularly supported by a recent study illustrating a “Th17 signature” that may or may not be present in distinct populations that lack a “Th2 signature” [126]. Where neutrophilic asthma is mediated by an IL-17 high state, IL-17 antagonists should theoretically be effective therapeutics. However, further studies will be needed, and may begin with identifying proper biomarkers to select patients suitable for treatment.

13. PROSTAGLANDIN D2

Prostanoids are a family of metabolites of the fatty acid arachidonic acid, which include prostaglandin (PG) D2, PGE2, PGF2α, PGI2, as well as thromboxane A2 [127]. They are derived by the hydrolysis of arachidonic acid from membrane phospholipids by phospholipase A2, its oxygenation by constitutive cyclooxygenase (COX)-1 and inducible COX-2 isofoms, and isomerization by specific terminal synthases [128]. Prostaglandin D2 is a potent eosinophil chemoattractant acting through the chemoattractant receptor homologue on Th2 cells, CRTH2 [129].

Chemoattractant receptor homologue on Th2 cells has emerged as a promising target in the treatment of allergic diseases given its various immunomodulatory effects. It is involved in mast cell mediated allergic inflammation and is expressed on Th2 cells, eosinophils, basophils, epithelial cells and ILC2s [130-132]. This receptor is expressed in significantly higher numbers in asthmatic cells and its activation in this population are associated with airway remodeling [132]. Prostaglandin D2 is also found in 150 fold
higher quantities in bronchoalveolar lavage fluid when stimulated by an antigen [133]. Fevipiprant (QAW039) is an oral treatment for asthma that competitively and reversibly inhibits CRTH2.

Fevipiprant reduces sputum eosinophils by 4-5 fold [134]. In uncontrolled asthmatic patients with low dose ICS, fevipiprant demonstrated an improvement in pre-dose FEV1 and was well tolerated, the most common adverse event being nasopharyngitis [135]. Another study demonstrated an improvement in FEV1 in mild to moderate asthmatics with uncontrolled asthma, particularly if their baseline FEV1 is less than 70%, as well as improved ACQ scores [136]. Further phase III clinical studies are ongoing to evaluate its efficacy in Th2-high uncontrolled asthma. If successful, it will have an enormous impact on the treatment paradigm for asthma and will potentially widen access for pre-biologic treatment to a larger population [137].

14. BRONCHIAL THERMOPLASTY

Bronchial thermoplasty (BT) is a relatively new bronchoscopic treatment for select subjects with severe asthma. The 2017 GINA guidelines mention BT as a treatment option in severe asthma [13]. Many patients with moderate to severe asthma undergo airway remodeling which leads to structural and functional consequences. One of many changes involved in this remodeling process is hypertrophy and hyperplasia of ASM.

Bronchial thermoplasty is considered a minimally invasive treatment and delivers radio frequency (RF) energy to the proximal airways, thereby preventing excessive bronchoconstriction by reducing ASM volume [138]. The Alair BT system (Boston Scientific, Natick, MA, USA) comprises of the Alair Radiofrequency Controller, disposable single-use catheter, foot pedal, and gel-type patient return electrode. The distal end of the 1.4 mm diameter catheter has a basket-like array of expandable electrodes. The basket-like arrays can expand to a maximum of 13 mm. The catheter is used in a flexible bronchoscope with a 2.0 mm working channel [139]. Patients with uncontrolled severe persistent asthma should be clinically stable at the time of the proposed procedure. Prednisone at a dose of 50 mg per day is started 3 days prior to the procedure and continued until the day following the procedure. The procedure is performed over 3 sessions with at least a 3-week interval between sessions. Each session treats a different area from the right lower lobe, left lower lobe, and finally the bilateral upper lobes. By convention, the right middle lobe is not treated as it has a narrow orifice and could obstruct post-procedure secondary to inflammation.

The first procedures were performed in dogs and demonstrated that the use of BT reduced airway responsiveness to methacholine challenge [140]. These benefits were observed for the 3 years of follow up. In the pilot human study, 16 mild-moderate asthmatic subjects underwent BT and showed a benefit for at least 2 years in reduced AHR [141]. The procedure was well tolerated and most of the adverse events occurred within 1 week of the procedure, resolving spontaneously, with antibiotics, oral corticosteroids, or increased inhaler usage.

Subsequently, the larger randomized (Asthma Intervention Research) AIR trial was an unblinded study of 112 moderate-severe asthma subjects. Improvements in the morning peak expiratory flow, percentage of symptom free days, ACQ and AQLQ scores, and a reduction in mild exacerbation rates were observed [142]. However, there was no improvement in AHR or FEV1. Common adverse events were dyspnea, wheezing, cough, and chest discomfort. Major adverse events included asthma exacerbation, partial collapse of the left lower lobe, and pleuritic chest pain leading to 6 hospitalizations in 4 patients (compared to 2 hospitalizations in 2 patients in placebo group). Most of these events often occurred within 1 day of the procedure and would resolve by 1 week.

The RISA study was a randomized, unblinded trial of 34 severe asthma subjects and demonstrated significant improvements in pre-bronchodilator FEV1 % predicted, AQLQ, and ACQ scores [143]. However, patients receiving BT in RISA had a short-term increase in asthma-related morbidity (7 hospitalizations: 5 asthma exacerbations and 2 partial collapse of a lower lobe). RISA was followed by the large 12 months double blind AIR 2 trial. Patients were randomized to BT or a sham bronchoscopy control. Patients receiving BT had a significant improvement in AQLQ and experienced significantly fewer severe asthma exacerbations, ED visits, and absenteeism from work or school [144].

These trials were performed with 5-year longitudinal follow up. The AIR trial demonstrated no increase in hospitalizations, ED visits, or decline in FEV1 or FVC [145]. Patients from the AIR 2 trial experienced significantly fewer severe exacerbations and ED visits compared to the 12 months before BT [146]. Similar to AIR, there was stability in FEV1 and lack of airway abnormalities as visualized by high resolution computed tomography (HRCT). A decrease in hospitalizations and ED visits was also observed in RISA [147]. AIR, AIR 2, and RISA have all demonstrated the clinical effectiveness of BT with a strong safety profile lasting at least 5 years. The mechanism by which BT exerts its benefits is not fully understood at this point but may involve the airway epithelium, ASM reduction, reduced inflammatory compounds in the airway wall, extracellular matrix, or denervation. It needs to be established whether subjects with a particularly severe asthma endotype would derive greater benefits from BT than others [139].

CONCLUSION

In this era of personalized medicine, many aspects in the pathobiology of asthma have been uncovered. There are now several treatments available for consideration in uncontrolled moderate to severe asthma with many options on the horizon, including anti-IL4/13, anti-TSLP, anti-IL-33 and non-biological treatments such as CRTH2 antagonists. The challenge as these therapies become available is determining which patients are best suited to which novel treatment. Reliably identifying the correct endotype will be paramount to achieving the best response. Another pertinent issue shall be the significant healthcare-associated costs of these medications. Unfortunately, to date, novel non-Th2-high asthma clinical trials have proved to be disappointing. As more is known about specific asthma endotypes and ways to
measure them, these shall lead to better stratification of these patients and improve clinical responses.

**LIST OF ABBREVIATIONS**

- **ACQ** = Asthma Control Questionnaire
- **AD** = Atopic Dermatitis
- **ADCC** = Antibody-Dependent Cell-mediated Cytotoxicity
- **AHR** = Airway Hyperresponsiveness
- **AQLQ** = Asthma Quality of Life Questionnaire
- **ASM** = Airway Smooth Muscle
- **BT** = Bronchial Thermoplasty
- **cLT** = Cysteinyl Leukotrienes
- **COX** = Cyclooxygenase
- **CPK** = Creatine Phosphokinase
- **CRTH2** = Chemoattractant Receptor Homologous Molecule on Th2 Cells
- **CXCR2** = CXC Chemokine Receptor 2
- **DC** = Dendritic Cell
- **ED** = Emergency Department
- **EDC** = Epithelial Derived Cytokine
- **EGPA** = Eosinophilic Granulomatosis with Polyangiitis
- **FDA** = Food and Drug Administration
- **FeNO** = Fraction Exhaled Nitric Oxide
- **FEV1** = Forced Expiratory Volume in 1 Second
- **GINA** = Global Initiative for Asthma
- **GM-CSF** = Granulocyte Macrophage Colony Stimulating Factor
- **HDM** = House Dust Mite
- **HRCT** = High Resolution Computed Tomography
- **ICS** = Inhaled Corticosteroid
- **IFN** = Interferon
- **IgE** = Immunoglobulin E
- **IL** = Interleukin
- **IL-13Ra1** = Interleukin-13 Receptor a 1
- **IL-25R** = Interleukin-25 Receptor
- **IL-4Ra** = Interleukin-4 Receptor a
- **IL-5R** = Interleukin-5 Receptor
- **ILC2** = Innate Lymphoid Cells Type 2
- **IV** = Intravenous
- **kDa** = kiloDalton
- **LABA** = Long Acting Beta Agonist
- **LAMA** = Long Acting Anti-muscarinic Antagonists
- **LTB4** = Leukotriene B4
- **mAb** = Monoclonal Antibody
- **NICE** = National Institute for Health and Care Excellence
- **PEF** = Peak Expiratory Flow
- **PGD2** = Prostaglandin D2
- **RF** = Radiofrequency
- **ROS** = Reactive Oxygen Species
- **S/C** = Subcutaneous
- **ST2** = Suppression of Tumorigenicity
- **TSLP** = Thymic Stromal Lymphopoietin
- **TSLPR** = Thymic Stromal Lymphopoietin Receptor

**CONSENT FOR PUBLICATION**

Not applicable.

**CONFLICT OF INTEREST**

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