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STATE OF THE ART REVIEW

Asthma: pathogenesis and novel drugs for treatment

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ABSTRACT

Asthma affects almost 20 million people in the United States and more than 300 million people worldwide. Of these, 10-15% have severe asthma, which is refractory to commonly available drugs. New drugs are needed because those that are currently available cannot control symptoms and exacerbations in all patients and can cause adverse reactions. In the past 10 years, there have been substantial advances in the understanding of asthma genetics, airway biology, and immune cell signaling. These advances have led to the development of small molecule therapeutics and biologic agents that may improve asthma care in the future. Several new classes of asthma drugs—including ultra long acting β agonists and modulators of the interleukin 4 (IL-4), IL-5, IL-13, and IL-17 pathways—have been evaluated in randomized controlled trials. Other new drug classes—including dissociated corticosteroids, CXC chemokine receptor 2 antagonists, toll-like receptor 9 agonists, and tyrosine kinase inhibitors—remain in earlier phases of development. Despite some preliminary efficacy data, there is insufficient evidence to make strong recommendations about the use of these newer agents. Future research on the clinical efficacy of these biologic agents, the effect of newer agents on severe asthma in pediatric patients, and the biology of non-eosinophilic and corticosteroid resistant asthma is needed to reduce the morbidity of asthma worldwide.

Introduction

Asthma is a heterogeneous disease characterized by varying levels of bronchoconstriction, airway hyper-responsiveness, mucus secretion, and chronic inflammation. Asthma affects about 300 million people worldwide, causes 250 000 deaths annually, and is responsible for billions of dollars of healthcare expenditure.[1 2] Although death from asthma has decreased with the regular use of inhaled glucocorticoids, the global impact of asthma remains high, and the prevalence of asthma seems to be increasing.[2-5] There is a clear need for new drugs for asthma that overcome the shortcomings of those that are currently available.

This review focuses on the need for new treatments for asthma, important pathophysiologic pathways, and drugs that are currently available or in late phase clinical development. Each drug is discussed in terms of its effect on symptoms, physiology, or exacerbations, depending on the relevant clinical trials. Because most of the data on newer agents are for use in adults only, the review focuses mainly on adults. However, pediatric data are mentioned when available.

Epidemiology

Asthma symptoms are reported in 11.6% of 6-7 year old children worldwide.[6] In 2010, in the United States alone, an estimated 18.7 million adults and seven million children were reported to have asthma.[7] Although the reported prevalence of the diagnosis and the symptoms of asthma vary globally, possibly because of variable diagnostic criteria and available confirmation strategies in epidemiologic studies,[6] specific groups in the population have higher rates of asthma than the general population. For example, the prevalence of asthma seems to be higher in urban areas than in rural ones.[8] In the US, race and ethnicity strongly affect the prevalence of asthma, with the highest rates occurring in Puerto Rican, multiple race, and African-American people, respectively.[7] Asthma is more common in children and people on a low income than in the general population[7]—17% of African-American children and 13.5% of children from low income families have asthma.[9]

SOURCES AND SELECTION CRITERIA

The references from this review came from a PubMed search from 2004 to May 2014 and our personal libraries. To obtain a broad range of articles, we used the term "asthma" with the filters "clinical trials" and "year". We initially screened more than 4000 articles and gave particular attention to articles on drugs that were in the late phase of development. The reference lists of clinical trials were also screened and relevant articles included. The 2014 systematic review from the Global Initiative for Asthma was also included.

Independent of high prevalence, increases in prevalence of asthma are outstripping the effect of improved diagnostic capabilities in certain parts of the world.[5] In the US from 2001 to 2009 the overall prevalence of asthma increased from 7.3% to 8.2%.[9]

Reasons behind the increased prevalence are unclear, but several plausible hypotheses have been put forward. Increasing rates of atopy in Western society probably contribute to the increased prevalence.[10] In addition, exposure to particulate matter is associated with higher rates of asthma and it clearly affects asthma symptoms.[11 12] As the prevalence of smoking and obesity has increased, it has become apparent that the frequency of asthma is higher in children of smokers and that the severity of obesity is strongly associated with asthma in adult women.[13 14] Changes in the diversity and timing of microbial exposures during development may also play a role.[15 16] Finally, there is evidence that maternal and childhood dietary factors modulate the likelihood of the development of asthma.[17 18] Increased understanding of the proposed mechanisms behind these increases in prevalence may ultimately lead to improved preventive and therapeutic strategies.

In other parts of the world the trend of increased prevalence is not so clear. The ISAAC III study showed that the prevalence of asthma symptoms is declining in western Europe and some English speaking countries, while simultaneously increasing in many developing nations.[19]

Impact of asthma

Asthma has a substantial impact on public health. Asthma causes an estimated 250 000 deaths per year worldwide.[2] In the US in 2009, 2% of patients with asthma were admitted to hospital (>500 000 admissions) and 8.4% were treated in an emergency department (more than two million visits).[7] Around 53% of patients with asthma report an asthma attack in the previous year, and 42% of patients report exacerbations that lead to more than one day of missed school or work over that time period.[9]

Patients with asthma are less likely to be employed than those without asthma, and they are more likely to have activity limitation at their place of employment, at school, or within the home.[20] Similarly, children with asthma have higher rates of school absenteeism than controls, despite available treatments.[21 22] The average US patient with asthma incurred $1900 (£1180; €1467) to $3200 in additional healthcare expenses than controls from 2003 to 2005, accounting for $50bn-$60bn in costs attributable to asthma.[20 23]

Specific populations of patients with asthma have higher rates of mortality and morbidity. In the US, death from asthma is 30% higher in female than in male patients, 75% higher in African-Americans than in white people, and roughly seven times higher in people over 65 years than in children.[7] Children have higher rates of visits to the doctor's surgery and emergency department than adults.[7] Importantly, patients with severe or difficult to treat asthma (5-10% of patients with asthma) have higher levels of morbidity than the general population with asthma.[24]

Asthma phenotypes, endotypes, and representative inflammatory signatures

To decrease the impact of asthma through treatment directed towards specific groups of patients, research in the past two decades has attempted to define asthma subtypes. In recent years, multiple inflammatory profiles and multiple phenotypic clusters of patients with asthma have been identified, although precise definitions of these clusters remain elusive. Although patients can be subdivided according to several clinical, physiologic, radiographic, and pathologic variables, multiple analyses suggest that adult patients are likely to fall into one of five clusters.[25-27]

One group of adults with severe asthma has early onset allergic disease with a prominent T helper type 2 cell (T_H2) signature. This group has high levels of airway eosinophils, mast cells, IgE, and exhaled nitric oxide (FeNO). Candidate gene analyses in this cohort have indicated that T_H2 inflammatory pathways are active in these patients.[26]

A second group of patients has adult onset asthma with notable eosinophilia generally in the absence of other important allergic disease. T_H2 pathways are important in this group too, with notable patterns of interleukins (IL) such as IL-4, IL-5, and IL-13 in the blood. In a third group symptoms are mainly exercise induced. Mast cells play an important role in this group. A fourth group shows a minimal T_H2 response but notable obesity. The fifth group shows a minimal T_H2 response and notable sputum neutrophilia with a T_H type 17 cell response.[26] Children may also fall into clusters, although the determinants of pediatric clusters do not mirror those of adult ones.[28 29]

Although efforts to identify phenotypic clusters help distinguish different subtypes of patients, clustering has not yet led to differential treatment strategies. However, as newer treatments emerge, and as specific biologic agents are developed, it is hoped that endotyping (defining disease subtypes by predominant molecular mechanisms or treatment response) will lead to more targeted approaches.

Pathogenesis

The pathogenesis of asthma is complex and varies across clinical endotypes. Complex interactions between genetic, epigenetic, and environmental factors predispose patients to develop a limited number of dysfunctional immunologic regulatory patterns, which in turn dictate the presentation of clinical endotypes.

Using classic genetic calculations from twin studies, it is estimated that asthma is roughly 60% heritable.[30] Genome-wide association studies have identified several candidate genes that are potentially involved in the pathogenesis of asthma. The *ORMDL3*/*GSDMD* locus on chromosome 17q21 has been reproducibly associated with childhood onset asthma. Other genes, including *IL33* on chromosome 9 and *IL2RB* on chromosome 22, have been variably implicated.[31]

Epigenetic changes in DNA methylation provide a means by which environmental changes can cause important changes in disease prevalence over time. Mouse models of allergen exposure have demonstrated epigenetic changes associated with genes involved in T_H1 and T_H2 responses.[32] A study in humans identified increased methylation in a CpG island in the *ACSL3* gene in response to high levels of maternal exposure to traffic related polycyclic aromatic hydrocar-

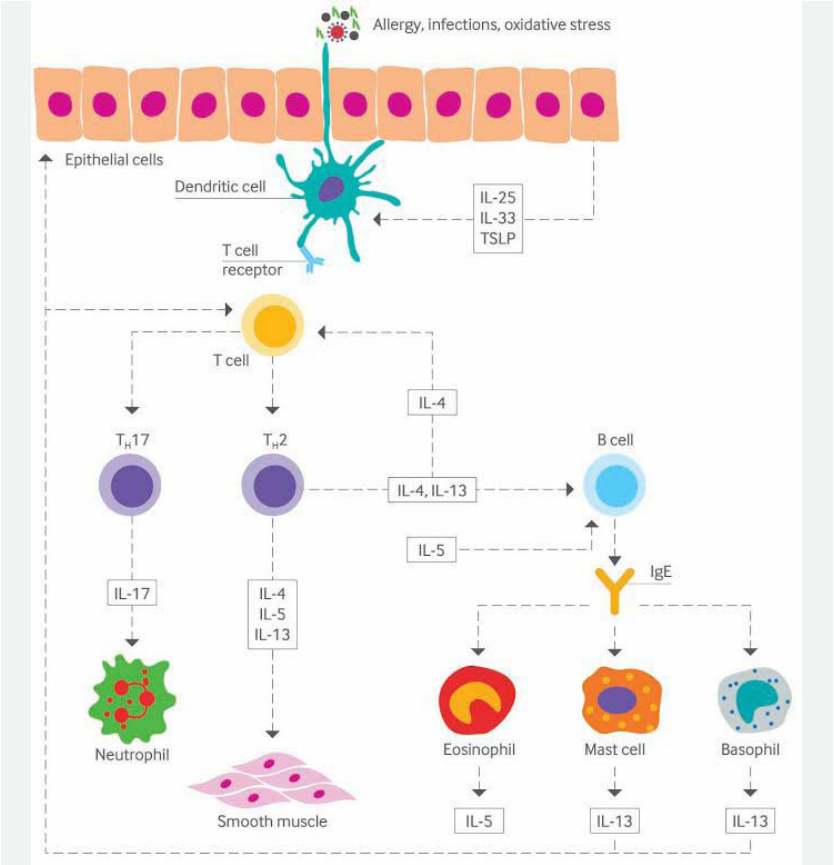

Fig 1 | Important host responses in the pathogenesis of asthma. Several asthma drugs in clinical trials target the cytokines (or their receptors) that are central to these pathways, including interleukin 4 (IL-4), IL-5, IL-13, and IL-17. TSLP=thymic stromal lymphopoietin

bons.[33] Interestingly, maternal smoking during pregnancy has been associated with epigenetic changes in children, although strong links to asthma have not been made.[34]

Several environmental exposures are associated with asthma. Severe infection with respiratory syncytial virus in infancy predisposes patients to asthma later in life, with an attributable rate of asthma due to the virus of roughly 20%, depending on age.[35] Conversely, early exposure to environments with a high degree of microbial content (for example, rural farm environments and day care centres) is associated with lower odds of asthma compared with controls.[15 16] The mechanism by which these effects are mediated is unclear. However, a study in mice showed that administration of bacterial extracts to mice that were later subjected to allergic challenge inhibited allergic airway inflammation through IL-10 dependent pathways.[36] As novel genomic targets are identified and new treatments are established, it is expected that asthma pharmacogenomics will result in a more personalized approach to the management of asthma. However, strategies directed by pharmacogenomics are probably several years away.

Host responses in the pathogenesis of asthma

Different asthma endotypes show variable degrees of inflammation, bronchial hyper-reactivity, mucus production, and remodeling. These pathologic changes are mediated by several airway cells and cells involved in the immune response (fig 1). Important signaling molecules expressed by and directed to these cells are important therapeutic targets.

Airway epithelial cells

Airway epithelial cells are the main cells that form the barrier against mechanical stress, oxidant stress, allergens, pollutants, infectious agents, and leakage of endogenous solutes. These cells also have important roles in mucociliary clearance and signaling. Various types of pattern recognition receptors, including Toll-like receptor 4 (TLR4), are expressed on epithelial cells, enabling responses to allergic and infectious stimuli.[37] In asthma, epithelial cell derived cytokines and chemokines (including IL-25, IL-33, thymic stromal lymphopoietin (TSLP), and granulocyte-macrophage colony stimulating factor (GM-CSF)) signal effector cells (including basophils, eosinophils, mast cells, and lymphocytes) and dendritic cells to shape characteristic asthmatic immune response patterns to allergens, pollutants, and infectious agents.[38]

Dendritic cells

Like airway epithelial cells, dendritic cells are also directly exposed to the external environment. Pulmonary dendritic cells act as antigen presenting cells and express a variety of pattern recognition receptors on their cell surface. Dendritic cells can also be recruited to the airway in response to allergens and pathogens.[39 40] They can be directly stimulated by surface binding of allergens or infectious agents or indirectly stimulated by airway epithelial cells (by mediators such as IL-25, IL-33, TSLP, and GM-CSF).[41]

Locally, dendritic cells can recruit eosinophils.[37] Migration of dendritic cells through the lymphatics to regional lymph nodes is mediated by multiple factors including C-C chemokine receptor type 7 (CCR7), CCR8, and CCRL2.[42 43] Dendritic cells affect T cell differentiation and under certain circumstances generate the T_H2 response commonly seen in atopic asthma.[44]

T cell subsets

Several T cell subsets are important in asthma. Traditionally, T_H2 cells have been thought to predominate, with characteristic raised levels of IL-4, IL-5, and IL-13.[45] IL-4 and IL-13 promote inflammation (through signaling to eosinophils and B cells) and remodeling (through signaling to fibroblasts, airway smooth muscle, dendritic cells, and epithelial cells).[46] IL-5 is crucial for B cell survival and maturation and for stimulating eosinophils. Some patients with asthma show a predominance of T_H1 cells. This pattern can develop under the influence of IL-18 and interferon γ (IFN- γ) and is characterized by further production of IFN-γ.[47] T_H17 cells, which are CD4 positive T cells that express IL-17, also play a role in a subset of patients with asthma. This pattern is unusual, in that the resulting T_H17 pathways result in neutrophils being the primary effector cells.[48 49] T_H9 cells are CD4 positive T cells that secrete IL-9. Numbers of T_H9 numbers are raised in people with atopy, and these cells promote allergic responses, probably through activation of mast cells.[50] T regulatory cells, characterized by secretion of transforming growth factor β (TGF-β) and IL-10, are thought to be important because of their role in blunting atopic responses.[51]

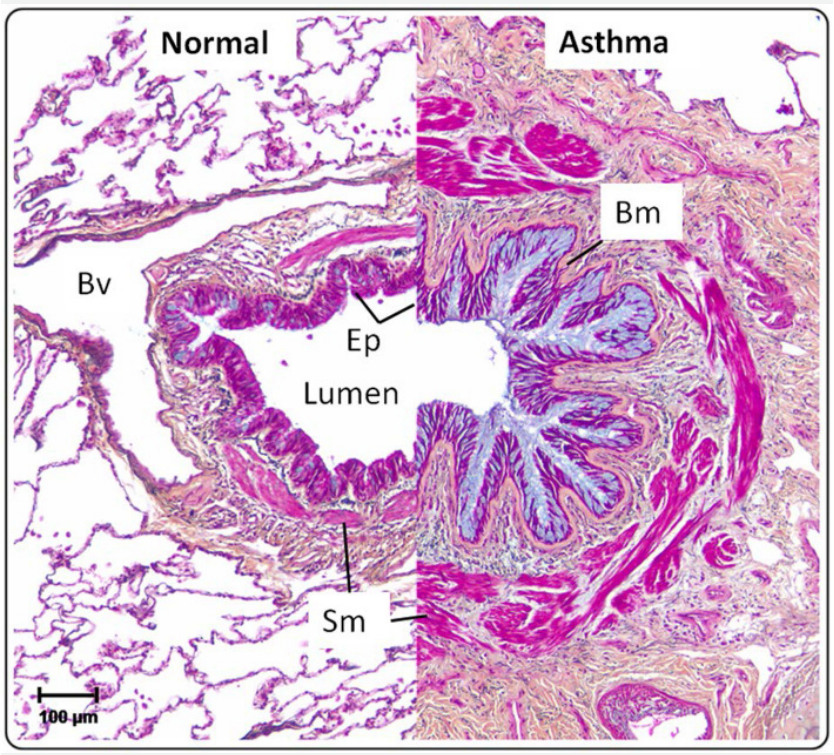

Fig 2| The airways in asthma undergo substantial structural remodeling. Histological section of a medium sized airway from a person without asthma and a patient with severe asthma stained with Movat's pentachrome stain. In asthma the epithelium (Ep) shows mucus hyperplasia and hypersecretion (blue), and thickening of the basement membrane (Bm). Smooth muscle (Sm) volume is also increased in asthma. Bv=blood vessel. Reproduced, under an open access agreement, from Wadsworth and colleagues. IL-13, asthma, and glycosylation in airway epithelial repair. In: Chang C, ed. Carbohydrates—comprehensive studies on glycobiology and glycotechnology. InTech, 2012[67]

B cells

B cells are important in atopic asthma because they produce IgE. IL-5 and B cell activating factor promote B cell survival. Under the influence of IL-4 or IL-13, B cells need to bind to T cells (through CD40 and the CD40 ligand, respectively) to be activated to produce IgE, generally within regional lymph nodes. Secreted IgE is primarily bound through the high affinity Fc epsilon receptors on mast cells and basophils, and when crosslinked by aeroallergen causes these cells to degranulate and release their mediators.[52]

Innate lymphoid cells

The innate lymphoid cell is a recently described effector leukocyte that is stimulated by IL-25 and IL-33 (seen in response to viral illness) and requires the transcription factor RORα for signaling. These cells have the potential to differentiate into macrophages and granulocytes while producing notable quantities of T_H2 cytokines and stimulating eosinophils in the process.[53]

Eosinophils

Eosinophils are bone marrow derived granulocytes that play a central role in asthma. The biology of the eosinophil is complex, and the effects of its secreted products are diverse. Cellular differentiation in the bone marrow is mediated by IL3, IL-5, and GM-CSF.[54] Recruitment of eosinophils is mediated by IL-13, histamine, prostaglandin type 2, and eotaxins (through the CCR3 receptor).[55] The survival of eosinophils is promoted by IL-5 and apoptosis is signaled through binding of the siglec-8 and siglec-F receptors.[56 57] In addition to releasing toxic granular proteins, such as eosinophilic cationic protein and eosinophil derived neurotoxin, eosinophils secrete dozens of cytokines and chemokines, which promote inflammation through the T_H2 pathway and airway epithelial damage.[58 59]

Mast cells

Mast cells are also important in the pathogenesis of asthma. Maintained near mucosal surfaces by IL-9, these cells can be activated by binding of stem cell factor to the surface receptor c-kit, IgE crosslinking, or binding of tyrosine kinase.[60] Activated mast cells are an important source of histamine, cysteinyl leukotrienes, and prostaglandins.[61] These mediators are central to bronchoconstriction, vasodilation, and the allergic inflammatory cascade.

Neutrophils

Neutrophils probably play a role in specific asthma endotypes. Recruited through T_H17 pathways, neutrophil numbers are raised in patients with asthma, especially those who are relatively unresponsive to inhaled steroids.[62] It has been difficult to prove that neutrophils are involved in the pathogenesis of severe asthma because the use of inhaled steroids may suppress eosinophilia and result in airway neutrophilia.[26 63-65]

Airway remodeling

Airway remodeling refers to a constellation of structural changes in asthma including epithelial injury, increased thickness of the basement membrane, increased volume of airway smooth muscle, goblet cell metaplasia, and increased airway angiogenesis and lymphangiogenesis (fig 2).[66]

Airway epithelial injury

Several biopsy studies have shown that injury, including disruption to tight junctions and cell denudation, occurs to the airway epithelium in asthma.[68-70] Epithelial cells demonstrate rapid repair mechanisms and initiate signal cascades central to asthma in response to several stimuli.[71 72] This process is mediated at least in part by epithelial growth factor.[73] Abnormal repair processes and decreased barrier function have also been demonstrated.[70]

Basement membrane thickness

Biopsy studies have shown increases in reticular basement membrane thickness, thought to be mediated by myofibroblasts, in patients with asthma.[74] The functional relevance of this finding is unclear. In children these changes did not correlate with T_H2 cytokine profile or with future lung function.[75 76] The role of connective tissue outside of the basement membrane is also unclear. It has also been reported that certain patients with asthma have notable hyperinflation and decreased elastic recoil, possibly because of changes in connective tissue.[77]

Airways smooth muscle mass

Increased airways smooth muscle mass has been a recognized feature of asthma for decades. These increases are mediated in part by the release of cysteinyl leukotriene from eosinophils. Smooth muscle has a role in bronchoconstriction, which is triggered by several direct and indirect stimuli, and contributes to symptoms, exacerbations, and the remodeling process.[78 79] The increase in smooth muscle mass is associated with increases in growth factors including TGF-β_1 and platelet derived growth factor.[80 81] The muscle itself may also act as a secretory organ in asthma, promoting maladaptive growth and immunologic responses. A recent review of these properties highlighted IL-5, IL-13, TGF-β_1, IL-1β, and tumor necrosis factor α as important mediators in this process.[79]

Goblet cell metaplasia

Goblet cell metaplasia is another important structural change that occurs in asthma. It has been observed in models of T_H2 driven asthma, but is not a feature of T_H1 models of asthma.[82 83] The process seems to be dependent on the actions of the epidermal growth factor receptor as well as IL-13 and may be inhibited by IFN-y.[84] Calcium activated chloride channel proteins may mediate mucus hypersecretion at a downstream level.[85]

Currently available treatments

As noted above, asthma is a disease that involves airway epithelial cells, cells involved in the immune response, and several structural cell types. Details of the interactions between these cell types and between currently available treatments and the host response are under investigation. Observations on the biologic response and efficacy of different drugs in specific populations may lead to targeted therapies in the future.

Although allergen avoidance and the management of comorbidities such as smoking and obesity are essential, drugs remain the cornerstone of treatment. Several drugs have been approved for asthma and the role of many of them has been well defined in patients with mild to moderate disease, most recently in a comprehensive systematic review from the Global Initiative for Asthma.[86 87]

Short acting β agonists counteract bronchoconstriction regardless of the trigger for contraction. In most patients with asthma, inhaled corticosteroids are a highly effective controller therapy (defined as a daily treatment designed to decrease the frequency of baseline symptoms and exacerbations that require short acting β agonists). Consistent use of inhaled corticosteroids (such as beclometasone, budesonide, ciclesonide, fluocinolide, fluticasone, and mometasone) can improve asthma symptoms, quality of life, measures of airway function, hyper-responsiveness, and the frequency and severity of exacerbations.[86] Long acting β agonists (such as formoterol and salmeterol) are effective when used in combination with inhaled corticosteroids in patients with symptoms or exacerbations.[88] Leukotriene antagonists (such as montelukast) also show efficacy in asthma, alone or combined with other controller therapy, especially in patients with prominent allergic disease or exercise symptoms.[89] Long acting muscarinic antagonists (such tiotropium and aclidinium) result in bronchodilation and show modest efficacy as adjuncts to inhaled corticosteroids and long acting β agonists.[90 91]

Omalizumab, a monoclonal antibody directed against IgE, is currently recommended by US National Heart, Lung, and Blood Institute's commissioned national asthma and education prevention program guidelines for use in severe treatment refractory asthma in patients with atopy on the basis of data from several randomized controlled trials (RCTs).[86] It reproducibly decreases the number of exacerbations in adults and children with various severities of asthma.[92] However, its use is limited by its high cost.[93]

Bronchial thermoplasty is an endoscopic procedure available at specialized centers that uses thermal energy to disrupt bronchial smooth muscle.[94] Recent large open label studies have shown a sustained decrease in the frequency of exacerbations for as long as five years in patients with severe asthma who undergo this procedure, suggesting that it has benefit in exacerbation prone populations.[95 96]

Rationale for the development of new drugs to treat asthma

Currently available drugs have helped millions of patients with respect to both the control of asthma symptoms and asthma exacerbations. It has been estimated that 90-95% of patients will achieve symptom control with smoking cessation; proper prescription of inhaled steroids and long acting β agonists; and optimization of drug availability (through production of generic drugs), adherence, and administration technique.[24]

However, despite the general success of currently available asthma drugs, there are several reasons to pursue new ones. As discussed above, the prevalence of asthma is increasing and its burden on society remains high. To date, there is no effective preventive strategy for asthma or a known cure.[97 98] Unfortunately, the effects of inhaled corticosteroids on asthma rapidly disappear when the drug is discontinued.[98] Moreover, current asthma drugs generally do not reverse or slow down most of the long term remodeling changes that occur in various cell types in the airway.[99] This may be partly because inhaled corticosteroids to not inhibit IL-33, a mediator thought to play a role in remodeling.[100]

Despite prescription of drugs to control asthma, many patients still experience ongoing symptoms.[101 102] Asthma remains uncontrolled in about 10% of patients who are adherent to their prescribed drugs.[103] Patients with severe, refractory asthma are responsible for a disproportionately high use of medical resources.[104]

Another rationale for the development of new drugs is related to concerns about adherence, tolerability, and the side effects of conventional asthma drugs. Adherence to inhaled regimens is problematic across many drug classes.[101 102 105] Inhaled corticosteroids have effects on linear growth, bone density, adrenal function, cataracts, and bruising.[106 107] The Salmeterol Multicenter Asthma Research Trial raised concerns about the potential mortality risk associated with long acting β agonists (which should always be used in conjunction with inhaled corticosteroids, preferably in one device).[108] Montelukast was associated with reports of behavioral instability in 2008, but a review of clinical trials data did not demonstrate a significant increase in the risk of behavioral related adverse events or suicide.[109 110]

Furthermore, as we gain more information on asthma endotypes, novel drugs could provide the opportunity to personalize asthma management and directly target mechanisms responsible for the underlying disease.

Modifications of current treatments

Some of the new treatments aim to improve currently successful ones—for example, by improving delivery systems. Long acting muscarinic antagonists have shown efficacy in RCTs in patients with uncontrolled asthma on low dose inhaled corticosteroids (primary outcome of morning peak flow) and those whose disease remains uncontrolled receiving combined inhaled corticosteroids and long acting β agonists (primary outcome of time to first exacerbation).[90 91]

Ultra long acting β agonists aim to maintain efficacy while improving dosing convenience. Indacaterol, a 24 hour long acting β agonist, has demonstrated safety (in clinical trials settings) and efficacy in terms of airway function.[111 112] Fluticasone furoate-vilanterol—a combination of inhaled corticosteroid and long acting β agonist—showed equivalent efficacy to fluticasone propionate-salmeterol in a phase III trial.[113] A new class of glucocorticoids, called dissociated corticosteroids, is still in preclinical development despite promising data published in animal models of asthma; these drugs are aimed at maintaining efficacy while decreasing side effects.[114] Research is also ongoing into compounds that bypass or reverse the mechanistic causes of glucocorticoid resistance—such drugs would be useful in patients who respond poorly to glucocorticoids.[115 116]

Pathways amenable to future therapeutic intervention and emerging compounds

Cytokine modulation

As well as trying to improve existing drug classes, there is a strong push to develop biologic agents aimed at modulating cell signaling and the immunologic responses seen in asthma. The benefits of omalizumab, especially with respect to exacerbations, have encouraged several lines of research into biologic agents that target pathways known to be central to the pathogenesis of asthma.

IL-5

The production of IL-5 is increased in asthma, both in the peripheral circulation and in the airways.[117 118] It is produced by several cells including T_H2 cells, natural killer cells, eosinophils, basophils, and CD34 positive cells.[119-123] The IL-5 receptor has a unique subunit as well as a subunit shared by the IL-3 and GM-CSF receptors, and it signals through multiple pathways including the JAK-STAT (Janus kinase-signal transducer and activator of transcription), Ras-MAPK (mitogen activated protein kinase), PI3K-ERK (phosphatidylinositol-4,5-bisphosphate 3 kinase-extracellular signal regulated kinase), and p38-NF-κB (nuclear factor κ light chain enhancer of activated B cells) pathways.[124] IL-5 enhances eosinophil growth, maturation, and migration, while inhibiting eosinophil apoptosis.[125-127] It also enhances basophil development.[128]

Targeting the IL-5 pathway

Several clinical trials have involved manipulation of IL-5 signaling in patients with asthma. Early trials of mepolizumab, a monoclonal antibody that targets IL-5, decreased eosinophil counts in blood and sputum, but had no noticeable effects on airway function.[129 130] However, in trials of patients with sputum eosinophilia despite the use of high dose inhaled corticosteroids or prednisone, mepolizumab significantly decreased the number of exacerbations when compared with placebo.[131-133]

Reslizumab, another monoclonal antibody to IL-5, improved airway function in patients with persistent sputum eosinophilia but had no significant effect on asthma symptoms or exacerbations when compared with placebo.[134] Results of phase IIb and III trials have not yet been reported for benralizumab, a monoclonal antibody that targets the IL-5 receptor α, but this agent has been shown to decrease eosinophils in blood, sputum, and airways. A drug company sponsored phase III trial (ClinicalTrials.gov identifier NCT01914757) of benralizumab is currently in progress.[135 136]

IL-4 and IL-13

IL-4 and IL-13 are also central to the allergic response and are found in increased levels in the airways and sputum of people with asthma.[137 138] IL-4 is produced mainly by T_H2 cells and mast cells, whereas IL-13 is produced by a variety of cells including T_H2 cells, mast cells, eosinophils, and basophils.[45 139-143] Although these two cytokines do not show a high degree of sequence homology, they share a common receptor, IL-4Rα.[144] Both IL-4 and IL-13 affect transcription through the STAT6 signaling pathway.[145] IL-4 promotes T_H2 cell development and B cell isotype switching, and it affects the production of chemokines by the airway epithelium.[146] IL-13 promotes the allergic phenotype through effects on hematopoetic cells as well as airway epithelium, smooth muscle, fibroblasts, and the endothelium.[147]

Targeting the IL-4 and IL-13 pathways

Several compounds in various phases of development aim to modulate IL-4 and IL-13 responses.[46]

Nebulized IL-4R has been shown to be safe (in a clinical trial setting) and efficacious (in terms of symptoms and airway function) when compared in an RCT with placebo in the context of inhaled steroid withdrawal.[148 149] In a placebo controlled RCT of AMG 317, an IL-4Rα blocker, the intervention did not show statistical and clinical benefit in symptoms (as measured by the asthma control questionnaire) or lung function (as measured by pre-bronchodilator forced expiratory volume in one second).[150] An RCT found that dupilumab, a monoclonal antibody that inhibits IL-4Rα, was superior to placebo in preventing asthma exacerbations in the context of withdrawal of long acting β agonists and inhaled corticosteroid in patients with blood or sputum eosinophilia despite the use of these two treatments.[151] Lebrikizumab, a monoclonal antibody that targets IL-13, was superior to placebo with respect to airway function in patients whose asthma was uncontrolled despite the use of inhaled corticosteroids. This effect was most prominent in those with a high level of periostin, a stable blood marker of IL-13 activity.[152]

IL-17

IL-17, a cytokine produced by T_H17 cells, plays an important role in the immunologic responses seen in asthma.[153] Higher levels of IL-17 than normal have been found in the blood, sputum, and human airway cells of patients with asthma.[154-156] There are multiple IL-17 receptors, the functions of which may differ slightly.[153] Receptor activation leads to the secretion of several inflammatory mediators including IL-1β, IL-6, TNF-α, and GM-CSF, which ultimately leads to neutrophil recruitment.[153 156]

Targeting the IL-17 pathway

Brodalumab is a human monoclonal antibody that binds the IL-17Rα, effectively inhibiting signaling of several members of the IL-17 family, including IL-25. Three doses of brodalumab were compared with placebo in a phase IIa trial of adults with moderate to severe asthma. In this trial, safety was demonstrated, but efficacy (defined by the primary outcome of change in the asthma control questionnaire) was not apparent in the group as a whole. A prespecified subgroup with high bronchodilator reversibility reported improved scores on the asthma control questionnaire (although the results were not adjusted for multiple comparisons). No other clinically meaningful differences were found between the brodalumab groups and the placebo group.[157] Of note, groups in this study were not stratified by predetermined inflammatory profiles.

Looking ahead to future asthma treatments

Several novel classes of drugs are in the early phase of development.[158] An antisense oligonucleotide CCR3 antagonist (co-administered with an antisense oligonucleotide targeting the β_c subunit of the IL-3, IL-5, and GM-CSF receptors) has shown some early efficacy in phase II trials, decreasing sputum eosinophils in response to allergen challenge.[159]

CXC chemokine receptor 2 antagonists, which may help in the management of neutrophilic disease by decreasing IL-8 activity, have shown some promise in early human trials by decreasing sputum neutrophilia in an ozone challenge model.[160]

The Toll-like receptor 9 agonist QbG10 showed efficacy with respect to symptoms and airway function in the context of inhaled corticosteroid withdrawal.[161] Tyrosine kinase inhibitors, which may affect both airway inflammation and remodeling, are being tested in animal models and in early clinical trials.[162] The safety evaluation of all of these novel treatments will require larger studies in patients who receive drugs for prolonged periods of time.

Pediatric considerations

Of the clinical trials referenced, only the DREAM study enrolled adolescents, with the other trials exclusively enrolling adults.[133] Although limited information on safety in the pediatric population is available from trials of mepolizumab and reslizumab in conditions other than asthma, conclusions from the above trials on these agents should be extrapolated to younger age groups with caution.

Guidelines

Because no biologic agents other than omalizumab are currently approved by regulatory authorities, there are no consensus guidelines from the large respiratory societies that advocate for use of biologic agents other than omalizumab at this time. Until these treatments are approved, it would be premature to recommend newer biologic agents in uncharacterized asthma populations. Owing to the heterogeneity of asthma, the selection of the most appropriate patients to demonstrate the clinical efficacy of newer agents in clinical trials remains a major challenge. This is also likely to be the case as some of these agents become available for clinical use. In the near future, the use of newer biologic agents will probably be limited to patients with severe asthma who have frequent exacerbations and a clearly defined phenotype.

Future research

The agents described above have shown potential benefit with respect to mechanistic endpoints. Safety remains a concern in patients who will probably need to use these immunomodulatory agents over prolonged periods because these agents could have an impact on the frequency of infections, autoimmune phenomena, and oncologic processes. Clinical efficacy has varied, and it is currently unclear whether these agents will have an effect on symptoms, lung function, or the frequency or severity of exacerbations in larger populations (all of which are important). There are notable feasibility challenges to detecting all of these features over prolonged periods of time in appropriate populations. Moreover, certain populations—specifically those with a lack of eosinophilia and decreased corticosteroid responsiveness—require extra attention.

Emerging strategies for improved asthma care: predictors of response

It is clinically challenging to predict which patients will respond to a given treatment. It is also difficult to develop clinical trials that can demonstrate efficacy of novel drugs that are used in addition to existing treatments. This is partly because the existing agents control symptoms and exacerbations in a large proportion of patients.[158] In addition, because asthma is a heterogeneous disorder made up of various imperfectly defined endotypes, there is a risk of a type II error occurring in clinical trials of newer drugs that evaluate patients without previous endotyping. As new asthma drugs emerge, it will be crucial to identify biomarkers of responsiveness within patients to guide clinical trial design and future clinical management of patient subsets, especially with regard to the next generation of inhibitors of the T_H2 inflammatory response.

Several biomarkers are under investigation as predictors of responsiveness to treatment. FeNO, which is associated with several markers of atopy, can be used to predict responsiveness to omalizumab and inhaled corticosteroids.[163 164] The evaluation of eosinophils in blood and sputum can identify potential responders to anti-IL-5 and anti-IL-4 therapies (with respect to exacerbations). Serum periostin seems to identify those patients who will respond to lebrikizumab (with respect to airway function). Measures of gene expression in sputum can

FUTURE RESEARCH QUESTIONS

What is the safety profile of biologic agents for the treatment of asthma that are used over long time periods?

What is the long term efficacy of biologic agents for the treatment of asthma? Can these novel drugs prevent airway remodeling?

What is the safety and efficacy profile of biologic asthma drugs in children?

How will clinicians choose between different biologic therapies as they become available and can we identify novel biomarkers that can predict responsiveness?

What are the potential therapeutic targets in patients with non-eosinophilic and corticosteroid resistant asthma?

identify subtypes of asthma characterized as T_H2 high and T_H2 low, although currently this classification has not enabled the response to treatment to be predicted.[165]

Pharmacogenetics may also help identify potential responders, as was shown in phase III trials of the IL-4 and IL-13 pathway antagonist pitrakinra and in several studies of β2 receptor polymorphisms and response to β agonists.[166-168] Ethnicity may be a predictor of responsive to treatment because the prevalence of asthma and response to drugs vary across races.

Finally, metabolomics, the study of small molecules generated by cellular metabolic activity, may help distinguish asthma endotypes by processing large datasets rather than a single marker.[169]

Currently, FeNO and blood and sputum eosinophilia are the main predictive biomarkers in wide use and the others remain research tools. Although FeNO is potentially available to primary care physicians, it does not clearly affect management outcomes when added to other available tools.[170] Management targeted towards normalization of sputum eosinophilia has been shown to decrease asthma exacerbations.[171] However, difficulties in acquiring sputum specimens and variability in interpretation preclude the use of these biomarkers in primary care.

Conclusions

Despite the notable clinical successes of inhaled corticosteroids, long acting β agonists, and leukotriene modifiers, the burden of asthma, especially severe asthma, remains high. Several biologic pathways have been identified in the past 20 years that may lead to effective asthma treatments in the near future. Several novel classes of agent remain in preclinical or early phase development. Major hurdles in the advancement of asthma care include the design of clinical trials that can detect meaningful clinical changes in patients already receiving multiple effective drugs and the identification of predictors of medication responsiveness.

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