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Review Article

Role of Biologics in the Management of Asthma

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Abstract

The treatment of asthma has entered a new frontier with the discovery of drugs that target the inflammatory pathways thought to be at the root of the disease. It is estimated that up to 10% of patients with asthma have the severe form and have persistent symptoms even on maximal doses of conventional therapy. Consideration for biological therapy (i.e., drugs that are manufactured by biological processes mostly with the use of recombinant DNA technology) targeted at the underlying mechanism, is essential for successful management of their disease. With the development of biologics, a hope for control of their asthma is on the horizon for these patients. Unfortunately, most of these medications have far reaching effects beyond the beneficial ones on the disease only and thus, side effects are common. Many pathways are still incompletely understood and plausible anti-inflammatory mechanisms have not always translated into effective treatment. As a result, there are a few options available to us today. The discovery of distinct asthma phenotypes and their underlying molecular signature means that patients can no longer be considered to be a homogenous group.

With the availability of new resources to tackle the difficult-to-treat asthma patient, the responsibility of identifying these phenotypes comes to the physician. With that goal in mind, this review of biological therapies targeted towards asthma will identify those agents that have been approved and are available, and also briefly touch upon those that are in the early stages of development.

Keywords: Biologics; Asthma; Cytokine

Abbreviations

US FDA: United States Food and Drug Administration; ASM: Airway Smooth Muscle; AHR: Airway Hyper Responsiveness; TNF: Tumor Necrosis Factor; IL: Interleukin; GM-CSF: Granulocyte Macrophage- Colony Stimulating Factor; NAEPP: National Asthma Education and Prevention Program (NAEPP) Expert Panel; GINA: Global Initiative for Asthma; FEV1: Fractional Expiratory Volume in One Second

Introduction

Asthma is a very common inflammatory disease of the airways; 15% to 20% of the general population in many countries around the world suffers from asthma [1]. From a clinical perspective, asthma has a wide spectrum of patterns that are often difficult to identify, but can be crucial to its successful management.

Asthma had been described and treated in nearly the same manner from antiquity until nearly the 20th century, first with bronchodilators, and later with nonspecific anti-inflammatory agents like inhaled corticosteroids (which, 50 years later, remain the cornerstone of treatment) [2]. Recent advances in molecular biology, however, have shed new light on the underlying pathologic mechanisms. The result has been the introduction of the first novel therapies for asthma in decades. The challenge in managing asthma not uncommonly stems from the difficulty in identifying the different phenotypes which are now being associated with the disease, particularly those that seem to be steroid-resistant [3]. Even then, while the underlying complicated sequence of inflammatory events that lead to structural and functional changes in the lungs has been extensively studied, & published upon countless times, there have been no novel additions to the armamentarium since the approval of Omalizumab in 2003.

The pathophysiology of asthma can be loosely explained in terms of goblet cell hyperplasia, Airway Smooth Muscle (ASM) hypertrophy and sub-epithelial fibrosis in the airways. These in turn give rise to Airway Hyper Responsiveness (AHR) and reversible airflow limitation that are the hallmark of asthma [4]. A cytokine-based inflammatory milieu involving multiple cell types, most notably T cells, B cells, mast cells, eosinophils, dendritic cells, and cytokines derived from these cells characterizes the disease. Control of such inflammation can be achieved by targeting the cells itself or intermediary inflammatory cytokines. Omalizumab, for example, works by binding free IgE, preventing it from binding to and activating mast cells and basophils thus preventing transmission and amplification of inflammatory signals.

With the success of omalizumab, and other agents (notably mepolizumab) in the pipeline, biologics are likely to become an ever-increasing part of treatment of carefully selected patient populations with difficult to treat asthma. The challenge facing the modern age clinician lies in the prompt identification of the asthma phenotype and awareness of the existence of tailor-made biologics suited to an individual's asthma phenotype [5,6]. There are more than 300 million people worldwide affected by asthma and an ever-growing segment of that population is living with severe, uncontrolled asthma. Undoubtedly, the need for new biologic therapies is greater than ever [7].

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Classification of asthma and guidelines for management

There are two major guidelines for management of asthma, the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 [6] which was last published in 2007 and the Global Initiative for Asthma (GINA) guidelines were last updated in 2010 [5,8]. Inhaled Corticosteroids (ICS) and beta-agonists are the cornerstones of therapy, with other agents such as Long Acting Beta Agonists (LABA), added on in "steps". Other agents, typically non-selective phosphodiesterase inhibitors such as theophylline and Leukotrienes Inhibitors (LTRA) such as montelukast, are also used in selected patients. Escalation to the next step in the therapeutic regimen is required in the event of suboptimal control [9]. Omalizumab is to be considered at later stages for the management of difficult to control asthma. It is anticipated that other biologics (once available) will be sequentially added in these later stages as we are able to better and more completely characterize the specific drug for the specific asthma phenotype.

Newer phenotypes of asthma and importance of their identification with regard to potential for biologic therapy

Both the identification of newer mechanistic pathways and a deeper understanding of ones that have long been studied have given rise to hope for more effective and targeted treatments. It is conceptually easier if we consider asthma not as a discrete disease but rather as a syndrome caused by multiple biochemical processes. There have been suggestions of a unique yet overlapping pathogenic mechanism that is exclusive to the different asthma phenotypes (Table 1) [10].

There exists an intricate interplay of the respiratory epithelium with both innate and adaptive immunity that initiates and drives a chronic inflammatory response in asthmatics. As seen with multiple other immunologic diseases, the interaction between genes and environment results in an aberrant immune response to allergens and other environmental triggers in those who are inherently susceptible [9-15]. A phase of chronic inflammation driven by different environmental inflammatory stimuli drives the synthesis of mediators from the airway epithelium and recruits further inflammatory cells. This leads to bronchoconstriction and epithelial damage, and subsequently drives remodeling of the airway. Also contributing to this inflammatory process is our body's defense mechanism. T-lymphocytes play an important role in the regulation of airway inflammation through the release of numerous cytokines. Other constituent airway cells, such as fibroblasts, endothelial cells, and epithelial cells, contribute to the chronicity of the disease.

Inflammatory response in asthma has been characterized into two types of Th pathways: Th2-high and Th2-low. The Th2 high response has been associated with consistent clinical and inflammatory characteristics including increased blood and airway eosinophilia, airway hyper-responsiveness, a thickened basement membrane, higher IgE levels and tissue expression of IL-5 and IL-13. They consistently show an association with good response to ICS. They also have a higher level of blood and airway eosinophilia, subepithelial fibrosis, and airway mucin gene expression [16].

The"Th2 low" phenotype, in contrast, is more neutrophil-predominant and predicts a poor response to inhaled steroids. These patients are consistently found to be largely resistant to steroid treatment, and thus have limited treatment options [17,18].

Other than above mentioned cytokines some other cytokines have also been associated with the Th2–High phenotype and a potential role for IL-17 and hence its antagonists were explored recently [19,20]. Results from the study demonstrated minimal efficacy of an anti-IL-17R antibody in moderate to severe asthma. It is important to keep in mind that neither phenotype is definitively associated with a greater severity of disease compared to the other.

Other T helper cells - TH9 and TH17 -have been identified to contribute to asthma pathogenesis; the process leading to formation or aggravation of asthma. Furthermore, TH25 cells, TH3 cells, and regulatory T cells have also been implicated in asthma pathogenesis [21]. As an end result, the sequence of inflammation leads to changes in the structure of the airway on a microscopic level [22].

This results in the following structural cellular changes -

1. subepithelial fibrosis.
2. mucus hyper secretion and goblet cell hyperplasia.
3. epithelial cell injury.
4. smooth muscle hypertrophy.
5. angiogenesis and exudation of fluid.

Currently available biologic agents:

1. IgE Inhibitors

Table 1: Demonstrating the different pathogenic mechanisms of asthma based on the phenotypes [10].

Endotype	Clinical Features	Proposed Mechanism	Treatment Response
Allergic Asthma	Allergen-associated symptoms, allergic rhinitis, childhood onset, history of eczema	Th2 dominant	Responds to glucocorticoids and omalizumab [32-37]
Allergic bronchopulmonary aspergillosis	Severe mucous production, adult onset, long duration	Airway colonization by fungi	Responds to glucocorticoids and antifungals
API-positive preschool wheezer	3 episodes/yr, family history of asthma	Th2 dominant	Responds to daily inhaled corticosteroids
Aspirin-sensitive asthma	Nasal polyposis, often severe asthma, aspirin sensitivity, adult onset	Eicosanoids-related	Responds to antilukotrienes, aspirin desensitization
Severe late-onset hypereosinophillic asthma	Severe exacerbations, peripheral blood eosinophilia	Nonatopic, mechanism unclear	Often dependent on oral glucocorticoids [38-60]
Exercise-induced bronchospasm	Symptoms related to exercise, frequently in elite athletes	Dehydration of airways	Mixed response to glucocorticoids

Adapted from Journal of Allergy and clinical immunology, 127(2), Lotvall J et al. [10]. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome.

*API, Asthma Predictive Indices: children with repeated wheezing episodes and history of atopic dermatitis, parental asthma or aeroallergen sensitivity and peripheral eosinophilia, wheezing unrelated to common cold, or sensitization to food allergen.

2. Anti IL-5 agents

3. Anti IL-4 and IL-13

4. IL-4Rα Activity Inhibition

5. Anti-IL-9 Monoclonal Antibodies

6. Anti-TNF-α for Refractory Asthma and Neutrophilic Asthma

Anti-T-lymphocyte Monoclonal Antibodies

Table 2 provides us with a list of biologics being investigated for the treatment of asthma. Only one (omalizumab) is currently available in the US, with the likely approval of mepolizumab pending by the FDA as of this writing.

IgE inhibitors

IgE binds to high-affinity (Fc€RI) receptors on mast cells and basophils, and to low-affinity (Fc€RI) receptors on macrophages, dendritic cells and B lymphocytes. The attachment of allergens to the unoccupied Fab component of the antibody cross links adjacent cell surface Fab components and activates the release of preformed mediators leading to bronchospasm and inflammation. Indeed, an increased presence of Fc€RI receptors (a high affinity receptor for IgE) in the bronchial biopsies of asthmatic patients regardless of atopic status has been observed [23]. Omalizumab is the first developed IgE inhibitor and is the first biologic agent to be approved by the FDA for use in asthma [24]. The Fc epsilon RI receptor is located on the IgE molecule to which omalizumab will bind. With neutralization of IgE levels, there is a substantial decline in sputum and tissue eosinophil counts, along with interleukin-4 (IL-4) levels. Additionally, the Fc epsilon RI receptor also becomes down regulated. If therapy is stopped, serum IgE and receptor activity return to previous levels fairly quickly, however, a "rebound" in disease activity is generally not noted [25-27]. It is important to keep in mind that omalizumab binds only to free IgE molecules, and not those that have already become bound to cells and activated. This makes it ineffective in the acute management of asthma.

Adverse reactions and interactions

The most common troublesome side effect reported from omalizumab therapy is injection-site reaction. Hypersensitivity reactions, particularly an unusually high rate of anaphylaxis seen in the early trials have been a concern [28]. The FDA has issued a "black box" warning for such reactions [24]. The risk of Churg-Strauss Syndrome has been another source of worry for prescribers but studies have shown that there is, if any, minimal evidence for a causal relationship beyond the "unmasking" of preexisting CSS as corticosteroid therapy was being tapered [29]. Another reported adverse effect of questionable significance is an increased rate (an odds ratio of 2.2) of helminthic infections noted in a trial from Brazil [30,31]. There was some suggestion of an increased risk of malignancy associated with omalizumab therapy, but again the evidence is conflicting [25].

Clinical use

There are three pivotal phase 3 trials [32-35] that led to the approval of omalizumab for the treatment of allergic asthma. Patients who were on monotherapy with moderate or high-dose Inhaled Corticosteroids (ICS, beclomethasone propionate) alone were selected for these three trials. The difference in exacerbations was not statistically significant until after 16 weeks, with 18% of patients in the omalizumab group experiencing an exacerbation compared with 38.5% with placebo. However, a significant reduction in ICS and rescue inhaler use and fewer missed school days in the omalizumab arm are also important to take note of. Finally, unlike in the adult trials, there were more study drug–related adverse events in the omalizumab (6% *vs.* 0.9%) group, and there was a higher rate of hypersensitivity reactions (primarily urticaria).

The INNOVATE (Investigation of Omalizumab in Severe Asthma Treatment) trial [36] examined its efficacy in patients with poor asthma control despite step 4 therapy as determined by the 2002 GINA guidelines. The primary end point was the rate of "clinically significant" exacerbations, requiring treatment with systemic corticosteroids. This revealed a decrease in the rate of exacerbations by 26%, which did reach significance ($P < 0.042$). The number

Table 2: Newer biologics currently under development for the treatment of asthma.

Newer anti-IgE monoclonal antibodies
Quilizumab (MEMP1972A)
8D6
Anti-IL-5 biologics
Mepolizumab (anti-IL-5)
Reslizumab (anti-IL-5)
Benralizumab (anti-IL-5Rα)
TPI-ASM8 (anti-IL-5Rβc and anti-CCR3 receptor antisense oligonucleotides)
IL-4/IL-13 antagonist
Pascolizumab (anti-IL-4 mAb)
Altrakincept (soluble human recombinant IL-4R)
Pitrakinra (IL-4 mutein)
Anti-IL-13 monoclonal antibodies
Lebrikizumab
Anrukinzumab
Tralokinumab
Dulipumab (anti-IL-4Rα mAb)
Anti-IL-9 monoclonal antibodies
MEDI-528
Anti-TNF-α treatments
Etanercept (TNFR2/p75 fusion protein and human IgG1 Fc)
Anti-TNF-α monoclonal antibodies
Infliximab
Adalimumab
Golimumab
Anti-T-cell monoclonal antibodies
Daclizumab (anti- IL-2 receptor α chain)
Keliximab (anti-CD4)
Oxelumab (OX40 ligand blocker)
KB003 (anti-GM-CSF)

needed to treat for 1 year to prevent 1 exacerbation was 2.2. Thus, one of the chief take home messages from the INNOVATE trial is that omalizumab may help patients who are already on otherwise maximal therapy. Few, if any, other agents have comparable data in patients with such difficult to control asthma.

Also, patients should therefore be given an extended therapeutic trial of 12–16 weeks before assessing for a positive therapeutic response. Thus, in practice, patients with most severe asthma are on this medication. They would generally meet the following criteria:

1. are above the age of 12 years.

2. have moderate to severe persistent asthma.

3. have inadequate control with ICS (regional variations as noted above).

4. have skin or serum allergen testing positive for a year-round allergen such as dust mites, molds, animal dander.

5. have an elevation in total serum IgE.

The recommended range of IgE for which omalizumab is dosed is between 30 and 700 IU/mL.

There are newer anti-IgE molecules on the horizon which might be superior to the currently available agent. A new human anti-IgE monoclonal antibody (8D6) possesses a unique set of binding specificities and hence binds to a conformational epitope on the CH3 domain of human IgE. As with omalizumab, this molecule (8D6) does not bind to IgE already bound to the high-affinity IgE receptor (Fc€RI) on basophils and mast cells. But unlike omalizumab, it can bind to IgE already bound to the low-affinity receptors (Fc€RII or CD23) [37]. Thus, it may offer additional pharmacological mechanisms other than neutralization of IgE.

Quilizumab (MEMP1972A, Genentech/Roche) is another anti-IgE monoclonal antibody currently under study in a phase IIb, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety in adults with allergic asthma not controlled with IC and a second maintenance medication (NCT01582503).

Anti IL-5 agents

Eosinophils are not normally present in healthy lung tissue, but their accumulation is a well-defined feature of the inflammatory processes in the lungs of patients with eosinophilic asthma. In the lung, tissue eosinophils release pro-inflammatory chemicals including granule-derived basic proteins, lipid mediators, cytokines and chemokines. These mediators potentiate airway inflammation and contribute to lung remodeling. This results in airway thickening, fibrosis and angiogenesis, which contributes to exacerbation of asthma [38]. Interleukin-5 (IL-5) also stimulates eosinophils development in bone marrow, increases their adhesiveness to endothelial cells lining the post capillary venules. It also prolongs their survival in tissues by inhibiting eosinophil apoptosis [39,40], and is a potent survival factor for eosinophils, playing a key role in patients with asthma [41].

Systemic administration of IL-5 to patients with asthma increases circulating eosinophils and their precursors from the bone marrow. Blockade of IL-5 with monoclonal antibodies in animal studies has reduced eosinophil numbers in the blood and lungs and inhibited allergen-induced asthma. The role of IL-5 in disease in humans is complex and may be more important in patients with certain asthma phenotypes (e.g., the severe late-onset hypereosinophilic endotype). Although, IL-3 and GM-CSF (granulocyte-macrophage colony-stimulating factor) also play a role, it is clear that IL-5 is the primary inflammatory mediator in eosinophil development and function. IL-5 also modulates histamine release by basophils [42]. IL-5 was therefore identified as a promising target to prevent or blunt eosinophil-mediated inflammation in patients with asthma and other eosinophil-related conditions. This led to development of humanized anti-IL-5 monoclonal antibodies, such as mepolizumab and reslizumab, or benralizumab, which is a monoclonal antibody against the human IL-5Rα [43].

a) Mepolizumab

This is a fully humanized anti-IL-5 IgG1 mAb that binds to free IL-5 and prevents it from binding to α chain of the IL-5 receptor on the eosinophil cell surface.

Studies among patients with mild-to-severe asthma have reported significant reductions in blood and sputum eosinophil numbers. However; clinical outcomes have been less than satisfactory in general asthma populations [44-47]. When patients with increased sputum eosinophils were only considered, mepolizumab administration resulted in a statistically significant reduction in AQLQ scores and exacerbations, and both sputum and peripheral eosinophil counts compared with placebo [48]. Similar end results have also been reported from another study that specifically enrolled patients with refractory asthma and eosinophilic airway inflammation There was a significant reduction in severe exacerbations requiring oral prednisolone and sputum and blood eosinophilia, but no change in FEV1 [49]. The DREAM study was a phase IIb multicenter study (GlaxoSmithKline) designed to determine the optimal dose of mepolizumab and to confirm its efficacy and safety in patients with severe eosinophilic asthma [50]. A total of 621 patients were randomized to placebo or 1 of 3 mepolizumab doses (75, 250 or 750 mg) in parallel groups for 1 year. Mepolizumab reduced the number of severe exacerbations by around 50% in all treatment groups compared to placebo, irrespective of the dose. Thus no dose–response effect was reported in this study. Another multivariate analysis established that only the level of blood eosinophilia and the number of exacerbations in the 12 months prior to the study were associated with response to mepolizumab, presumably making it easier to identify those patients with potential for higher benefit from the medicine.

A meta-analysis performed on published clinical trials with mepolizumab, which included a total of 1131 patients, has also concluded that mepolizumab reduces the number of exacerbations and improved asthma-related quality of life in those with eosinophilic variety of asthma [51].

To summarize, mepolizumab is efficacious in patients with specific phenotypes of severe asthma characterized by persistent, glucocorticoid-resistant eosinophilia; strengthening the putative role of IL-5 in selected subgroups of patients with severe asthma, and its role in recurrent asthma exacerbations.FDA approval is likely as of this writing given the unanimous support of the advisory committee. They recommend approval as a 100mg fixed dose (via subcutaneous

injection) every four weeks in adults 18 years of age and older with severe eosinophilic asthma.

b) Reslizumab:

This is a humanized form of an anti-IL-5 antibody (JES1–39D10) originally raised in rats [52,53].

Initial studies had displayed a disconnect between reduced circulating eosinophil counts and asthma symptom control with this drug. A 2011 randomized, placebo-controlled, multicenter Phase II trial evaluated the effect of intravenous reslizumab in asthmatic patients with symptoms not controlled by high-dose inhaled glucocorticoids and who had a sputum eosinophilia >3%. Compared with placebo (n = 53), the reslizumab group (n = 53; 3.0 mg/kg) exhibited a nonsignificant reduction in exacerbations and a strong trend towards improvement in asthma control ($p = 0.054$) as assessed by the Asthma Control Questionnaire score (the primary study end point). This effect was more prominent in those with concomitant nasal polyposis [54]. In that group, reslizumab treatment was associated with improvements in asthma symptoms, decreased sputum eosinophilia, and notably, a statistically (and arguably clinically) significant ($p = 0.002$) difference in FEV1 of 0.26L, after 15 weeks, compared to the placebo group.

A pooled analysis of two longer-duration (52 weeks) trials of reslizumab was recently published. There was a significant reduction in total asthma exacerbations (but not hospitalizations or ED visits) in the reslizumab group, irrespective of the presence of nasal polyps. The improvement in FEV1 at 52 weeks was also statistically significant; the overall reported effect was of questionable clinical significance (between-group difference of only 0.09L) but no subgroup analysis of those with nasal polyps was included. Notably, there was a trend towards all of the observed benefits increasing along with the baseline severity of disease (as measured by medication use at enrollment), particularly those on chronic oral steroids. Adverse events for reslizumab were similar to placebo without evidence of rebound eosinophilia in all of the studies [55].

c) Benralizumab

This is another novel humanized a fucosylated IgG1κ mAb indicated for the treatment of asthma and chronic obstructive pulmonary disease that binds to a distinct epitope within the extracellular domain of recombinant human IL-5Rα. Benralizumab binds to human lung tissue-resident eosinophils expressing IL-5Rα and induces cellular apoptosis [56]. A recently published phase IIb study demonstrated the efficacy of benralizumab in eosinophilic asthma. Using this drug at two different doses (20 and 100 mg) was associated with decreased rates of exacerbations compared to placebo among patients with baseline hypereosinophilia (>300 cells/cmm) [57]. Practical application of this drug is undefined and will depend on results of further studies.

d) Other Anti-IL-5 Biologics

TPI-ASM8 is a new anti-IL-5 treatment. It consists of 2 antisense oligonucleotides that target IL-5Rβc and the CCR3 chemokine receptor expressed by various leukocytes, including eosinophils, basophils and Th1 and Th2 lymphocytes [58]. TPI-ASM8 reduced allergen-induced eosinophilic inflammation [59] and eosinophil progenitor levels in sputum [60].

Anti IL-4 and IL-13

IL-4 and IL-13 are complimentary central coordinators of asthmatic inflammation [61]. They regulate eosinophil activation and stimulate IgE synthesis by B cells; they also contribute to bronchoconstriction [62-66]. IL-13 induces a hypersecretory state [67] and reduced barrier function through down regulation of proteins associated with maintaining epithelial tight junctions [68]. It acts as a potent promoter of epithelial cell TGF-β production, which in turn activates myofibroblasts and contributes to airway remodeling [69-71].

a) Lebrikizumab

This is an anti-IL-13 biologic which has recently been found to improve lung function in patients with inadequately controlled asthma. They seemed to work only in patients with high serum levels of periostin [72]. Periostin exhibits effects on epithelial cells and fibroblasts that may contribute to airway remodeling in asthma [73,74]. A post-hoc analyses shows that lebrikizumab-treated patients with nitric oxide values above the group median exhibited larger improvements in FEV1 than those patients with lower levels. Exhaled nitric oxide is a marker in asthma. This drug has an acceptable safety profile with similar frequency of adverse events compared to placebo groups (74.5% in the lebrikizumab group and 78.6% in the placebo group).

b) Tralokinumab

This is an injectable anti-IL-13 humanized IgG4 monoclonal antibody that could be a potential treatment for severe asthma. It neutralizes IL-13 and has been shown to be effective across a wide physiological range. A recent proof-of-concept study evaluated the effect of subcutaneous injections of tralokinumab (150, 300 or 600 mg) or placebo among 194 patients with moderate-to-severe uncontrolled asthma [75]. Improved lung function (FEV1) with a dose–response effect was noticed. There was also a reduction in the need to use rescue short-acting β2-agonists but without significant improvement in Asthma Questionnaire (ACQ)-6 score. Sputum IL-13 levels did not have any impact on the results on further sub-analysis. All adverse events were mild to moderate and were not determined to be related to treatment with tralokinumab. These findings support the possibility of asthma treatment with lebrizumab.

c) Pitrakinra

This drug is a recombinant human IL-4 variant, which was developed to competitively inhibit the IL-4Rα receptor complex and interfere with the actions of both IL-4 and IL-13. A recent double-blind, randomized, placebo-controlled trial of inhaled pitrakinra in 534 patients with uncontrolled, moderate-to-severe asthma reported significant improvements in exacerbations rates and symptom scores in patients with an elevated blood eosinophilia [76]. However, another recent 12-week clinical trial with a similar monoclonal antibody (AMG-317, Amgen) directed at IL-4Rα reported significant reductions in blood IgE levels and eosinophils, but found no significant change in measured asthma outcomes [77]. Thus the use of Pitrakinra and other drugs using similar mechanism of action is still unclear and needs further studies.

d) Dupilumab

This is a fully humanized monoclonal antibody to the IL-4Rα/IL-13Rα1 receptor complex. Dupilumab is given by subcutaneous injection. In a unique multicenter Phase IIa RCT of 104 patients with eosinophilic asthma, dupilumab allowed for reductions in inhaled medications (ICS and LABA) and decreased asthma exacerbations compared to placebo (6% *vs.* 44%, OR: 0.08; 95% CI: 0.02–0.28; $p < 0.001$); with an impressive 87% relative reduction in the proportion of patients experiencing exacerbations in the 12-week study period. Dupilumab treatment was also associated with a significant increase from baseline in both predicted and actual FEV1 that was maintained through to week 12 despite the instruction to subjects to discontinue their long-acting β-agonist therapy at week 4 and to taper and stop inhaled glucocorticoids during weeks 6–9 [78]. These initial results, while impressive, need to be validated in future studies [79].

e) Anti-IL-13 Monoclonal Antibodies

Anrukinzumab is another anti-IL-13 monoclonal antibody that has been tested in patients with mild allergic asthma in studies that show a small but significant reduction in both immediate and late allergen-induced asthmatic responses that were found at 14 days but not at 35 days after administration [80]. Doubts about its clinical efficacy still exist.

Anti-IL-9 monoclonal antibodies

MEDI-528 is an IgG1 monoclonal antibody that binds to IL-9, and has been associated with reduced exacerbations among patients with mild to moderate asthma [81]. However, other studies have not shown any benefit and no significant change was found in the asthma control questionnaire scores, exacerbations, lung function or quality of life.

Anti TNF-α for refractory asthma and neutrophilic asthma

a) Etanercept

This is a dimeric protein synthesized by fusion of two soluble extracellular domain of the human tumor necrosis factor receptor-2 (TNFR2/p75), bound to the Fc domain of the human IgG1 which binds to free TNF-α, thus neutralizing it. In a large randomized, controlled, multicenter study to evaluate the efficacy and safety of this product (25 mg twice a week) in patients with moderate to severe persistent asthma, no improvement was reported in any of the asthma parameters [82].

b) Infliximab

This is a humanized monoclonal antibody which has been noted to reduce circadian variation in peak flow rates and reduces asthma exacerbations in patients with moderate persistent asthma [83]. Clinical improvement has been reported in asthmatic patients receiving infliximab for rheumatoid arthritis [84]. However, this drug has not been investigated in patients with chronic asthma.

c) Golimumab

This is an anti-TNF-α monoclonal antibody for severe asthma tested among 309 patients with severe persistent asthma, randomized to receive placebo or 3 different doses of golimumab (50, 100 and 200 mg) [85]. There may however, be a subgroup of patients who might benefit from this treatment as suggested by a post hoc analysis. These are patients with a preexisting history of sinusitis and FEV1 reversibility (≥12%) who receiving golimumab (100 and 200 mg) had demonstrated fewer severe asthma exacerbations this effect was noted to be dose–dependent.

Anti-T-lymphocyte monoclonal antibodies

a) Daclizumab

Daclizumab is a humanized monoclonal antibody targeting the IL-2 receptor (IL-2R) at the α-chain level, FDA-approved for prophylaxis against rejection of renal transplants. A single early-phase study had reported significant improvements in FEV1, daytime asthma symptoms, use of rescue medication and time to first exacerbation patients with moderate or severe asthma not controlled despite treatment with high dose ICS [86].

b) Keliximab

A report of the use of this medicine is available from a study on a group of 22 patients with steroid dependent asthma which revealed that the patients who received the highest doses had showed a significant improvement in maximum peak flow rate. There are no further studies investigating the role of keliximab in asthmatic patients.

Safety in children:

Omalizumab has been shown to be safe and effective in IgE-mediated childhood asthma. Using Omalizumab as an add-on may provide them with an option for better symptom control. Adding Omalizumab also permits a reduction in the doses of inhaled corticosteroids without an increased risk of exacerbations [87,88].

Conclusion

Asthma is a very common disease that has been diagnosed for thousands of years. Despite this, there has been a comparatively glacial pace of therapeutic innovation: Until the 1960's when inhaled corticosteroids were first marketed in Europe, arguably none to minimal progress had been made in nearly 100 years.

Despite the revolution in genetics and molecular biology that has fundamentally changed our knowledge of how the human body works, asthma therapy still remains comparatively stagnant. Only two truly novel classes of treatment have been developed over the past 40-plus years, represented by a scant list of 4 agents approved by the FDA (one of which, zileuton, is no longer even in use) [89]. Hopefully one or more of the agents discussed here, likely starting with mepolizumab, will bring the treatment of asthma more fully into this new age.

A major barrier, which affects not only the newer biologics but even LTRA's as well, is the fact that asthma is not a single disease process, and identifying patients that benefit from certain targeted therapies is more a process of trial-and-error process than one would hope.

The redundancy and overlapping of many of the pathogenic pathways in asthma could be responsible for the limited targets for drug development. Side effects are bound to be common when targeting such fundamental immunologic pathways, and high

production costs of biologic medications continue to be a hindrance to development as well Fortunately, the success of omalizumab demonstrates that there is clear benefit to be found, paving the way for development and research into other antibodies targeting the IL-4, 9 and IL-13 pathways, among others [90].

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