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BIOLOGIC THERAPY IN THE MANAGEMENT OF ASTHMA

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Abstract

Purpose—Current asthma management relies on inhaled corticosteroids, but some asthma is not well controlled with inhaled steroids alone or in combination with long-acting bronchodilators or leukotriene pathway inhibitors. The field of biologic therapy has grown dramatically in the past two decades, with current availability of three molecules, with two distinct, and highly selective approaches to interfering with the allergic and eosinophilic airway inflammation common to most asthma. This review summarizes current and future options for incorporating biologic therapy into the overall management of asthma.

Recent Findings—Two new biologic agents have recently come on the US market, supported by well-controlled, randomized clinical trials. These trials have provided insight into the types of patients who are most likely to benefit from these novel agents.

Summary—In asthma patients with frequent exacerbations, the addition of a biologic agent targeting the IL-5 pathway, or IgE, can significantly reduce exacerbations and improve asthma control. The clinical predictors of utility of specific agents overlap with one another, highlighting the importance of clinical judgment in the overall management of this complex disorder.

Keywords

Biologic therapy; omalizumab; mepolizumab; benralizumab; IL-4; IL-13; IL-17

Introduction

Asthma is a heterogeneous, chronic disease of the airways characterized by reversible airflow obstruction, bronchial hyperresponsiveness, airway inflammation and recurrent symptoms [1]. It is estimated that 300 million people worldwide have asthma, and the prevalence of disease has been increasing over the last 40 years [2]. The mainstay of asthma therapy is based on severity of disease and control of symptoms and relies on inhaled glucocorticoids (ICS) for patients with persistent disease or worse [1]. For the majority of

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patients, current treatment options offer good control of their disease, however 10–20% of patients do not achieve control with current gold standards of care [3, 4]. This remaining population of severe refractory asthmatics is at increased risk of morbidity and mortality related to their disease and make up the majority of economic costs of asthma [5–7].

Over the last decade, a shift towards evaluating specific phenotypes and endotypes of asthma has lead to the creation of targeted therapies to fit patient specific disease [4, 8–11]. Through a better understanding of the inflammatory modulators involved in asthma, a number of monoclonal antibodies have emerged with the aim of providing patient tailored asthma treatment.

Asthma pathogenesis

Asthma has traditionally been described as a Th2 lymphocyte mediated condition in which allergen presentation by antigen presenting cells to naïve T cells results in Th2 cell differentiation. The Th2 lymphocytes produce IL-4, IL-5, and IL-13 cytokines that then drive B cells to secrete immunoglobulin E. Mast cell bound IgE is able to bind allergens causing degranulation and release of chemical mediators such as histamine, prostaglandins, and leukotrienes, which induce smooth muscle bronchoconstriction and further stimulate the inflammatory response. IL-5 also acts as a potent regulator for eosinophil proliferation, differentiation, and activation [12]. Patients who have this allergic mediated phenotype generally respond well to inhaled corticosteroids. IgE, IL-4/13, and IL-5 have also been targets recently for the development of biologic agents as discussed below. However, there is a subset of patients with severe disease that do not respond well to ICS. These patients may have a Th-17 predominate disease with high levels of IL-17 leading to more neutrophil predominance and inflammation, less reversible airflow obstruction, and less bronchial hyper-responsiveness with methacholine challenge testing [12]. Another distinct group of asthmatics exists with normal levels of both eosinophils and neutrophils. Similar to neutrophilic asthma, this subset, paucigranulocytic asthma does not respond well to inhaled corticosteroids [13].

IgE

IgE is one of the key contributors to the proinflammatory cascade in allergic asthma. Allergens enter the airways and are presented by antigen presenting cells to T lymphocytes, which initiate the cell-mediated immune response [14]. Th2 cells and their associated cytokine milieu stimulate B cells to produce IgE antibodies and proallergic cytokines, such as IL-4, IL-5, IL-9, and IL-13. Free IgE released from B cells binds to the high affinity FCεRI receptor on the surface of mast cells and basophils. The receptor bound IgE is then cross-linked by an allergen and triggers degranulation and release of prostaglandins, leukotrienes, histamine, proteases, and cytokines which all lead to the early allergic response [15].

Omalizumab

Omalizumab was the first FDA approved biologic for the treatment of severe asthma. It is a humanized anti-IgE antibody that specifically binds the Fc portion of unbound IgE and

forms omalizumab:IgE complexes. This reduces free IgE levels and prevents IgE from binding to FCεRIs [16]. Without the binding of IgE to FCεRIs, there can be no degranulation of mast cells and the release of inflammatory mediators is inhibited. IgE also is responsible for regulating its own receptor and by reducing the levels of free IgE, omalizumab also deceases the expression of FCεRI [16].

Several large clinical trials involving adults, adolescents, and children have shown clinical benefit of treatment with omalizumab in patients with severe allergic asthma. Phase III studies involving these populations have demonstrated a reduction in the rate of asthma exacerbations compared to control or best standard of care [14, 17–23]. Bousquet et al pooled the data from seven of these studies and found an average reduction in asthma exacerbations of 38% in the omalizumab group compared to placebo [20]. This reduction in asthma exacerbations was also despite reduction in ICS doses. Several studies have shown the ability to reduce total daily steroid dose by 50% or greater in 72–79% of those receiving omalizumab versus 50–55% in placebo group [14, 17, 18]. Other studies have shown a reduction in rates of unscheduled outpatient visits, emergency department visits, and hospitalizations for exacerbations compared to placebo [20, 24, 25]. Since FDA approval has increased availability of omalizumab treatment to more patients, several “real-world” effectiveness studies including the PERSIST study and the eXperience study have been published that confirm the findings of earlier clinical trials. The PERSIST trial showed that after 1 year of treatment there was an 84% improvement in AQLQ (Juniper Asthma Related Quality of Life scale) and 65% were severe exacerbation free [26]. The eXperience study demonstrated similar results showing that the rate of clinically significant asthma exacerbations decreased by 54% at 12 months and 67% at 24 months. There was also a greater than 50% reduction in symptoms and rescue medication use from baseline and maintenance doses of oral corticosteroids decreased as treatment continued [27]. These studies also showed that patients receiving omalizumab had fewer hospitalizations, ED visits, and clinic visits [26, 27].

Omalizumab was designed to be long-term therapy and no specific guidelines have been established for duration of treatment. The INNOVATE trial examined the relationships among free IgE, omalizumab, and clinical outcomes. Once omalizumab is started, free IgE is very rapidly suppressed, however total symptom score, PEF, and rescue medication use does not reach their new equilibrium until 12 to 16 weeks. After treatment cessation, free IgE returns to baseline values 18 to 20 weeks after the last dose in the majority of patients. The return of this value back to baseline correlates with return of symptoms [28]. The XPORT trial was conducted to further evaluate omalizumab persistence after long-term therapy but data has not been published yet. A multicenter, retrospective study conducted in France showed discontinuation of omalizumab was not associated with any rebound effect or exacerbation of the disease and control was sustained at 6 months in nearly half of all patients [29].

Investigators have tried to identify markers in patients with moderate to severe persistent asthma that would predict the most beneficial response from omalizumab. Several groups have analyzed data from the INNOVATE trial and reported that total serum IgE and antigen specific-IgE are not predictive of response [30, 31]. Another group analyzed data from the

EXTRA trial evaluating the Th2 inflammatory biomarkers FE_{NO}, peripheral blood eosinophils, and serum periostin as potential targets to predict response. Hanania et al found that higher levels of these biomarkers were associated with greater response to anti-IgE therapy and reduced exacerbations, however the authors cautioned that additional studies are required to explore the value of these biomarkers in clinical practice [32].

A few studies have looked at the anti-inflammatory effects of omalizumab as well as the pathologic changes on airways. Djukanovic et al showed patients with mild steroid-naïve asthma who received omalizumab had a decrease in eosinophils, IgE+ cells, FcεRI+, IL-4 secreting cells, and CD3+ T lymphocytes within the epithelium and submucosa compared to those who received placebo [33]. This was supported by a study that showed omalizumab reduced the level of circulating T lymphocytes and eosinophils [34]. Hoshino et al showed omalizumab significantly reduced airway wall thickness relative to placebo [35].

Omalizumab is generally very well tolerated and overall incidence of adverse events with omalizumab is similar to that of the control group. The most common side effects in both adults and children were nasophayngitis, headache, upper respiratory infection, and sinusitis [36]. Omalizumab has a black box warning for anaphylaxis but occurs rarely. Anaphylaxis developed in 0.14% of patients compared to 0.07% in the placebo group and can occur anytime in the treatment course. There also has been increased interest recently in the possibility of increased risk in malignancy with omalizumab. Initial data from phase I to III clinical trials showed a numerical imbalance in the incidence of malignancy between placebo (0.18%) and omalizumab (0.5%) however the rate in the omalizumab group is comparable to that in the general population [36]. The EXCELS (The Epidemiologic Study of Xolair) study was a postmarketing prospective cohort study that was conducted to look at this issue further. Results did now show any increase in the risk of primary malignancy with long-term omalizumab [37]. Analysis of data from the EXCELS trial also noted an increased rate of transient ischemic attacks and ischemic stroke for those treated with omalizumab. This conclusion prompted the FDA to request a thorough analysis of arterial thromboembolic events (ATE) in all omalizumab studies but the pooled data did not support an increased risk of ATE with omalizumab [38].

IL-4/IL-13

IL-4 and IL-13, expressed by Th2 cells and mast cells, are key cytokines in the pathogenesis of atopic asthma. Redundancy in the IL4/IL-13 pathways results from the complex receptor system that shares IL-4 receptor α (IL-4Rα). Binding of this receptor mediates downstream signaling through signal transducer and activator of transcription factor 6 (STAT-6) leading to airway inflammation via eosinophil, macrophage and dendritic cell activation, airway remodeling via fibroblast proliferation and activation, B cell activation leading to IgE class switching, stimulation of airway epithelial and goblet cells leading to mucus secretion, and activation of airway smooth muscle cells resulting in airway hyperresponsiveness[39].

Lebrikizumab

Lebrikizumab is an IgG4 humanized monoclonal antibody that blocks IL-13. In a randomized, double-blind, placebo-controlled study in patients with poorly controlled

asthma despite ICS, lebrikizumab treatment was associated with improved lung function [40]. At 12 weeks, the mean FEV1 was 5.5% higher in the lebrikizumab group than in the placebo group. Interestingly, improvements in lung function were more marked in patients receiving lebrikizumab with a high pretreatment serum periostin levels compared to patients with low pretreatment periostin levels. Periostin is a matricellular protein secreted by bronchial epithelial cells in response to IL-13 [41, 42]. These results suggest that serum periostin may be an important serum biomarker for patients with IL-13-induced asthma and may help identify those patients that will be most responsive to anti-IL-13 treatment [43]. However, a more recent dose-ranging study, evaluating subcutaneous (SC) lebrikizumab at 125, 250, or 500 mg versus placebo in asthmatics not receiving ICS, found that although FEV1 increased in all lebrikizumab groups compared to placebo the increase was not statistically or clinically significant [44]. In addition, unlike previous studies there was no meaningful difference in FEV1 in patients with high serum periostin versus patients with low serum periostin. Further studies are needed to evaluate these findings.

Tralokinumab

Tralokinumab is a IgG4 monoclonal antibody to IL-13 that has been shown to inhibit bronchial hyperresponsiveness and airway eosinophilia in preclinical trials [45]. In a recent, phase II study in moderate to severe asthma, tralokinumab was associated with improved lung function as measured by FEV1 as well as decreased use of short acting beta agonists [46]. Interestingly, the increase in FEV1 was higher in the tralokinumab treated group with elevated sputum IL-13 when compared to patients with no sputum IL-13. In addition, the increase in FEV1 remained elevated for 12 weeks following tralokinumab cessation. The study did not however show any improvement in ACQ-6 (6-item Asthma Control Questionnaire) scores in the tralokinumab group compared to placebo. In general, tralokinumab was well tolerated with an acceptable safety profile.

Pitrakinra

Pitrakinra is a recombinant human IL-4 variant that competitively inhibits the IL-4Rα complex thus interfering with downstream signaling of both IL-4 and IL-13. In patients with atopic asthma, pitrakinra was shown to lessen the effects of the late asthmatic response after allergen challenge noted by more attenuated decreases in FEV1 in the pitrakinra treated group compared to placebo [47]. In a pharmacogenetic investigation of patients with moderate to severe asthma, patients with specific single nucleotide polymorphisms in the 3′ untranslated region of IL-4Rα had significantly reduced exacerbation rates when treated with pitrakinra 10 mg compared to placebo suggesting that this subgroup of patients may be more responsive to pitrakinra therapy [48].

Dupilumab

Another, IL-4Rα target is dupilumab, a fully human monoclonal antibody to the IL-4Rα subunit that inhibits the actions of both IL-4 and IL-13. In a randomized, double-blind, placebo-controlled phase 2A study, once weekly dupilumab 300 mg SC versus placebo significantly reduce asthma exacerbation in patients with moderate to severe asthma and elevated eosinophil levels [49]. In addition, dupilumab lead to marked improvement in FEV1, improvement in ACQ scores, decreased symptoms, nocturnal awakening and short

acting beta agonist usage. Moreover, dupilumab reduced biomarkers associated with Th-2 inflammation including FE_{NO}, eotaxin-3, TARC (thymus and activation-regulated chemokine), and serum IgE.

IL-5

As mentioned earlier, eosinophils are believed to play an important role in the pathogenesis and severity of asthma. Several studies have shown a reduction in acute exacerbations when sputum eosinophil counts were maintained at low levels by adjustments in inhaled corticosteroids [50–52]. IL-5 is a proinflammatory cytokine secreted by T lymphocytes, mast cells and eosinophils. It is heavily involved in the regulation of eosinophil differentiation, proliferation and activation [53]. For these reasons, targeting IL-5 as a therapeutic option in patients with eosinophilic asthma has been pursued.

Mepolizumab

Mepolizumab is a humanized monoclonal antibody against IL-5 that selectively inhibits eosinophilic inflammation and reduces the number of eosinophils in both sputum and blood [54, 55]. Despite showing reduction in blood and sputum eosinophilia, initial trials failed to show improvement in outcomes with mepolizumab in patients with asthma [54, 56]. However, more recent targeted studies have shown benefit in patients with a severe eosinophilic asthma phenotype. Nair et al evaluated the steroid sparing effect of mepolizumab in patients with sputum eosinophilia and airway symptoms despite treatment with prednisone and high dose ICS. In this small study, they found that mepolizumab, when compared to placebo, reduced the number of blood and sputum eosinophils and allowed prednisone sparing without the development of asthma exacerbations [57]. Mepolizumab therapy was also shown to reduce the number of exacerbations and improve AQLQ scores in patients with refractory eosinophilic asthma and a history of recurrent severe exacerbations despite high doses of corticosteroids [58].

The DREAM (Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma) study, a large, multicenter, double blind, placebo controlled study, investigated the effect of mepolizumab therapy on the rate of asthma exacerbations in patients with a history of recurrent severe asthma exacerbations and signs of eosinophilic inflammation. Over a year of treatment, mepolizumab reduced the rate of clinically significant exacerbations and was well tolerated in this population. Interestingly, the reduction in the rate of clinically significant exacerbations varied only according to baseline peripheral blood eosinophil count and exacerbation frequency in the previous year. In addition, IgE concentration and atopic status at baseline were not associated with response to mepolizumab [59].

More recently, the MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma) [60] and SIRIUS (Steroid Reduction with Mepolizumab Study) [61] studies have noted benefit with mepolizumab in patients with eosinophilic asthma. The MENSA study compared the rate of exacerbations in patients with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high doses of ICS in patients on intravenous (IV) or subcutaneous (SC) mepolizumab to placebo. When compared with placebo, the rate of exacerbations of patients receiving IV mepolizumab was reduced by 47% and 53% for SC

mepolizumab, and exacerbations requiring emergency room visits or hospitalization decreased by 32% for IV and 61% for SC mepolizumab. In addition, patients in both the IV and SC mepolizumab groups showed significant improvement in quality of life and asthma control as assessed by SGRQ (St. George's Respiratory Questionnaire) and ACQ-5 (5-item Asthma Control Questionnaire). The SIRIUS study evaluated the steroid sparing effects of mepolizumab compared to placebo in patients with severe asthma and peripheral blood eosinophilia while on maintenance systemic glucocorticoids and found that the likelihood of a reduction in glucocorticoid-dose was 2.39 times greater in the mepolizumab group than placebo with the median percentage reduction in glucocorticoid dose being 50%. In addition, despite being on lower doses of glucocorticoids the mepolizumab group had reduced exacerbation rates and improved asthma control. Taken together, these studies further support evidence showing the effectiveness of mepolizumab in patients with a severe eosinophilic asthma phenotype.

It is important to note that cessation of mepolizumab therapy resulted in return of pretreatment blood and sputum eosinophilia levels within 3 months of cessation and was associated with a loss of asthma control as patients were back to pretreatment exacerbation levels within 3–6 months of cessation of therapy [62]. In addition, despite promising data related to decreased exacerbation rates in patients with severe eosinophilic asthma, in the majority of studies mepolizumab fails to show a significant effect on more traditional markers of asthma control, like FEV1, PEF (peak expiratory flow), airway hyperresponsiveness (AHR), AQLQ, ACQ [63].

Mepolizumab, under the trade name Nucala, has recently received FDA approval for add-on maintenance treatment of patients 12 years and older with severe asthma and an eosinophilic phenotype.

Reslizumab

Reslizumab, an alternative humanized monoclonal IL-5 antibody, neutralizes circulating IL-5 by preventing its binding to eosinophils. Castro et al evaluated the effectiveness of reslizumab in patients with eosinophilic asthma poorly controlled on high dose ICS over a 15-week protocol [64]. Compared to placebo, patients receiving reslizumab showed significant improvements in airway function and a trend toward greater asthma control as measured by ACQ score. Interestingly, these effects were most pronounced in patients with asthma and nasal polyps—an eosinophil mediated disorder. More recently, the results of two duplicate, multicenter, double blind placebo controlled phase III studies showed efficacy for the use of reslizumab for patients with asthma and eosinophilia who are poorly controlled on ICS therapy [65]. In these studies, reslizumab when compared to placebo significantly reduced the frequency of asthma exacerbation rate. Reslizumab, under the trade name CINQAIR, recently received FDA approval for add-on maintenance treatment of patients with severe asthma 18 years and older with an eosinophilic phenotype.

Benralizumab

Benralizumab is a humanized afucosylated monoclonal antibody that targets the human IL-5 receptor alpha (IL5Rα) found on eosinophils and basophils. In vitro, the lack of a fucose

moiety on the oligosaccharide core improves binding affinity of benralizumab and enhances antibody-dependent cell-mediated cytotoxicity leading to apoptosis of target cells [66]. In an initial study evaluating patients with mild atopic asthma, a single IV dose of benralizumab was found to decrease peripheral blood eosinophil counts [67]. Subsequently, in a phase I trial evaluating the safety of benralizumab and its effects on eosinophil counts in patients with eosinophilic asthma showed benralizumab was safe and reduced eosinophil counts in airway mucosa, sputum, bone marrow and peripheral blood [68]. More recently, a year-long phase 2b dose-ranging study found that benralizumab 100 mg tended to reduce exacerbations and improve lung function and quality of life in patients with uncontrolled, eosinophilic asthma [69]. Improvements in exacerbation rate, FEV1, and ACQ-6 scores were noted specifically for patients with increased blood eosinophil counts compared to patients without peripheral eosinophilia suggesting blood eosinophil counts may be helpful in identifying those patients who will respond best to benralizumab therapy. Further, evaluation and confirmation of these initial promising data are underway in ongoing phase 3 studies.

Taken together, these three drugs targeting IL-5 show the effects of IL-5 inhibition on eosinophilic inflammation and exacerbations in asthma.

IL-17

Th17 cells are a subset of CD4+ T cells associated with a more severe phenotype of asthma that is less responsive to corticosteroids and are responsible for secreting the cytokines IL-17A, IL-17F, IL-22, and IL-21. Studies have demonstrated increased levels of Il-17A, IL-17F, and IL-22 in the bronchoalveolar lavage (BAL) fluid and bronchial biopsies of patients with moderate and severe asthma [70]. IL-17A, IL-17F, and IL-22 have all been implicated in causing increased neutrophilic airway inflammation, mucous cell metaplasia, and smooth muscle proliferation [71, 72].

Secukinumab and Brodalumab

Biologic agents targeting IL-17A or IL-17RA signaling are currently in clinical trials for asthma. Secukinumab is a monoclonal antibody targeted at IL-17A and has shown a reduction in clinical symptoms in other Th17-mediated diseases such as psoriasis and rheumatoid arthritis. A Phase II clinical trial has been completed involving patients with uncontrolled asthma but results are not yet available. Brodalumab, a monoclonal antibody directed against IL-17RA, was recently tested in a phase II clinical trial for patients with moderate-to-severe asthma using change in Asthma Quality Control (AQC score) as the primary outcome. Results showed no difference in the AQC score between those treated with brodalumab and those who received placebo however a clinically meaningful response was seen in bronchodilator reversibility [71–73].

Conclusion

Asthma is a complex disease afflicting millions worldwide and is associated with a significant financial healthcare burden. As we have developed a better understanding of the inflammatory markers involved in the disease and the various phenotypes and endotypes of asthmatics, biologic agents, like the ones described in this review, present new therapeutic

options for the treatment of severe disease (Table 1). Biologic agents are promising as they allow for the specific inhibition of relevant asthma pathways, have a long duration of action allowing for infrequent dosing schedules, have generally good safety profiles with few off-target effects, and provide a means to accomplish personalized treatment. Although promising, there is significant cost associated with these agents. In addition, as they only offer specific inhibition of particular asthma pathways, their spectrum of efficacy is narrower than standard therapy and does not address all the objectives of asthma management possibly necessitating predictive biomarkers for practical implementation. Despite some of these disadvantages, biologic agents have significant promise for the treatment of refractory asthma and further investigation into their therapeutic benefits is warranted.

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KEY POINTS

- Biologic agents for asthma treatment provide targeted therapy for patients with specific asthma phenotypes.
- Ongoing clinical trials are evaluating new biologic agents to help broaden the current arsenal of asthma treatment options.
- Currently omalizumab, mepolizumab and reslizumab are the only FDA approved monoclonal antibodies available for the treatment of asthma.
- Despite significant costs related to these agents, the benefits of reduced exacerbations, reduced steroid burden, and the potential for decreased healthcare utilization are encouraging.

Table 1

Biologic Agents and Their Targets

Target	Treatment	Stage of Development
IgE	Omalizumab	Marketed
IL-5	Mepolizumab Reslizumab	Marketed
IL-5R	Benralizumab	Phase III
IL-4Rα (IL-4/IL-13)	Dupilumab Pitrakinra	Phase III Phase II
IL-13	Lebrikizumab Tralokinumab	Phase III Phase III
IL-17	Secukinumab Brodalumab	Phase II Phase II