



IgE and eosinophils as therapeutic targets in asthma

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Purpose of review

Asthma is a chronic inflammatory disorder characterized by reversible airflow obstruction, which is being more widely recognized as a broad-spectrum disease that encompasses multiple patient characteristics and pathophysiologic mechanisms. Suboptimal asthma control leads to increasing burden of healthcare costs and loss of productivity to society. Biologic therapies targeted at IgE and eosinophils can be used in poorly controlled allergic and eosinophilic asthma, respectively. The purpose of this review is to analyze the advancements in currently available biologic therapies targeted at IgE and eosinophils in asthma and to identify how these therapies may impact overall healthcare costs.

Recent findings

Omalizumab is an anti-IgE antibody that is approved for use of poorly controlled moderate-to-severe asthma. Many studies have confirmed that omalizumab not only improves quality of life and symptom scores, but also decreases urgent care and emergency department visits and hospitalizations. Dupilumab is a biologic agent targeted at Th2 cytokines, but indirectly impacts IgE and is an important biologic agent for atopic disease. Mepolizumab, reslizumab, and benralizumab target IL-5, a key cytokine for eosinophils. For patients with poorly controlled eosinophilic asthma, these biologic agents improve asthma symptoms, reduce exacerbations, and reduce emergency visits and hospitalizations.

Summary

Poorly controlled severe asthma affects a small portion of patients with asthma in the United States and yet it accounts for large portion of healthcare utilization. Biological therapies in poorly controlled severe persistent asthma have been identified to reduce healthcare utilization, including emergency visits and hospitalizations. Biologic agents have a clear beneficial role in the management of severe asthma, and further evaluations should be continued in identifying optimal patient characteristics for the various agents and overall benefit toward healthcare utilization and cost.

Keywords

biologic targets in asthma, eosinophils, IgE, severe asthma

INTRODUCTION

Asthma is a chronic inflammatory disorder characterized by reversible airflow obstruction. As of 2014, over 24 million individuals were living with asthma in the United States [1]. Approximately 1.3–4.6 million asthmatic individuals have poorly controlled asthma, despite the use of daily controller medications [2]. Suboptimal asthma control leads to not only increasing healthcare costs, but also loss of productivity to society in terms of missed work and school days. Children with one or more asthma exacerbations in the previous 12 months, missed a total of 10.5 million school days in 2008 [3]. The total cost of medical expenditures for asthma in adults in the United States was \$18 billion in 2008 [4]. Patients with severe or difficult-to-treat

asthma cost over twice as much as controlled patients to the healthcare system [5,6].

Over recent years, asthma is being more widely recognized as a broad spectrum that encompasses multiple patient characteristics and pathophysiologic mechanisms, defined as phenotypes, rather than a single underlying disorder. Although asthma phenotypes are still being defined, certain

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KEY POINTS

- Poorly controlled severe asthma encompasses a small proportion of asthma patients in the United States, however, contributes to a large portion of healthcare utilization and cost.
- Asthma is a broad spectrum of disease that comprises multiple patient characteristics and pathophysiologic mechanisms, which can be identified to develop targeted therapies.
- Use of biologic agents targeted at IgE and eosinophils in patients with poorly controlled moderate-to-severe asthma have resulted in improvement in patient symptoms and quality of life. Additionally, these agents have reduced exacerbation rates, emergency visits, and hospitalizations.
- Further analysis into the true cost-effective nature of these biologic therapies needs to be investigated.

characteristics of asthma are well known and can be used to create targeted therapies. Overall, the goal of asthma therapy is to reduce impairment and risk by preventing chronic symptoms, decreasing use of short-acting β -2-agonists, maintaining activity levels, preventing loss of lung function, preventing exacerbations, and minimizing emergency care and hospitalizations [7]. These goals are particularly important when considering the extensive cost and burden severe asthmatic patients suffer due to the inability to appropriately control their asthma. With the use of targeted biologic therapies to IgE and eosinophils currently available, there is great potential to help improve control in patients with severe asthma, and thereby reduce the overall burden of emergency visits, hospitalizations, and missed work and school days. In this review, we focus on the current biologic treatments available to create targeted therapies for patients with severe asthma and discuss the potential impact these medications may provide to asthma management.

Asthma pathophysiology and phenotypes

Asthma is a very complex, heterogeneous disorder. Subclasses of asthma have been identified using cluster analysis of patient characteristics and cytokine profiles, leading to the concept of patient directed therapy [8–10]. Two of the several identified phenotypes include atopic asthma and nonatopic asthma, the latter characterized by later onset of disease and inhaled corticosteroid (ICS) resistance. These phenotypes of asthma are likely to respond well to biologic therapies targeted at IgE and eosinophils when standard therapies do not yield adequate asthma control.

Mild-to-moderate atopic asthma and nonallergic asthma has been associated with allergen exposure and typically presents with elevated IgE levels [11,12]. When respiratory mucosal surfaces are exposed to allergen, dendritic cells play a key role in initiating and maintaining T helper 2 (Th2) responses to the inhaled allergen [10,13,14]. Initiation of Th2 response leads to the secretion of IL-4, IL-5, IL-13, and other cytokines. IL-4 binds to receptor IL-4R α leading to dimerization with IL-2R γ component. Alternatively, IL-4R α can form a receptor complex with IL-13 bound to IL-13 receptor α 1 [15]. Either of these receptor complexes leads to the activation of signal transducer and STAT6, which can then bind to target genes. In addition to IL-4 stimulating continued differentiation of Th2 cells, it also promotes B-cell class switch to IgE synthesis [15]. Allergens that bind IgE bound to mast cells and basophils then cause degranulation and release of mediators, such as histamine, prostaglandins, and leukotrienes, furthering the inflammatory response and causing airway smooth muscle contraction. In severe asthma, IL-13 is also believed to regulate airway hyper-reactivity [16,17]. Patients with atopic asthma are associated with elevations in IgE and respond well to ICS and anti-IgE therapies.

Th2 cells also lead to secretion of IL-5 and IL-33, among other cytokines, which leads to stimulation of eosinophils, basophils, and mast cells. Nonatopic asthmatic individuals typically have a delayed presentation of disease, an eosinophilic predominance, and are occasionally associated with nasal polyposis [15]. These patients also have a higher incidence of ICS resistance, but are responsive to systemic steroids and anti-IL-5 therapies [15]. IL-33 promotes naïve T-cell differentiation into Th2 cells causing IL-5 secretion [18]. When IL-5 binds receptor IL-5R α leading to the recruitment of β c chain leading to the formation of a receptor complex, that causes alteration of gene expression, which induces the growth, survival and activation of eosinophils [15,19]. Upon activation, eosinophils then release multiple mediators, such as leukotrienes and thromboxane, causing further inflammation [20]. Additionally, eosinophils release major basic protein and eosinophil cationic protein, which are tissue-damaging proteins [21]. Overall, the release of these mediators leads to bronchoconstriction, bronchial hyperresponsiveness, and airway remodeling [22–25]. IL-33 also plays a crucial role in chronic inflammation and airway remodeling in asthma [26].

Current mainstays of asthma therapy include short-acting β -agonists for intermittent asthma and either single or combination therapy of ICS, long-acting β -agonists (LABA) and leukotriene modifiers for more persistent asthma with short-acting

β -agonists as rescue [27]. Most patients respond to this course of therapy; however, a small proportion of patients, especially those with severe persistent asthma, continue to have frequent exacerbations. These patients do however respond to biologic agents targeted at IgE and eosinophils via IL-5 [28].

IgE AS THERAPEUTIC TARGET IN ATOPIC ASTHMA

Omalizumab

Omalizumab is an anti-IgE monoclonal antibody that is approved for the use in patients older than 12 years of age with moderate-to-severe persistent asthma that is uncontrolled with ICS therapy. It is the first biologic therapy that was US Food and Drug Administration (FDA) approved for use in asthma. Omalizumab's structure allows it to inhibit IgE interactions for both the high and low affinity IgE receptors [29²²]. Additionally, due to homeostatic mechanisms, omalizumab causes dissociation of high-affinity IgE receptors from IgE [29²²]. Many trials have demonstrated reductions in asthma exacerbations and improved asthma control with the use of omalizumab.

The benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE (INNOVATE trial) examined the effect of omalizumab in severe persistent asthma patients who were inadequately controlled despite high-dose ICS and LABA therapy. This trial was a randomized, double-blind, placebo-controlled trial over 28 weeks and resulted in a 26% decrease in asthma exacerbations in the omalizumab group during this time [30]. Additionally, omalizumab has been found to improve quality-of-life and symptom scores [30,31]. Other initial trials also revealed that in moderate-to-severe asthmatic individuals omalizumab has been shown to reduce urgent care and emergency department visits and hospitalizations and decreases requirements of corticosteroid and other medications, including rescue medications [32–34].

In the omalizumab in severe allergic asthma inadequately controlled with standard therapy (EXTRA trial) study Hanania *et al.* [35] performed a prospective, multicenter, randomized, double-blind, placebo-controlled trial revealing that patients with severe asthma on combination ICS and LABA therapy who received omalizumab had a relative reduction of exacerbations by approximately 25%. They also experienced decreased use of rescue inhaler, and overall improved symptoms and quality-of-life scores. Further evaluations of the EXTRA study revealed that omalizumab had a greater effect on percentage reduction of

exacerbations in patients with higher levels of biomarkers, including fractional exhaled nitric oxide (FeNO), peripheral blood eosinophil count and serum periostin. It is speculated that these high-biomarker subgroups likely have greater risk of exacerbations compared with the low-biomarker subgroups [36].

Selecting patients who are ideal candidates for omalizumab is the key component to achieving maximal benefit from omalizumab. Investigators have analyzed the data from the INNOVATE trial but have not been able to correlate either serum total or specific IgE as a predictive marker for omalizumab response [37,38]. Clinically significant benefit may not be noted from omalizumab until after 3 months of treatment, and therefore patients should be re-evaluated after 16 weeks of therapy to ensure patient improvement and assessment of treatment continuation [39]. The eXpErience study was a 2-year observational registry that evaluated the effectiveness and safety of omalizumab in patients with uncontrolled, persistent allergic-type asthma. Variables that were assessed included exacerbation rate, symptoms, rescue medication use and oral corticosteroid use. A greater than 50% reduction in symptoms and use of rescue medication was observed at 24 months. Oral corticosteroid use was also reduced and no significant adverse events were reported. This study [40] confirmed the findings of previous clinical trials regarding the safety and efficacy of omalizumab therapy in poorly controlled allergic asthma patients, under 'real-life' settings.

Cases do arise where patients exceed dosing guidelines for total IgE and body weight. A review of patients in the Australian Xolair Registry revealed that patients with severe persistent allergic asthma who exceeded recommended dosing for IgE (30–1500 IU/ml) and body weight (30–150 kg) criteria for omalizumab were found to have significant improvements in symptom control, quality of life, and forced expiratory volume in 1 second (FEV₁) compared with patients within recommended ranges. For these patients who exceed recommended dosing guidelines, dose escalation was not required beyond 750 mg/month to achieve improvement in asthma [41].

Omalizumab therapy has also been found to be beneficial in children. Over a 24-week period, Lanier *et al.* [42] found that omalizumab significantly reduced asthma exacerbations by 31% and over 52 weeks by 43% compared with placebo in children 6–less than 12 years of age with moderate-to-severe persistent, allergic asthma. A study of omalizumab on inner-city children, adolescents, and young adults was performed by Busse *et al.* [43], the inner-city anti-IgE therapy for asthma (ICATA) study, which revealed that these patients had significant improvements in asthma control with the

use of omalizumab. Patients in this study experienced significant improvements in seasonal peaks of exacerbations and decreased the requirements for other controller medications. Adding omalizumab to these patients with allergic asthma not only showed a reduction in symptoms but also resulted in fewer hospitalizations: 1.5% in the omalizumab group compared with 6.3% in the placebo group.

Treatment with omalizumab has been found to be overall well tolerated [30,34]. There have been rare reports of anaphylactic reactions (0.1% of patients) with the use of omalizumab [39]. However, health professionals should be aware of a possible association of omalizumab and serious cardiovascular/cerebrovascular events. An observational study from epidemiologic study of xolair (omalizumab): evaluating clinical effectiveness and long-term safety in patients with moderate to severe asthma (EXCELS trial) evaluated for potential cardiovascular or cerebrovascular risk with use of omalizumab in patients greater than 12 years of age with moderate-to-severe asthma compared with a similar cohort of patients not on omalizumab therapy. A higher rate of cardiovascular and cerebrovascular events was noted in the omalizumab group, although the rate of severe asthma was significantly greater in the omalizumab group [44].

Slavin *et al.* [45] in the United Kingdom reported that free IgE was rapidly reduced (<50 ng/mL) on omalizumab, and this correlated well with symptom control. After treatment cessation, IgE levels returned to baseline and there was a delay in return of asthma symptoms. However, a retrospective study [46] performed in France revealed that omalizumab discontinuation was not associated with any rebound symptoms or exacerbations of asthma, and in about half of the patients asthma control was maintained up to 6 months after discontinuation.

Overall, omalizumab is very promising for add-on therapy in moderate-to-severe persistent, allergic-type asthma. It is generally well tolerated and reductions in asthma exacerbations are significant. The overall improvement in symptoms also leads to decreased healthcare utilization, by marked reductions in emergency department visits and hospital admissions.

Dupilumab

Dupilumab is a human monoclonal antibody to IL-4 receptor α , inhibiting binding and downstream signaling of both IL-4 and IL-13, and thereby indirectly inhibiting the production of IgE by preventing B-cell IgE class switch. Although dupilumab is traditionally known as a Th2 cytokine pathway modulator, we describe dupilumab here as a modulator of IgE, as

it indirectly affects IgE production. Wenzel *et al.* [47] evaluated the efficacy and safety of dupilumab in moderate-to-severe persistent asthma in patients with elevated eosinophil levels (blood eosinophil level ≥ 300 cells/ μ L or sputum eosinophils of 3%) and currently on ICS and LABA therapy. Throughout the trial, all patients were taken off of their LABA and tapered off of ICS medications, and patients on dupilumab were found to have significantly fewer exacerbations and better control of severe persistent asthma compared with placebo. There were also improvements in lung function and asthma control with use of dupilumab. This study also revealed that dupilumab reduced serum IgE levels in the treatment group and also other biomarkers of Th2 inflammation, including FE_{NO}, eotaxin-3, and thymus and activation-regulated chemokine (TARC). A more recent phase IIB trial by Wenzel *et al.* [48^{***}] looked at the efficacy of dupilumab in patients with uncontrolled, persistent asthma on ICS along with LABA therapy as add-on therapy, irrespective of their baseline eosinophil counts. This trial revealed significant increases and lung function and reductions in exacerbations in patients treated with dupilumab, irrespective of patients' baseline eosinophil levels. The most common adverse events with dupilumab include injection-site reactions, upper respiratory tract infections, nasopharyngitis, nausea, and headache [47,48^{***}]. Although dupilumab does not directly affect IgE function, it does reduce IgE production and therefore may play a key role in atopic asthma treatment. Dupilumab is not currently FDA approved for asthma, but is continuing to undergo clinical trials.

IL-5 AS THERAPEUTIC TARGET IN EOSINOPHILIC ASTHMA

Eosinophils are known to play a key role in the manifestations of asthma, including airway remodeling. Eosinophilic asthma phenotype is characterized with the persistent presence of eosinophils in lung and sputum. Previous studies [49–51] reveal that management directed at reduction of sputum eosinophil counts with the use of ICS has reduced asthma exacerbations and admissions. IL-5 is a key cytokine required for the development, recruitment and activation of eosinophils [19]. Inhibiting IL-5 has proven to not only reduce blood and sputum eosinophils, but also has a steroid-sparing effect in the management of asthma [52–54]. However, patients in initial studies [52,53,55] were not specifically selected for eosinophilic asthma; therefore, results did not reveal any reduction in the signs or symptoms of asthma. There are currently two monoclonal antibodies targeting the IL-5 pathway that have been approved by the US FDA for

eosinophilic asthma: mepolizumab and reslizumab. Benralizumab is currently under development.

Mepolizumab

Mepolizumab is a humanized anti-IL-5 antibody, thereby blocking the binding of IL-5 cytokine to IL-5 receptor complex on eosinophil cell surface [55]. Initial studies [52,53,55] revealed reductions in blood and sputum eosinophils with use mepolizumab, but did not yield any significant clinical improvements, including lung function or symptom scores. However, in later studies, patients were selected for eosinophilic asthma. In these studies [54,56], use of mepolizumab not only reduced blood and sputum eosinophil levels, but also reduced exacerbation frequency. There were also reports of improvements in the asthma quality-of-life questionnaire (AQLQ) scores. However, there were no improvements in overall symptoms, FEV₁, or airway hyper-responsiveness [56].

The 'Dose Ranging Efficacy And safety with Mepolizumab' DREAM trial was the largest randomized, double-blind, placebo-controlled trial that focused on establishing the efficacy, safety and response to treatment with mepolizumab [57]. In total, 621 patients were randomized to placebo and three treatment groups of varying doses, 75, 250, and 750 mg, with the primary outcome focusing on frequency of asthma exacerbations over a 12-month period. Mepolizumab reduced the number of asthma exacerbations in eosinophilic asthma patients compared with placebo in all dosage groups. Reductions in blood and sputum eosinophils were also dose responsive. Percentage reduction in exacerbations between the three treatment groups were 48% for 75 mg, 39% for 250 mg, and 52% for 750 mg of mepolizumab. The overall number of exacerbations requiring admission or emergency room visit was also reduced with use of mepolizumab. Additionally, this study confirmed previous reports that mepolizumab was overall well tolerated without any serious adverse effects [52,53,55,56]. The most frequently reported adverse effects were headaches, nasopharyngitis, and infusion-related nonallergic reactions [57]. Unfortunately, the DREAM trial noted no significant difference in FEV₁ or AQLQ scores.

In the 'Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma' MENSA trial, Ortega *et al.* [58] confirmed the approximately 50% reduction in exacerbations, which was similar to both intravenous and subcutaneous routes of mepolizumab administration. Exacerbations requiring emergency department visits or hospital admissions were also reduced by 32–61%. Additionally, this trial reported that both intravenous and

subcutaneous routes of administration were not only effective, but also had limited adverse effects.

The steroid reduction with mepolizumab study (SIRIUS) confirmed the findings of a previously smaller trial evaluating the significant reduction in oral glucocorticoid dose with the use of mepolizumab [54,59]. In the SIRIUS trial, patients requiring daily oral glucocorticoid therapy were randomized into placebo and mepolizumab treatment groups. The mepolizumab group had significantly more reductions in the oral glucocorticoid dose, in addition to reductions in exacerbations and overall improvement in asthma control. Reducing oral steroid use is a key goal in patients with oral steroid responsive asthma, as the long-term adverse effects of glucocorticoids can be quite detrimental to patients' overall health.

Post-hoc analysis from the MENSA and SIRIUS trial revealed an overall 47% reduction in asthma exacerbation rate that was calculated versus placebo. There was up to a 52% reduction in the exacerbation rate in patients with eosinophil counts at least 150 cells/ μ l and 70% in patients with eosinophil counts at least 500 cells/ μ l. Predicted efficacy of mepolizumab was reduced in patients with baseline eosinophil counts of 150 cells/ μ l or less [60]. Other analyses also revealed that patients with eosinophilic asthma responded to mepolizumab, regardless of previous treatment with omalizumab [61[¶]]. However, within 3 months of cessation of mepolizumab, Halder *et al.* [62] found that eosinophil blood and sputum counts increased back to pretreatment levels. This increase was also associated with return of increased frequency of asthma exacerbations, and ultimately asthma control. Additionally, a meta-analysis of patients with severe eosinophilic asthma found that the use of mepolizumab in addition to standard treatment resulted in a 45% reduction in exacerbations requiring hospitalization when compared with placebo [63[¶]].

Overall, mepolizumab has the potential to reduce exacerbations of severe eosinophilic asthma by about 50%, and reduces levels of blood and sputum eosinophils and improves the AQLQ scores. However, mepolizumab fails to show statistically significant improvements in lung function [28,64].

Reslizumab

Reslizumab is an anti-IL-5 antibody that neutralizes circulating IL-5, thereby preventing binding to eosinophils. It is currently approved for the use of eosinophilic asthma for patients over the age of 18. Castro *et al.* [65] showed that patients with eosinophilic asthma phenotype, uncontrolled on high-dose ICS, greatly benefited with improvements

in lung function and reductions in blood and sputum eosinophil counts on reslizumab. Use of reslizumab revealed improvements in lung function and asthma control, especially in patients with severe eosinophilic asthma and nasal polyposis. Reslizumab has also been well tolerated through these studies, with nasopharyngitis being the most frequently occurring adverse symptom [65]. Recently performed follow-up trials by Castro *et al.* further assessed the efficacy and safety of reslizumab in poorly controlled moderate-to-severe asthmatic individuals. These duplicate, multicenter, double-blind, placebo-controlled phase III trials enrolled over 900 patients and revealed that patients receiving reslizumab had significant reductions in the frequency of asthma exacerbations [66]. This study revealed about 40–67% of patients receiving reslizumab had an adverse effect of worsening asthma symptoms and 11–19% having nasopharyngitis. There were also reports of two patients with anaphylactic reactions. Reslizumab is currently FDA approved for patients 18 years or older as add-on therapy for severe, eosinophilic-type asthma.

Benralizumab

Benralizumab is an anti-IL-5 receptor α antibody that targets blood and airway eosinophils in patients with uncontrolled eosinophilic asthma. A phase IIb dose-ranging study revealed that, in patients with eosinophilic asthma, there was a reduction in asthma exacerbations at the dose of 100 mg. Additionally, those patients with blood eosinophil levels of at least 300 cells/ μ l had lower exacerbation rates on benralizumab therapy [67]. In a recent double-blind, placebo-controlled trial benralizumab was found to reduce asthma exacerbations by 49% in patients treated with benralizumab as add-on therapy [68]. In several studies [69–71], benralizumab has reduced eosinophil counts in either the airway, sputum, bone marrow, or blood.

The most common adverse effects reported were nasopharyngitis and injection-site reactions in the benralizumab group. Other reported adverse effects include reductions in white blood cell counts and increased blood creatine phosphokinase [69]. The efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting- β 2-agonists (SIROCCO trial), which was a randomized, multicenter, placebo-controlled, phase III trial, confirmed previous findings regarding the efficacy and safety of benralizumab. The study [72] found that benralizumab reduced annual asthma exacerbations and improved lung function when dosed every 4 or 8 weeks, and the most common adverse events

reported included worsening asthma (13% in benralizumab-treated patients, compared with 19% in placebo-controlled patients) and nasopharyngitis (12% in both benralizumab-treated group and placebo-controlled group). The benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA trial), a randomized, multicenter, double-blind, placebo-controlled phase III trial, evaluated the use of benralizumab as add-on therapy over 56 weeks, and results from this trial confirmed findings of previous studies. Patients with add-on therapy with benralizumab were noted to have a significantly lower exacerbation rate and improved FEV₁. Additionally, the most common adverse event was nasopharyngitis (18–21% in the benralizumab groups versus 21% in the placebo group) [73]. Benralizumab is an intravenous medication awaiting FDA approval in the treatment of eosinophilic asthma.

CONCLUSION

Severe asthma affects only a small proportion of the patients with asthma in the United States, yet it accounts for significantly greater healthcare utilization and cost. Glucocorticoids are standard therapy for severe asthma, but many patients also experience resistance to glucocorticoids. More recently with the increased availability of immunomodulatory medications, there has been a shift to consider the use of biologics as add-on therapy in those patients with severe persistent asthma with underlying atopic and eosinophilic disease [7]. In these patients, targeting underlying pathogenesis of IgE production and eosinophil proliferation and activation has been beneficial in attaining asthma control. The 2016 Gina guidelines recommend that biologic agents be used as the ultimate add-on step for severe persistent asthma. The use of omalizumab for allergic asthma and mepolizumab for eosinophilic asthma should be considered when standard therapy does not provide optimal control of asthma [74]. However, it should also be noted that these latest guidelines have not included the use of FDA approved reslizumab. Through the development and use of biologic agents targeted at the role of IgE and eosinophils in asthma, there is a greater chance for improved asthma control and ultimately reductions in healthcare utilization and cost.

Evaluation of applicability of omalizumab therapy to patients with moderate-to-severe asthma that is poorly controlled on standard therapy reveals that the patients treated with addition of omalizumab had significantly lower use of systemic steroids, unscheduled healthcare visits, and fewer missed

school and work days [75]. These data suggest that use of biologic therapy not only improves overall control of asthma, but thereby also reduces health-care utilization and improves patient productivity by reducing missed work and school days. If similar studies are performed with other biologics, then we speculate that similar results will be found. However, use of many biologic agents is limited by high cost, so further consideration needs to be placed on cost-effective analysis. In an analysis performed in the United Kingdom, a cost-benefit was seen in patients with severe asthma who were treated with omalizumab, especially when factoring in asthma mortality and improvements in asthma quality of life [76]. In a cost-effective analysis in Japan, omalizumab was found to be cost-effective in children with severe asthma, as those children treated with omalizumab experienced a significantly increased number of hospital-free days, which over a 2-year period outweighed the medical cost of the drug [77]. Further evaluation into cost-effective analysis should be considered not only with omalizumab but with other biologics as well.

As more biologic therapies become readily available and more patients are identified for use of these medications, it will be imperative for us to consider the true cost-effective approach with the use of these biologic medications. Through these types of studies further analysis may yield more information in identifying which types of patients are likely to benefit the greatest with each biologic agent available for the treatment of asthma. Creating this individualized approach may be a key factor in maximizing asthma control and ultimately health-care utilization and costs.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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