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Perspectives

What is the current role of biologics in the management of patients with severe refractory asthma?

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Approximately 300 million people worldwide have asthma, with the number of affected individuals projected to continue to increase during the next decade.[1] Current asthma therapy guidelines indicate a stepwise approach to asthma treatment.[2] Although a significant number of patients may be able to achieve control with guideline-based therapy, as many as 50% of patients with asthma may continue to have uncontrolled asthma despite intervention.[3] Furthermore, 20% to 30% of patients with asthma may not achieve complete control despite undergoing combination high-dose inhaled corticosteroid (ICS) and long-acting β-agonist (LABA) therapy.[4] A common consequence of uncontrolled asthma is the potential for requiring oral corticosteroid therapy. Unfortunately, oral corticosteroids can result in a number of adverse effects, including higher risks of infectious, cardiovascular, metabolic, gastrointestinal, and ocular disease.[5] Furthermore, some patients with severe uncontrolled asthma may not even clinically respond to prednisone.[6]

The reasons for failure of attaining control among patients with asthma include underlying comorbidities, difficulties with adherence to prescribed therapy, and a patient's underlying phenotype and genotype. Active smoking status, allergies, psychiatric conditions, and low socioeconomic status are common comorbidities that contribute to exacerbations and complicate the treatment of patients with asthma.[7,8] Lack of control in patients with asthma is further confounded by inappropriate inhaler technique or poor adherence to medical therapy, which combined have been detected in up to as many as 50% of patients with asthma.[9,10] Ultimately, in patients with uncontrolled asthma, physicians are responsible to reconfirm the diagnosis objectively, ensure adherence, review inhaler technique, and treat confounding comorbidities before diagnosing the patient as having severe refractory asthma. Unfortunately, a significant subset of patients with severe uncontrolled asthma remains despite appropriate care and the use of recommended therapies.

The lack of uniform response to therapy among patients with asthma reinforces that asthma is actually a heterogeneous disorder within which there are subpopulations. It follows that anticipated response to individual therapy varies, depending on unique phenotypes and endotypes.[6] Unfortunately, current and prior descriptions of specific phenotypes remain highly subjective and difficult to correlate clinically. Initial categorizations included late-onset eosinophilic asthma, late-onset obese asthma, and neutrophilic asthma, among others.[11] More recent classifications have focused on placing patients with severe asthma into high and low T_H2 groupings because these have direct relevance to anticipated response to newer biologic therapies.[12,13]

It is clear that additional therapeutic options are necessary because, despite adherence to guideline therapy, a significant number of patients continue to have uncontrolled asthma. However, the advent of new therapies comes with a significant economic cost. It is becoming increasingly imperative to identify biomarkers or other indicators that enable targeted selection of therapy on an individual basis. We present here a clinical perspective aimed at providing a practical insight into therapeutic options for the treatment of severe refractory asthma. Our goal is not to discuss all developing therapies in detail but rather to attempt to provide guidance on how best to use new biologic therapies. A summary of available data can be found in Table 1 with further discussion below.

Anti–Tumor Necrosis Factor α

Tumor necrosis factor α (TNF-α) is a known proinflammatory cytokine typically associated with a T_H1 response. However, elevated levels of TNF-α have been found in bronchial biopsy specimens and the induced sputum of patients with severe asthma.[29] Inhalation of TNF-α by individuals with and without asthma increases airway responsiveness and neutrophil counts in induced sputum.[30] The successful use of TNF-α inhibitors in other

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Table 1
Biologics

Name	Mechanism of action	Studied populations	Clinical efficacy end points
Etanercept	TNF-α	• Moderate-to-severe asthma, requiring high-dose ICS	No significant difference of morning PEF, prebronchodilator percentage of predicted FEV_1 or ACQ scores when compared with placebo[14]
Infliximab	TNF-α	• Symptomatic asthma, moderate-to-severe asthma, using inhaled corticosteroids	Reduced number of exacerbations and diurnal PEF, no significant difference compared with placebo of morning PEF, SABA use, exhaled nitrous oxide, or asthma symptom scores[15]
Golimumab	TNF-α	• Severe-uncontrolled asthma, requiring high-dose ICS and LABA	No significant difference compared with placebo in percentage of predicted FEV_1 or severe exacerbations, increased serious adverse events in treatment group compared with placebo group[16]
Omalizumab	Anti-IgE	• Patients >12 years of age, moderate-to-severe allergic asthma, inadequately controlled with ICS or ICS/LABA, total IgE levels of 300–700 IU/mL	Reduced number of asthma exacerbations, mean daily albuterol use, asthma symptom score, and improved AQLQ scores[17]
Altrakincept	Anti–IL-4	• Moderate atopic asthma, daily inhaled ICS of 4–8 puffs, positive skin prick test result	Initial improvement AQLQ section 3, SABA use, FEV_1, and Total Asthma Symptom score[18]; subsequent larger study on patients controlled solely with SABA found no effects on pulmonary function or asthma symptoms[19]
Mepolizumab	Anti–IL-5	• Patients >12 years of age, recurrent severe asthma exacerbations despite high-dose ICS, eosinophilic phenotype (>150 eosinophils on CBC) within 6 weeks before starting therapy	Significant reduction in exacerbations, baseline glucocorticoid dose, with improvement of FEV_1 compared to placebo[20–22]
Reslizumab	Anti–IL-5	• Poorly controlled asthma while taking high-dose ICS and one other agent, sputum eosinophils >3%	Improved FEV_1, mild improvement of ACQ score, reduced blood and sputum eosinophil counts, no significant change in exacerbation rate compared with placebo[23]
Benralizumab	Anti–IL-5	• Uncontrolled asthma with medium- to high-dose corticosteroids and LABA	Reduced exacerbation rates in patients with eosinophilic phenotype with associated decrease in blood and sputum eosinophils[24,25]
Lebrikizumab	Anti–IL-13	• Uncontrolled asthma with medium- to high-dose corticosteroids and second controller	Improved FEV_1 and reduced exacerbation rates in patients with high periostin levels in treatment compared with placebo groups[26]
Dupilumab	Anti–IL-4α	• Moderate-to-severe asthma, blood eosinophil count of 300/μL OR sputum eosinophil count of at least 3%, medium- to high-dose ICS with LABA	Reduction of asthma exacerbations, nocturnal awakenings, SABA use, improved FEV_1 and ACQ5 score in duplimumab group compared with placebo group[27]
Pitrakinra	Anti–IL-4α	• Atopic asthma, required SABA on a regular basis	Improved FEV_1 markedly and reduced exhaled nitric oxide after 4 weeks therapy compared with placebo[28]

Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CBC, complete blood cell count; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; IL, interleukin; LABA, long-acting β-agonist; PEF, peak expiratory flow; SABA, short-acting β-agonist; and TNF-α, tumor necrosis factor α.

proinflammatory conditions has led to speculation that they may provide benefit in patients with severe refractory asthma.[31]

The TNF-α inhibitors etanercept, infliximab, and golimumab have been studied in patients with severe asthma. Initial studies with etanercept and infliximab are promising. In a small study of 30 patients, etanercept improved asthma-related quality of life and postbronchodilator forced expiratory volume in 1 second (FEV_1).[32] Similarly, in a trial of 38 patients with moderate asthma, infliximab was well tolerated and resulted in a decreased number of exacerbations with a reduction in the diurnal variation of peak expiratory flow by 8 weeks of therapy.[15] Unfortunately, larger controlled trials have not been able to replicate a favorable risk-benefit profile for this class of agents. Golimumab was studied in a cohort of 309 patients at varying doses and revealed an unfavorable risk-benefit profile with a significantly higher number of serious adverse events in the treatment arm compared with the placebo arm.[16] In addition, no significant changes in the percentage of predicted FEV_1 were observed, and there was no reduction of exacerbations in the treatment arm.

These mixed results of TNF-α therapy suggest an underlying phenotype in which TNF-α may be of benefit. It would be of interest to see the effect of TNF-α inhibitors in a cohort of patients with neutrophilic asthma. However, any further study of these drugs in asthma would need to take into account the potential safety signal observed with golimumab.

Omalizumab and Anti-IgE

Omalizumab is a monoclonal antibody that binds up free circulating IgE. Omalizumab has been approved since 2003 for use in patients with moderate to severe asthma with positive perennial allergen testing unable to be controlled despite use of ICSs. Treatment with omalizumab has a small (0.2%) but significant anaphylactic risk and a possible increased risk of arteriothrombotic events.[33,34] Currently available long-term safety data addressing the association between omalizumab administration and malignant disease detected no significant correlation.[35] Despite candidacy for therapy involving IgE level (30–700 IU/mL), levels have not necessarily correlated with a decrease in exacerbations.[36] Furthermore, one study evaluating the effect of omalizumab in a cohort of 81 allergic patients with asthma with and without chronic rhinosinusitis, improvements in pulmonary function tests were only seen in the chronic rhinosinusitis group.[37] This finding suggests the need for further biomarkers to better classify patients who will be anticipated responders.

More recent data analyzing a subset of the EXTRA (Omalizumab [Xolair] in Subjects With Moderate to Severe Persistent Asthma) cohort suggests that omalizumab may demonstrate the greatest efficacy when targeting specific populations of patients with severe refractory asthma with a high T_H2 profile.[17] When assessing patient phenotype based on cutoffs of peripheral blood eosinophils (260/μL), fractional exhaled nitric oxide (24 ppb), and periostin (50 ng/mL), it was found that the time until first exacerbation was significantly longer in individuals with test results above these thresholds (considered high T_H2 individuals). In contrast, individuals with results below these thresholds in the low T_H2 group had an almost indistinguishable change in time until first exacerbation when compared with the placebo groups. These markers have not yet been implemented in guidelines or in the indications for omalizumab therapy but bear strong consideration when choosing patient candidacy for omalizumab. Further replication of these results would likely change current indications for omalizumab administration. Appropriate use of biomarkers to guide clinical practice will be of sentinel importance as increased numbers of biologic therapies become available.

Anti–Interleukin 4

Interleukin 4 (IL-4) is well recognized as playing an active role in eosinophil aggregation and as part of the T_H2 pathway of inflammation. IL-4 is responsible for modulating production of IgE and also up-regulates vascular cell adhesion molecule 1, thereby causing aggregation of eosinophils.[19] IL-4 has been found to be increased in bronchoalveolar lavage of patients with asthma and to be associated with increased eosinophilia of the airway.[38]

An initial trial in 25 individuals using the anti–IL-4 agent altrakincept revealed improvement in patients with moderate asthma already receiving ICS therapy.[18] Using higher-dose altrakincept (1,500 vs 500 μg), FEV_1, forced expiratory flow between 25% and 75% vital capacity, and asthma symptom scores all stabilized even after removal of ICS therapy, as per the predetermined protocol. Treatment groups also required less rescue short-acting β-agonist (SABA) use and had reduced fractional exhaled nitric oxide levels compared with the placebo groups. Unfortunately, larger subsequent trials of altrakincept and pascolizumab, another anti–IL-4 agent, failed to demonstrate any clinical efficacy.[19] It has been hypothesized that antagonists of IL-4 are ineffective because of redundancy with the IL-13 pathway, postulating that dual inhibition may be required.[28]

Anti–IL-5

IL-5 plays a key role in eosinophil differentiation, recruitment, and survival. IL-5 is also elevated in bronchoalveolar lavage and detectable in bronchial biopsy specimens in patients with asthma.[39,40] Anti–IL5 medications have been studied for some time based on the significant correlation between IL-5 levels and eosinophilia in both airways and peripheral blood. Initial studies of mepolizumab, the IL-5 inhibitor, in patients with asthma found a reduction in sputum and blood eosinophils but failed to find any significant change in clinical end points, such as FEV_1, symptom score, SABA use, quality of life, or exacerbation rates.[41] Only after post hoc analysis was it recognized that there was a subset of subjects with an eosinophilic phenotype who had proportionately greater response to therapy.

After this analysis, subsequent studies have targeted patients with an eosinophilic phenotype. The DREAM (Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication) trial used an enrollment eosinophil cutoff of 300/μL. In 2 more recent studies evaluating mepolizumab, an enrollment eosinophil cutoff of 150/μL during the weeks before randomization or 300/μL in the blood in the last year were used. These studies indicate a significant reduction in both glucocorticoid dosing and rate of exacerbations among the eosinophilic asthma population.[20–22] Furthermore, studies of both the IL-5 inhibitors reslizumab and benralizumab have demonstrated similar efficacy when treating patients with an eosinophilic phenotype.[23,25] Studies on reslizumab used inclusion criteria of an eosinophil cutoff greater than 400/μL during the 2- to 4-week screening period.[23] Although the results of treatment with the anti–IL-5 biologics are impressive, their history serves as an important reminder that asthma is a heterogeneous disorder. Clinical benefit of individual medications varies, and efficacy relies on correctly identifying the appropriate population for a given treatment.

Anti–IL-13

Increased IL-13 is found in the sputum of patients with uncontrolled asthma.[42] IL-13 induces secretion of periostin in airways, which likely plays a direct role in T_H2-mediated mechanisms of airway remodeling in asthma.[43] Initial studies of the IL-13 inhibitor lebrikizumab focused on patients with uncontrolled asthma despite use of medium- to high-dose ICSs.[44] Study populations were initially stratified into high and low T_H2 groups based on eosinophil count and total IgE levels. FEV_1 was increased in the lebrikizumab group compared with the placebo group by approximately 5%. Further evaluation by predetermined post hoc analysis of high vs low periostin levels revealed that the low periostin group had no significant benefit from lebrikizumab as opposed to the high periostin group in which the improvement of FEV_1 was approximately 8% compared with placebo.

Subsequent studies on lebrikizumab have had mixed results. One study of 212 patients with asthma stratified based on total IgE level and eosinophil count did not find a significant improvement in FEV_1 in treatment groups compared with the placebo group.[45] However, analysis performed based on stratification by periostin levels revealed a trend toward an improved response in active patients with high baseline periostin levels. More recently, both the LUTE (Lebrikizumab in Patients Whose Asthma Is Uncontrolled With Inhaled Corticosteroids and a Second Controller Medication) and VERSE studies have evaluated the effect of lebrikizumab in patients with moderate asthma maintained with medium- to high-dose ICSs with a second controller medication. In both studies, patients were stratified at study entry based on periostin level.[26] These studies found a significant reduction in asthma exacerbations and an improvement in FEV_1 in the high periostin groups compared with the low periostin groups.

Clinical trials have not found lebrikizumab to be beneficial in terms of asthma symptoms, β-agonist use, or quality-of-life measures. Findings of improvement of FEV_1 have been mixed with strong supporting data for greater improvement in high periostin groups. As noted earlier, part of this lack of robust response to IL-13 inhibitors may stem from redundancy of cytokine-signaling pathways, such as with IL-4. Furthermore, clinical application will likely be limited to patients based on biomarker stratification. Periostin levels remain unavailable in most commercial laboratories, which makes implementation of lebrikizumab in current clinical practice difficult.

Anti–IL-4, Anti–IL-13, and Anti–IL-4α

Both dupilumab and pitrakinra inhibit the shared α-subunit of IL-4 receptors, which creates a blockade in signaling of IL-4 and IL-13. Dupilumab was studied in patients with moderate-to-severe asthma with blood eosinophil counts greater than 300/μL or with an elevated eosinophil count of greater than 3%.[27] To be randomized, patients in the study needed to have a lack of control despite their asthma being maintained with medium-dose to high-dose ICSs plus LABAs. Patients in both the treatment group and placebo group were prescribed a predetermined taper of their ICS and LABA regimen. Of the 104 patients who underwent 1:1 randomization, only 3 receiving dupilumab had an asthma exacerbation through the 12 weeks of study protocol compared with 23 receiving placebo (an 87% decrease in exacerbations when compared with placebo). Furthermore, in the active treatment arm, there was an improvement of FEV_1 despite tapering of other therapies. In addition, patients randomized to the active arm used fewer SABAs, reported an improved Asthma Control Questionnaire 5 score, and had fewer nocturnal awakenings compared with the placebo arm.

Two parallel group trials with pitrakinra evaluated adults with atopic asthma who required regular use of β-agonists.[28] To be randomized, patients required an initial baseline FEV_1 of 70% or more of predicted at screening, with a late-phase response of at least a 15% or greater decrease in FEV_1 after allergen challenge. Allergen sensitivity was defined based on skin prick testing. The primary end point was diminution of FEV_1 after repeat allergen challenge, which was assessed after injection of the study drug. There was marked attenuation of the decrease in FEV_1 in the

treatment arms of both studies. This finding is particularly remarkable because patients were not selected based on an underlying eosinophilic phenotype.

Data from these studies suggest blockade of both IL-4 and IL-13 may have greater effects then blocking of either individually. With significant drug class benefits being seen in atopic and eosinophilic asthma, these data suggest that anti–IL-4α biologics will have broad clinical applicability in high T_H2 patients, but more data are required to assess response in low T_H2 individuals.

Clinical Application

When exploring the data regarding biologic agents in asthma, some of the mixed results are likely a consequence of lack of appropriate phenotype and endotype stratification during study recruitment. Examples can be observed in studies of both the IL-5 inhibitors and lebrikizumab, which found a lack of efficacy until a more appropriate stratification of population was undertaken. Although the need for additional therapies in patients with severe refractory asthma is clear, a number of limitations are still faced. Foremost among these issues is the ability to make guided decisions regarding treatment based on the underlying phenotype of the patient. Currently, we understand that certain phenotypes are anticipated to be poor responders to an individual therapy, such as low T_H2 populations with omalizumab and low periostin groups with lebrikizumab. In addition, there are certain phenotypes that we would expect to have little or no response to our present biologic therapies. These phenotypes would include the low T_H2 groups as identified in the Severe Asthma Research Project, such as patients with neutrophilic predominant asthma.[6] This group may account for as much as 5% to 10% of all patients with asthma. This finding is of significant importance because this group generally has more frequent exacerbations, more β-agonist use, and higher all-cause and asthma-related costs compared with patients with uncontrolled asthma as a whole.[6,46]

Furthermore, without stratifying appropriately for anticipated clinical benefit, any potential socioeconomic benefits of biologic therapy are unclear. Data are conflicting regarding the cost-effectiveness of omalizumab, despite the drug being used clinically since 2003.[47–51] It has previously been proposed that omalizumab is only cost-saving if given to patients who are anticipated to be hospitalized 5 times or more per year or for at least 20 days despite maximal therapy for asthma.[52] Additional information of cost-effectiveness can be gleaned by analyzing the quality-adjusted life-years (QALYs) gained through introduction of therapy. One recent model suggests that omalizumab may cost as much as $117,000 per QALY compared with standard combined therapy of ICS and LABA at a significantly reduced cost of $15,400 per QALY.[53] Similar data are unavailable at this time for other biologics, although the price for 1 year of mepolizumab has been estimated to be as high as $32,500.[54] The high costs observed with omalizumab and mepolizumab raise serious concerns regarding long-term sustainability and effect on the health care system. Firm guidelines regarding how long use of a biologic agent should be continued before being considered a treatment failure are also lacking. Prior steroid-sparing studies with omalizumab typically begin tapering ICSs after 16 weeks of therapy and provide an approximate timeframe during which physicians would expect a clinical response.[55] Additional data are required for omalizumab and other biologics because an accurate assessment of cost-effectiveness requires established time until efficacy plateau. Ultimately, any anticipated clinical benefit needs to be weighed carefully before initiating and throughout continuation of therapy. In an attempt to optimize the cost and benefit of these medicines, their use needs to be guided by an understanding of the patient's underlying clinical phenotype, as opposed to applying a roulette of biologic agents because no other therapies have proven effective in a specific patient.

At this time understanding and applicability of biologic therapy in severe refractory asthma are difficult to determine and still evolving. More research is required to distinguish select populations that will best benefit from an individual biologic agent. Head-to-head studies of these new agents are imperative. It is likely that appropriate use of any biologics will depend on further understanding of biomarkers, asthma phenotypes, and the socio-economic ramifications of their use.

References

[1] Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention – 2015 Update*. Washington, DC: Global Initiative for Asthma; 2015.

[2] National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007.

[3] Zahran HS, Bailey CM, Qin X, Moorman JE. Assessing asthma control and associated risk factors among persons with current asthma – findings from the child and adult asthma call-back survey. *J Asthma*. 2015;52:318–326.

[4] Bateman ED, Boushey HA, Bousquest J, et al. Can guideline-defined asthma control be achieved? the Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med*. 2004;170:836–844.

[5] Lefebvre P, Duh MS, Lafeuille MH, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol*. 2015;136:1488–1495.

[6] Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol*. 2007;119:405–413.

[7] Han YY, Forno E, Marsland AL, Miller GE, Celedon JC. Depression, asthma, bronchodilator response in a nationwide study of US adults. *J Allergy Clin Immunol Pract*. 2016;4:68–71.

[8] Chen W, Marra CA, Lynd LD, Fitzgerald JM, Zafari Z, Sadatsafavi M. The natural history of severe asthma and influences of early risk factors: a population-based cohort study. *Thorax*. 2016;71:267–275.

[9] Kaijoka EH, Itoman EM, Li ML, Taira DA, Li GG, Yamamoto LG. Pediatric prescription pick-up rates after ED visits. *Am J Emerg Med*. 2005;23:454–458.

[10] O'Conor R, Wolf MS, Smith SG, et al. Health literacy, cognitive function, proper use, and adherence to inhaled asthma controller medications among older adults with asthma. *Chest*. 2015;147:1307–1315.

[11] Wenzel SE, Schwartz LB, Langmack EL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med*. 1999;160:1001–1008.

[12] Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013;187:804–811.

[13] Nair P, Dasgupta A, Brightling CE, Chung KF. How to diagnose and phenotype asthma. *Clin Chest Med*. 2012;33:445–457.

[14] Holgate ST, Noonan M, Chanex P, et al. Efficacy and safety of etanercept in moderate-to-severe asthma: a randomized, controlled trial. *Eur Respir J*. 2011;37:1352–1359.

[15] Erin EM, Leaker BR, Nicholson GC, et al. The effects of a monoclonal antibody directed against tumor necrosis factor-alpha in asthma. *Am J Respir Crit Care Med*. 2006;174:753–762.

[16] Wenzel SE, Barnes PJ, Bleacker ER, et al. A randomized, double-blind, placebo-controlled study of tumor necrosis factor-alpha blockade in severe persistent asthma. *Am J Respir Crit Care Med*. 2009;179:549–558.

[17] Hanania NA, Alpan O, Hamilos D, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy. *Ann Intern Med*. 2011;154:572–582.

[18] Borish L, Nelson H, Lanz M, et al. Interleukin-4 receptor in moderate atopic asthma: a phase I/II randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 1999;160:1816–1823.

[19] Corren J. Cytokine inhibition in severe asthma: current knowledge and future directions. *Curr Opin Pulm Med*. 2011;17:29–33.

[20] Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicenter, double-blind, placebo-controlled trial. *Lancet*. 2012;380:651–659.

[21] Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371:1198–1207.

[22] Bel EG, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371:1189–1197.

[23] Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicenter, parallel, double-blind, randomized, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3:355–366.

[24] Laviolette M, Gossage DL, Gauvreau G, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol*. 2013;132:1086–1096.

[25] Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor a monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomized dose-ranging study. *Lancet Respir Med*. 2016; 2:879–890.
[26] Hanania NA, Noonan M, Corren J, et al. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomized placebo-controlled studies. *Thorax*. 2015;70:748–756.
[27] Wenzel SE, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013;368:2455–2466.
[28] Wenzel S, Wilbraham D, Fuller R, Getz EB, Longphre M. Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. *Lancet*. 2007;370: 1422–1431.
[29] Howarth PH, Babu KS, Arshad HS, et al. Tumour necrosis factor (TNFα) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax*. 2005;60:1012–1018.
[30] Thomas PS, Yates DH, Barnes PJ. Tumor necrosis factor-alpha increases airway responsiveness and sputum neutrophilia in normal human subjects. *Am J Respir Crit Care Med*. 1995;152:76–80.
[31] Thomas PS, Heywood G. Effects of inhaled tumour necrosis factor alpha in subjects with mild asthma. *Thorax*. 2002;57:774–778.
[32] Berry MA, Hargadon B, Shelley M, et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma. *N Engl J Med*. 2006;354:697–708.
[33] Limb S, Starke P, Lee C, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol*. 2007;120:1378–1381.
[34] Ali AK, Hartzema AG. Assessing the association between omalizumab and arteriothrombotic events through spontaneous adverse event reporting. *J Asthma Allergy*. 2012;5:1–9.
[35] Long A, Rahmaoui A, Rothamn KJ, et al. Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *J Allergy Clin Immunol*. 2014;134:560–567.
[36] Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest*. 2004;125:1378–1386.
[37] Clavenna MJ, Turner JH, Samuelson M, Tanner SB, Duncavage J, Chandra RK. Differential effect of omalizumab on pulmonary function in patients with allergic asthma with and without chronic rhinosinusitis. *Allergy Asthma Proc*. 2016;37:23–26.
[38] Takaku Y, Nakagome K, Kobayashi T, et al. Changes in airway inflammation and hyperresponsiveness after inhaled corticosteroid cessation in allergic asthma. *Int Arch Allergy Immunol*. 2010;152(suppl 1):41–46.
[39] Robinson DS, Hamid Q, Ying S, et al. Predominant TH2-like bronchoalveolar T-lymphyocyte population in atopic asthma. *N Engl J Med*. 1992;326:298–304.
[40] Hamid Q, Azzawi M, Ying S, et al. Expression of mRNA for interleukin-5 in mucosal bronchial biopsies from asthma. *J Clin Invest*. 1991;87:1541–1546.
[41] Flood-Page P, Swenson C, Faiferman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Respir Crit Care Med*. 2007;176:1062–1071.
[42] Saha SK, Berry MA, Parker D, et al. Increased sputum and bronchial biopsy IL-13 expression in severe asthma. *J Allergy Clin Immunol*. 2008;121:685–691.
[43] Takayama G, Arima K, Kanaji T, et al. Periostin: a novel component of subepithelial fibrosis of bronchial asthma downstream of IL-4 and IL-13 signals. *J Allergy Clin Immunol*. 2006;118:98–104.
[44] Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med*. 2011;365:1088–1098.
[45] Noonan M, Korenblat P, Mosesova S, et al. Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids. *J Allergy Clin Immunol*. 2013;132:567–574.
[46] Zelger RS, Schatz M, Dalal AA, et al. Utilization and costs of severe uncontrolled asthma in a managed-care setting. *J Allergy Clin Immunol Pract*. 2016;4: 120–129.
[47] Brown Turk F, Dale P, Bousquet J. Cost-effecitveness of omalizumab in patients with severe persistent allergic asthma. *Allergy*. 2007;62:149–153.
[48] Dominguez-Ortega J, Phillips-Angles E, Barranco P, Quirce S. Cost-effectiveness of asthma therapy: a comprehensive review. *J Asthma*. 2015;52: 529–537.
[49] Diaz RA, Charles Z, George E, Adler A. NICE guidance on omalizumab for severe asthma. *Lancet Respir Med*. 2013;1:189–190.
[50] Norman G, Faria R, Paton F, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systemic review and economic evaluation. *Health Technol Assess*. 2013;17:1–342.
[51] Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. *Allergy*. 2010;65:1141–1148.
[52] Oba Y, Salzman G. Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma. *J Allergy Clin Immunol*. 2004;114:265–269.
[53] Zafari Z, Sadatsafavi M, Marra CA, Chen W, FitzGerald JM. Cost-effectiveness of bronchial thermoplasty, omalizumab, and standard therapy for moderate-to-severe allergic asthma. *PLoS One*. 2016;11:e0146003.
[54] Tice JA, Ollendorf D, Campbell JD, et al. *Mepolizumab (Nucala, GlaxoSmithKline plc.) for the Treatment of Severe Asthma With Eosinophilia: Effectiveness, Value and Value-Based Benchmarks: Draft Report*. Boston, MA: Institute for Clinical and Economic Review; 2015.
[55] Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systemic review. *Chest*. 2011;139:28–35.