

Patient Characteristics and Individualization of Biologic Therapy



Steven Draikiwicz, MD¹, John Oppenheimer, MD^{*}

KEYWORDS

• Biologics • Patient characteristics • Asthma • Urticaria • Phenotypes

KEY POINTS

- An overview is provided of the current status of therapy for outlined disease states and the role for biologic therapy in treatment.
- Current literature is reviewed regarding studied patient characteristics and the effect on outcome in patients with asthma and urticaria.
- The need for appropriate patient phenotyping is identified and guidance on evidence-based biologic selection is provided.

INTRODUCTION

Progress in the understanding of disease processes has provided additional therapeutic targets. This progress is best exemplified by the increasing role of biologics in the clinical armamentarium. Biologic agents are therapeutics synthesized by living organisms and directed against a specific determinant.¹ This article provides a focused review of current treatment paradigms and pathophysiology for asthma and urticaria. A table highlighting the mechanisms of action of individual therapeutics is presented after each section in which they are introduced. The goal is to elucidate for practicing physicians the populations in which biologics were studied for the aforementioned disease states, emphasizing characteristics to consider when selecting therapy.

Disclosures: S. Draikiwicz has nothing to disclose. J. Oppenheimer has done consulting work for Glaxo, Myelin, Meda; adjudication for Quintiles; has research interests in AstraZenica, Genetec, Sanofi, Glaxo; has performed legal consultation for Malpractice Defense; and is a reviewer for Up-to-date, Annals of Allergy and Immunology, and the American Board of Allergy and Immunology.

Division of Allergy and Immunology, New Jersey Medical School, Newark, NJ, USA

¹ Present address: 57 Mounthaven Drive, Livingston, NJ 07039.

^{*} Corresponding author. Pulmonary and Allergy Associates, 1 Springfield Avenue, Summit, NJ 07901, USA.

E-mail address: nalopp@optonline.net

Immunol Allergy Clin N Am 37 (2017) 261–281

<http://dx.doi.org/10.1016/j.iac.2017.01.004>

0889-8561/17/© 2017 Elsevier Inc. All rights reserved.

immunology.theclinics.com

ASTHMA

Asthma is an ongoing public health concern with more than 24 million individuals, approximately 7.3% of the total population, affected in the United States and an increase in prevalence between 2001 and 2010.^{2,3} Total incremental cost of asthma in the United States was estimated to be \$56 billion in 2007.⁴ Current National Heart Blood and Lung Association and Global Initiative for Asthma guidelines recommend a stepwise approach to therapy.^{5,6} Even with adherence to guideline therapy, including combination inhaled corticosteroids (ICS) and long-acting beta-agonist (LABA) therapy, as many as 50% of patients may continue to have suboptimal control.^{7,8} Suboptimal control has been associated with lower physical and mental health-related quality of life, increased health care use, lower overall work productivity, and activity impairment.⁹

Studies show that a significant amount of uncontrolled asthma can be attributed to lack of adherence to prescribed therapy. Although approximately 60% to 70% of patients evaluated in an acute care setting fill initial prescriptions for asthma medication, one study suggests that only 14% to 16% of patients may maintain satisfactory ($\geq 80\%$ medication availability) adherence over a 6-month period.^{10,11} Beyond intentional nonadherence, failure of medication delivery may affect as many as 40% to 80% of adherent asthmatics because of inappropriate inhaler technique (nonintentional nonadherence).^{12,13} Attaining control may also be impeded by obesity, active smoke exposure, allergies, psychiatric conditions, low socioeconomic status, as well as other underlying health conditions.^{14,15} Accounting for these comorbidities still leaves approximately 10% or less of asthmatics on appropriate therapy who continue to have severe refractory asthma.¹⁶ Severe asthma is classified as asthma that requires treatment with high-dose ICS plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy.¹⁷ Patients with severe or difficult-to-treat asthma have higher health care use, with research showing as much as 3 times the direct medical costs and 10 times greater indirect medical costs compared with mild asthma.¹⁸ Taken together, these patients may account for approximately 50% of direct expenditure on asthma care.¹⁹

Advances in the understanding of the pathophysiology of asthma have revealed that asthma is a heterogeneous disorder.²⁰ Multiple subgroups have been identified within the severe asthma population, which can further be stratified into specific phenotypes and endotypes.²¹ The goal of phenotyping is to correlate cellular and clinical features with individual patient disease characteristics in an attempt to improve the choice of therapy.²² Coinciding with the better understanding of the pathophysiology of asthma, the advent of immunomodulatory biologic therapy has emerged as a potential treatment option for individuals with severe refractory asthma. Omalizumab was the first monoclonal antibody approved for treatment in asthmatics in 2003, followed by mepolizumab in 2015, and reslizumab in March 2016. Multiple additional biologics are under study and are likely soon to be available for use in severe asthmatics. Choosing the optimal individual biologic requires a thorough understanding of the severe asthmatic's clinical characteristics and correlating with the patient's phenoendotype.

ASTHMA PHENOTYPING

The severe asthma phenotype characteristically has a reduced or refractory response to corticosteroid therapy.²³ Although there is no current biomarker to definitively delineate this group of individuals and classification depends on clinical course, to optimize the likelihood of clinical efficacy of biologic therapy additional phenotyping is required. Many different phenotypes of asthma have been described, including classifications

stratified by causal or trigger factor, type of airflow obstruction, severity and response to treatments, radiological findings, or nature of airway inflammation.²³ A definitive method of classifying asthma phenotypes has not gained a consensus.²⁴

Cluster analysis has been used in an attempt to classify underlying asthma phenotypes because of its ability to quantify similarity between individuals and use these metrics to create distinct populations in a less biased form.²⁵ In a 2008 study by Halder and colleagues,²⁵ 4 clusters were identified in 187 refractory asthmatics receiving specialty care:

1. Early-onset atopic asthma with evidence of airway dysfunction and eosinophilic airway inflammation.
2. Obese subgroup with female preponderance with evidence of asthma symptoms but absence of eosinophilic airway inflammation.
3. Early-onset, symptom-predominant group with minimal eosinophilic disease.
4. Eosinophilic inflammation-predominant group with few symptoms, late-onset disease, and a greater proportion of men.

Cluster analysis was performed by Moore and colleagues²⁶ in the Severe Asthma Research Program (SARP) cohort, including 726 subjects diagnosed with severe refractory asthma. In this group, 5 distinct clusters were identified:

1. Early-onset atopic asthma with normal lung function treated with 2 or fewer controller medications.
2. Early-onset atopic asthma and preserved lung function but with increased use of medication and health care use.
3. Older obese women with late-onset nonatopic asthma, frequent oral corticosteroid use, and moderate reductions in forced expiratory volume in 1 second (FEV₁).
4. and 5. Severe airflow obstruction with bronchodilator responsiveness is shared between the groups.

However, cluster 4 had more frequent childhood onset and atopic disease with an equal gender distribution. Cluster 5 had the longest duration of asthma and a female predominance with the most severe airflow limitation at baseline and retained obstruction even after use of a bronchodilator.

The prognostic value of cluster analysis in the phenotyping of severe asthma is unclear. A subsequent analysis evaluating 4 of the SARP clusters showed no difference in asthma control-related outcomes, including exacerbation rate, time to first exacerbation, and treatment requirements.²⁷ The goal of identifying distinct groups is to correlate these with unique pathophysiologic mechanisms of disease to guide treatment decisions.²² Cluster analysis elucidates the marked heterogeneity of phenotypes within the severe asthmatic population. When considering the use of a biologic agent, correlation of patient clinical clustering with type 2 high (Th2 high) biomarkers provides insight when determining anticipated response to therapy.

ASTHMA ENDOTYPES

Th2 allergic inflammation is present in up to 80% of children and 50% of adults with asthma.²⁸ Suggested biomarkers of Th2 high asthma phenotypes include periostin, fraction of exhaled nitric oxide, and sputum/blood eosinophils.²⁹ Periostin stimulates transforming growth factor-B, which leads to increased secretion of type 1 collagen by airway fibroblasts.³⁰ Periostin expression in airway epithelial cells is regulated by Th2 cytokines interleukin (IL)-4 and IL-13.³¹ IL-13 has also been identified as a stimulator of

dipeptidyl peptidase-4 (DPP4) in bronchial epithelial cells. DPP4 has been shown to increase proliferation of lung fibroblasts, bronchial smooth muscle cells, and the production of fibronectin.³² Fractional excretion of nitric oxide (FeNO) is upregulated by cytokines IL-4 and IL-13, which induce nitric oxide synthase.³³ Besides its use as a marker of Th2 inflammation, FeNO has also been suggested as a marker of eosinophilic airway inflammation. Th2 cells release IL-5 and IL-13 into the airway epithelium and submucosa leading to the consequent increase in airway and serum eosinophilia. Genomic analysis of asthmatics has also associated increased immunoglobulin (Ig) E levels with an underlying systemic Th2 upregulation.³⁴ Noted that these markers in isolation are unable to classify a specific phenotype. The correlation between FeNO as a marker of a distinct eosinophilic phenotype and of Th2 inflammation has shown conflicting results. Studies involving mepolizumab have shown a dissociation between blood and sputum eosinophil counts and FeNO levels indicating that additional cytokines are responsible for regulating nitric oxide synthase, separate from those that control eosinophilia.³⁵ Furthermore, eosinophilic inflammation is found in both allergic as well as nonallergic patients with asthma, suggesting that eosinophilia is not the sole result of atopic habitus.³⁶ This suggestion is borne out by the cluster analysis from Haldar and colleagues.²⁵ These data suggest that further investigation is required to better delineate the likely multiple pathways that are associated with severe refractory asthma.

Data from SARP as well as prior cluster analysis have identified a distinct population of severe refractory patients with asthma with a neutrophilic predominance.²⁶ T-helper (Th)-1 and Th17 cell responses have been associated with this phenotype.³⁷ Th-1 cells are characterized by increased production of interferon-gamma, whereas Th-17 cells mediate neutrophil activation.³⁸ Mechanistically, Th-17 cells are also thought to contribute to steroid resistance in select populations based on mouse models.³⁹ In humans, bronchoalveolar levels of IL-17 have been found to correlate with disease severity in neutrophil-predominant asthma.³⁷ The identification of neutrophilic/Th-1 severe refractory asthma as a unique phenotype is reinforced by clinical evidence of reduced improvement in pulmonary function testing following beta-agonist treatment in this population, which is suggestive of airway remodeling.⁴⁰

Although a significant amount of data suggests an overlap of Th-1 responses and neutrophilic asthma, Th-1 cells have also been shown to induce airway hyperreactivity independently of neutrophilic inflammation.⁴¹ Similarly, independent environmental factors have a direct effect on neutrophilic asthma, with smoking, systemic inflammation, and infections increasing airway neutrophilia.^{42–44} This finding argues against a direct correlation between an underlying Th-1 genotype and neutrophilic asthma as a resultant phenotype. Furthermore, an association between obesity and late-onset neutrophilic asthma has also been detected.⁴⁵

Ultimately, sufficient data exist indicating that Th-1 and Th-17 pathways are possible therapeutic targets in asthma therapy. It is likely that a strata of subtypes exists within the non-Th2-driven asthmatic population. However, the precise clinical phenotype in which these agents offer maximal efficacy needs to be further identified.

THERAPEUTIC BIOLOGICS IN PATIENTS WITH ASTHMA

Anti-Immunoglobulin E

The first new biologic agent available for the treatment of asthma was omalizumab, which was approved by the US Food and Drug Administration in 2003 for use in patients 12 years of age and older with moderate to severe atopic asthma, a total serum IgE level between 30 and 700 IU/mL, and who are currently using ICS with incomplete

control.⁴⁶ Omalizumab is a recombinant monoclonal antibody that reduces circulating IgE levels by binding to the constant region of the human IgE molecule.⁴⁷ Initial approval of omalizumab was based on 3 randomized, double-blind, placebo-controlled, multicenter trials.⁴⁶ In a trial by Busse and colleagues,⁴⁸ 525 subjects with severe allergic asthma requiring daily inhaled ICS were randomized to receive placebo or omalizumab. There were significantly fewer asthma exacerbations in the omalizumab group, with approximately a 10% absolute reduction in frequency, compared with placebo. However, similar study recruitment criteria and designs led to equivocal results in trials by Soler and colleagues⁴⁹ and Milgrom and colleagues.⁵⁰

The EXTRA (Exploring the effects of omalizumab in allergic asthma) trial was a prospective, multicenter, randomized, parallel-group, double-blind, placebo-controlled study assessing omalizumab safety and efficacy in uncontrolled severe asthmatics. Enrolled patients required a diagnosis of severe persistent allergic asthma for greater than 1 year before trial screening and needed to remain inadequately controlled despite high-dose ICS and LABA. Omalizumab dosing was consistent with the drug's dosing table from its package insert (based on the patient's body weight and serum IgE level). Initial results indicated that asthma exacerbation rates were significantly lower during the trial period in the omalizumab group compared with the placebo group (incidence rate of 0.66 compared with 0.88).⁵¹ Posthoc analysis divided the 850 enrolled subjects into Th2 high and low groups, with the Th2 high group having an FeNO greater than or equal to 24 parts per billion, blood eosinophil level greater than or equal to 260/ μ L, and serum periostin level greater than or equal to 50 ng/mL at baseline. Comparing high versus low subgroups, the Th2 high group showed significant reductions of exacerbations in the high versus low group (53% vs 16% FeNO, 32% vs 9% eosinophils, and 30% vs 3% periostin). The difference between the high and low groups has strong clinical implications reinforcing the importance of appropriate phenotypic discrimination in current practice.

A retrospective case-control study assessed allergic asthmatics, comparing the efficacy of omalizumab on pulmonary function testing in 81 asthmatic subjects with chronic rhinosinusitis and those without.⁵² Analysis was performed on patients at a tertiary university clinic, analyzing outcomes of prescribed therapy over 7 years. An average treatment duration of 25 months with omalizumab revealed improved FEV₁, forced vital capacity, FEV₁/forced vital capacity ratio, and forced expiratory flow in 25% to 75% of subjects with chronic rhinosinusitis. Three of these parameters showed significant improvement compared with patients without chronic rhinosinusitis, who did not show a significant improvement in any of the study end points.

Current data indicate omalizumab to have anticipated clinical benefit in a Th2 high population and that IgE may not be the best prognostic indicator of effectiveness despite applicability criteria. Further data are required to delineate the effect of omalizumab on severe refractory intrinsic asthma compared with improved outcomes achieved from controlling exacerbating conditions, such as concomitant rhinosinusitis.

Anti-Interleukin-5

Mepolizumab is currently approved for use in patients with severe eosinophilic asthma.⁵³ Mepolizumab is a humanized monoclonal antibody against IL-5 that in turn reduces airway and systemic eosinophilia. Current prescribing parameters necessitate a blood eosinophil threshold of greater than or equal to 150 cell/ μ L at treatment initiation or blood eosinophil count of greater than or equal to 300 cells/ μ L in the 12 months before treatment initiation. Patients must also have uncontrolled asthma despite receiving maximal standard therapy with a high-dose ICS and at least

1 additional controller medication. Initial trials with mepolizumab failed to show significant changes in clinical measures of asthma (airway hyperresponsiveness, FEV₁, or peak flow recordings) despite reductions in blood and sputum eosinophil counts.^{54,55} In the initial trial, 24 volunteers with mild atopic asthma controlled with short-acting beta-agonists (SABA) were recruited. Following this, a dose-ranging trial of 362 subjects enrolled subjects with persistent asthma symptoms despite the use of ICS therapy (400–1000 µg of beclomethasone or equivalent). Subjects received injections of mepolizumab, either 250 mg, 750 mg, or placebo, at 4-week intervals for a total of 3 doses across 12 weeks. Although there was a trend toward improvement of exacerbation rates, SABA use, and quality of life in the 750-mg group, it did not reach statistically significant compared with other groups.

A subsequent trial by Haldar and colleagues³⁵ was conducted in a population of refractory asthmatics with a sputum eosinophil count of more than 3% on at least 1 occasion (within 2 years before study enrollment) despite high-dose ICS treatment. The study was a single-center, randomized, double-blind, placebo-controlled, parallel-group clinical trial in which subjects were randomized to receive either mepolizumab 750 mg or placebo. Subjects were treated monthly over the course of 1 year. The mepolizumab group showed an exacerbation relative risk of 0.57 compared with placebo, although there were no significant differences in change from baseline in symptom scores or between-group differences in changes in FEV₁ after bronchodilator use.

The DREAM (mepolizumab for severe eosinophilic asthma) trial with mepolizumab was a multicenter, double-blind, placebo-controlled trial evaluating subjects with a history of refractory asthma previously requiring systemic corticosteroid treatment 2 or more times in the period before screening and with 1 of the following criteria: a sputum eosinophil count of 3% or more, a FeNO of 50 ppb or more, serum eosinophil count of 0.3×10^9 , or deterioration of asthma control following a 25% reduction or less of inhaled or oral corticosteroids.⁵⁶ Subjects were randomized in a 1:1:1:1 fashion to 75 mg, 250 mg, 750 mg of mepolizumab or placebo and received 13 infusions at 4-week intervals. Compared with placebo, the mepolizumab groups showed significant reductions in exacerbations per patient year, ranging from 39% to 52% risk reduction.

Reslizumab is a humanized monoclonal antibody composed of complementarity-determining regions of a murine antibody to human IL-5, which prevents binding of IL-5 to eosinophils.⁵⁷ Current prescribing guidelines for reslizumab indicate use in patients greater than or equal to 18 years of age as add-on maintenance therapy in patients with an eosinophilic phenotype. An initial clinical trial was conducted with 106 subjects who had incompletely controlled asthma despite treatment with high-dose ICS and at least 1 other agent.⁵⁷ Subjects required a minimum of 3% eosinophils on sputum analysis as part of recruitment criteria. The study was a randomized (1:1), double-blind, placebo-controlled, multinational study with treatment of reslizumab (3.0 mg/kg) or placebo every 4 weeks for 3 total doses. At study end, significant improvements in the primary end point Asthma Control Questionnaire score was found in the reslizumab group compared with placebo (59% compared with 40%). Statistical improvements were also evident in FEV₁ in the reslizumab group with an associated reduction in sputum and blood eosinophil levels.

Further study of reslizumab was conducted in 2 duplicate, multicenter, double-blind, parallel-group, randomized (1:1), placebo-controlled trials.⁵⁸ Subjects were aged 12 to 75 years with at least 400 eosinophils/µL in serum during the run-in period of 2 to 4 weeks. During this time, subjects were required to have inadequately controlled asthma while receiving at least medium-dose ICS (with or without another controller medication). Placebo or reslizumab, at 3 mg/kg, were administered every

4 weeks for a total of 13 doses, with 489 and 464 subjects randomly assigned in each study respectively. In these populations reslizumab significantly reduced the annual rate of exacerbations by 50% to 59% compared with placebo. Significant improvements were also seen in FEV₁, patient-reported quality of life, patient-reported symptoms score, and blood eosinophil count compared with placebo.

Benralizumab is a humanized monoclonal antibody that targets human IL-5 receptor- α on eosinophils and basophils.⁵⁹ Initial clinical study included adult asthmatics requiring medium-dose to high-dose ICS in combination with LABA therapy for at least 1 year with 2 to 6 exacerbations during that time who were stratified by eosinophilic phenotype. Eosinophilic phenotype was determined by FeNO (used as a surrogate marker of eosinophilic status) or increased eosinophil/lymphocyte and eosinophil/neutrophil index. Individuals with an eosinophilic phenotype were randomized (1:1:1:1) to receive 2 mg, 20 mg, 100 mg of benralizumab, or placebo. Noneosinophilic individuals were included in the study and randomized (1:1) to either 100 mg of benralizumab or placebo. Three-hundred and twenty-four individuals were randomized by eosinophilic stratification with 285 randomized to the noneosinophilic group. In the eosinophilic arm, significant reduction of annual exacerbations was found in the group receiving 100 mg of benralizumab compared with placebo but not the 2-mg or 20-mg groups. FEV₁ and Asthma Control Questionnaire-6 score were also improved compared with placebo in the eosinophilic group across all benralizumab doses. In the noneosinophilic arm, no significant difference in exacerbation rates was evident between benralizumab 100 mg and placebo but there was a trend toward reduced exacerbation rates. Additional subgroup analysis was performed using 300 eosinophils/ μ L as a cutoff, finding exacerbation rates were significantly reduced by 40% to 60% compared with placebo across benralizumab 20-mg and 100-mg groups. In contrast, no significant reduction in exacerbations was noted with 20 mg or 100 mg of benralizumab in the subgroup analysis in subjects with fewer than 300 eosinophils/ μ L. All doses of benralizumab decreased blood eosinophil counts compared with placebo.

Overall, anti-IL-5 therapy seems to be most clinically effective in patients with an eosinophilic phenotype. As previously mentioned, FeNO may not be a consistent marker of an eosinophilic phenotype, as exemplified by the discrepancy in efficacy seen in the benralizumab trial when comparing the eosinophilic study arm (stratified by FeNO) with the subsequent subgroup analysis in which subjects were stratified by serum eosinophil count (<300 or >300 eosinophils/ μ L). Furthermore, although serum eosinophilia of greater than 150 cells/ μ L is sufficient in certain circumstances to warrant mepolizumab administration, accounting for the data from anti-IL-5 agents as a whole best supports the use of these agents in asthmatics with greater than or equal to 300 eosinophils/ μ L.

Anti-Interleukin-13

Lebrikizumab is a humanized monoclonal antibody that binds to soluble IL-13.⁶⁰ IL-13 has been implicated in the Th2 pathway of asthma pathogenesis, has been shown to induce B-cell production of IgE, and has been strongly correlated with production of periostin.^{61,62} Lebrikizumab was studied in 218 asthmatics using low-dose to high-dose ICS for 6 months before screening with evidence of uncontrolled asthma on day of randomization.⁶⁰ Subjects were allowed to continue LABA and other controller medications if already prescribed. Lebrikizumab 250 mg or placebo was given once per month for 6 total doses in this double-blind, placebo-controlled, parallel-group, multicenter study. Baseline FEV₁ was greater by 5.5% by week 12 in the lebrikizumab group compared with placebo, with effect maintained throughout the study duration.

Although not initially defined at study onset, subsequent subgroup analysis revealed a change in the baseline FEV₁ of the subjects of 8.2% in the periostin high group and 1.6% in the periostin low group compared with placebo. No significant effect was noted in exacerbation rate or asthma control scores in either the primary lebrikizumab group or analyzed subgroups. This finding highlights the importance of appropriate phenotypic discrimination and the effect it can have on therapeutic efficacy.

Subsequently a dose-ranging, randomized (1:1:1:1), double-blind, placebo-controlled study by Noonan and colleagues⁶³ evaluated efficacy and safety of lebrikizumab at varying doses (125 mg, 250 mg, 500 mg) in 212 subjects. Subjects were asthmatics not receiving ICS who received 4 total doses of lebrikizumab or placebo dosed every 4 weeks. Stratification across treatment arms was based on baseline IgE levels (> or <100 IU/mL) and peripheral blood eosinophil count (> or <0.14 × 10⁹). No statistically significant change in FEV₁ was noted in subjects in any treatment group compared with placebo, including subsequent subgroup analysis stratified by periostin. Significant reduction of protocol-defined treatment failure and FeNO was identified in the lebrikizumab group but there was no differential response by periostin level. Discrepancy between these results and those reported earlier were attributed by the investigators to either insufficient power or IL-13 possibly having a greater role in steroid-insensitive subjects (subjects in this trial were mild asthmatics on no ICS).

Additional data regarding lebrikizumab efficacy are available in LUTE and VERSE (Lebrikizumab in moderate-to-severe asthma: pooled data from two randomized placebo-controlled studies) trials, which were replicate, randomized, double-blind, placebo-controlled studies evaluating 463 subjects.⁶⁴ Study populations were uncontrolled adult asthmatics receiving medium-dose to high-dose ICS and a second controller. Randomization occurred in a 1:1:1:1 ratio between doses of 37.5 mg, 125 mg, 250 mg of lebrikizumab, and placebo. Median duration of treatment was 24.1 weeks with dosing of study drug or placebo occurring every 4 weeks. Prespecified subgroup analysis was conducted based on periostin levels (periostin high [>50 ng/mL]) versus periostin low [<50 ng/mL] groups). There was a significant reduction in asthma exacerbations of 60% in the periostin high group compared with placebo and a nonsignificant (5% reduction) in exacerbation rates in the periostin low group. No clear dose-response relationship was observed. Mean relative change in baseline FEV₁ was 9.1% and 2.6% for the pooled periostin high and periostin low lebrikizumab groups respectively compared with placebo.

Anti-IL-13 agents have the greatest data supporting efficacy in patients with an increased periostin level (>50 ng/mL). Data are present to account for reduced exacerbation rates and improved FEV₁ in this population. Earlier studies with lebrikizumab highlight the importance of identifying appropriate candidates before initiating treatment.

Anti-Interleukin-4 and Interleukin-13

Dupilumab is a fully human monoclonal antibody to the IL-4 receptor- α , which inhibits both IL-4 and IL-13 signaling pathways.⁶⁵ IL-4 and IL-13 share redundancy in signaling and additional benefit may be seen from blocking both pathways. One-hundred and four adult moderate to severe asthmatic subjects were studied in a randomized (1:1), double-blind, placebo-controlled study. Eligible subjects required a blood eosinophil count of greater than or equal to 300 cells/ μ L or an increased sputum eosinophil level ($\geq 3\%$) with poorly controlled symptoms despite the use of medium-dose to high-dose ICS and LABA therapy at study screen. Dupilumab 300 mg or placebo was administered once weekly for 12 weeks. A significant reduction in exacerbations of

87% was evident in the dupilumab group compared with placebo. Secondary end points, including lung function metrics, asthma symptoms, and beta-agonist rescue use, also were significantly improved compared with placebo. Although both FeNO and IgE levels were decreased in the dupilumab group, there was notably no decrease in peripheral blood eosinophils compared with placebo.

Similar to the other biologics described, dupilumab targets asthmatics with a Th2-driven response. The dual inhibition of both IL-4 and IL-13 pathways may account for what can initially be considered a more robust response compared with agents that target solely IL-4 or IL-13. More data are required to confirm its efficacy but preliminary data suggest a use in patients with an eosinophilic phenotype including increased serum or sputum eosinophil levels.

Anti-Interleukin-17

Brodalumab is a human anti-IL-17 receptor-A immunoglobulin monoclonal antibody that blocks activity of both IL-17 and IL-25.⁶⁶ Brodalumab was studied in 315 adult subjects with physician-diagnosed moderate to severe asthma who at screening were stable on ICS with or without additional LABA. Subjects were evaluated in a randomized, double-blind, placebo-controlled, dose-ranging study with randomization occurring 1:1:1:1 to receive brodalumab 140 mg, 210 mg, 280 mg, or placebo. Administration was performed subcutaneously at 7 visits across 10 weeks. No statistical significance was found in either the primary end point of improved Asthma Control Questionnaire score or in any secondary end points of lung function or asthma symptoms. The lack of clinical efficacy was suggested to be secondary to the heterogeneous nature of asthma and selective mechanism of action of monoclonal antibodies. A prespecified subgroup analysis showed a significant change in Asthma Control Questionnaire score in a subpopulation that best fit clusters 2 and 4 from the Moore and colleagues²⁶ cluster analysis (early-onset atopic asthma and preserved lung function and severe airflow obstruction with bronchodilator responsiveness). Study investigators hypothesized that additional study of brodalumab targeting a phenotype similar in characteristics to the aforementioned clusters may result in more significant clinical efficacy. This study highlights the importance of using phenotypic discriminators to carefully choose an optimal target population and without which a potential clinical utility may be missed.

Anti-Tumor Necrosis Factor

Infliximab is a recombinant human-murine monoclonal antibody that binds and neutralizes soluble tumor necrosis factor- α (TNF- α).⁶⁷ Infliximab was studied in a population of 38 adult subjects with moderate to severe persistent asthma in a double-blind, placebo-controlled, parallel-group study. Subjects underwent 1:1 randomization and received 3 infusions over a 6-week period with 5 mg/kg of infliximab or placebo. A significant increase was found in the primary end point of morning peak expiratory flow in the infliximab group. A significant difference was also found in the number exacerbations experienced in the infliximab and placebo groups, with 72% of patients in the placebo group experiencing exacerbations compared with 29% in the infliximab group. No significant difference was found between groups regarding SABA use, asthma symptom scores, or FEV₁.

Increased neutrophilia in sputum and airway responsiveness has also been observed in response to inhalation of TNF- α in normal individuals.⁶⁸ A subset of the SARP phenotype had neutrophilic-predominant asthma, suggesting a possible role for TNF- α inhibition and an effect on airway neutrophilia/inflammation. Evaluation of a TNF- α blocking agent was performed using golimumab in the uncontrolled severe

asthma population.⁶⁹ The study population was limited to subjects who showed asthma symptoms on more than a third of days for at least 3 months before screening despite being on high-dose ICS and LABA therapy. Assessment was conducted in a phase 2, multicenter, randomized, double-blind, dose-ranging, placebo-controlled study. Dosing was every 4 weeks for a total of 52 weeks with either 50 mg, 100 mg, 200 mg of golimumab, or placebo based on 1:1:1:1 randomization. No significant difference was found between placebo and golimumab for exacerbations or FEV₁ during study protocol, although a trend was noted toward reduced exacerbations in the higher dose groups. However, unfavorable risk-benefit data led to discontinuation of the study because an increased number of severe adverse effects, primarily infections, were noted in the treatment arms. Of greatest concern is a significant safety signal concerning malignancy seen with the use of TNF- α blockade. In a study by Wenzel and colleagues,⁶⁹ 8 malignancies were seen in the active group of one study of 309 subjects compared with none in the placebo group.

Anti-TNF- α agents are best classified as targeting asthmatics with a Th-1 response, whereas previous biologic therapies focus on an underlying Th2 phenotype. However, safety data preclude use in this population at this time (Table 1).

URTICARIA

Chronic spontaneous urticaria (CSU) is the spontaneous appearance of wheals, angioedema, or both for greater than 6 weeks.⁷⁰ CSU is a significant public health concern with an annual population prevalence of approximately 0.5% to 1% and an annual lifetime prevalence of 20%.^{71,72} Although most CSU resolves within 5 years, as many as 20% of cases can persist for longer.⁷² Wheals are characterized by a perivascular nonnecrotizing infiltrate, primarily composed of mononuclear cells and neutrophils 60 minutes after wheal onset.^{73,74} Disease activity is associated with reduced quality of life as well as increased health care use.⁷⁵

The mechanism of CSU remains to be elucidated, although current evidence suggests that mast cells are important contributors.⁷⁰ It has been identified that as many as 30% to 40% of patients with CSU have autoimmune involvement with a circulating antibody directed to the α subunit of the high-affinity type I IgE receptor (Fc ϵ R1) on mast cells.⁷⁶ The result of this antibody binding is degranulation of

Table 1 The mechanisms of action of individual therapeutics	
Drug Name	Mechanism of Action
Omalizumab	Reduces circulating IgE by binding to the constant region of the human IgE molecule ⁴⁷
Mepolizumab Reslizumab	Binds free IL-5, which reduces airway and systemic eosinophilia ^{53,57}
Benralizumab	Binds IL-5 receptor- α on eosinophils and basophils ⁵⁹
Lebrikizumab	Binds to circulating IL-13, reducing airway periostin and DPP4 levels ⁶⁰
Dupilumab	Inhibits both IL-4 and IL-13 signaling pathways by binding to IL-4 receptor- α ⁶⁵
Brodalumab	Anti-IL-17 receptor-A, which blocks IL-17 and IL-25 pathways
Infliximab Golimumab	Binds and neutralizes soluble TNF- α , a key regulator of innate immunity and the Th-1 response ^{67,69}

the mast cell and histamine release.⁷⁷ Attempts to further classify patients with CSU include a study in which subjects were stratified into 5 groups:

- Immunoreactive histamine-releasing anti-FcεR1 autoantibodies
- Immunoreactive anti-FcεR1 autoantibodies without histamine-releasing activity
- Anti-IgE-like autoantibodies
- Serum with a mast cell-specific histamine-releasing factor
- Others that remain unidentified⁷⁸

Classification of patients into these categories has direct clinical significance because patients with serum histamine-releasing activity typically have greater number, larger size, and more frequent wheals.⁷⁹

Current guidelines recommend confirmation of CSU with the exclusion of other possible causes, including physical urticarias, drugs, foods, and infectious agents.⁷⁰ Initial therapy is with second-generation H1-antihistamines, which may be increased up to 4-times the recommended dose. In patients who fail H1-antihistamine therapy, guidelines recommend the use of either cyclosporine, montelukast, or the biologic omalizumab. Additional therapeutics have been studied either with the rationale of limiting histamine-releasing autoantibodies or reducing inflammation and coagulation biomarkers.⁸⁰

THERAPEUTIC BIOLOGICS IN PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA

Omalizumab

Omalizumab has been approved for use in patients with refractory chronic spontaneous urticaria despite high-dose H1 antihistamines since March 2014 in both the United States and Europe. The known mechanism of IgG binding to the high-affinity IgE receptor in a significant proportion of patients with chronic autoimmune urticaria prompted investigation of the use of omalizumab in these patients.

The initial proof-of-concept study of omalizumab was performed by Saini and colleagues⁸¹ in 2011. The study was a prospective, double-blind, placebo-controlled, dose-ranging study evaluating the use of omalizumab in subjects 12 to 75 years of age with an Urticaria Activity Score of greater than 12 over 7 days despite antihistamine therapy. Ninety subjects were randomized 1:1:1:1 to receive either placebo, 75, 300, or 600 mg of omalizumab in addition to standard antihistamine therapy. Onset of effect was apparent within 1 to 2 weeks with a significant decrease in the Urticaria Activity Score in both the 300-mg and 600-mg groups with omalizumab.

Additional trials included several phase 3, multicenter, randomized, double-blind studies evaluating 323 subjects with moderate to severe chronic idiopathic urticaria who were symptomatic despite use of antihistamines.⁸² Subjects were required to have a history of at least 6 months of chronic idiopathic urticaria and hives associated with itching for at least 8 consecutive weeks at a time despite use of antihistamines. Subjects with physical urticarias were excluded from these studies. Subjects were randomized to receive 3 injections every 4 weeks of either 75 mg, 150 mg, 300 mg, or placebo. Significant reductions in itch-severity score, the primary outcome measure, was evident in the 150-mg and 300-mg group at week 12 compared with baseline itch scores. Improvements were also seen in all prespecified secondary end points, including change from baseline Urticaria Activity Score, weekly number of hives, angioedema-free days over 8 weeks, and improvement in Dermatology Life Quality Index.

Subsequently a trial was performed assessing the effect of 300 mg of omalizumab in subjects aged 12 to 75 years who remained symptomatic despite treatment with H1-

antihistamines at up to 4 times the approved dose plus H2-antihistamines, leukotriene antagonists, or both.⁸³ Subjects were enrolled from multiple centers in a 3:1 ratio to either omalizumab (n = 252) or placebo (n = 84) with dosing at 4-week intervals for a total of 24 weeks. Subjects were required to have active disease with an Urticaria Activity Score of 16 or greater over the week before randomization. Omalizumab was effective irrespective of the combination of concomitant medications, including angioedema-free days over an 8-week period, and proportion of patients who were itch and hive free. In the omalizumab group, 34% of subjects were completely itch and hive free compared with 5% in the placebo group at 12 weeks. Clinical trials support the use of omalizumab in patients with chronic spontaneous urticaria who are refractory to initial treatment with antihistamines or leukotriene antagonists. Additional phenotypic descriptors are unavailable at this time and it should be noted that, unlike its use in asthma, studies did not stratify by IgE level. Note also that the efficacy of omalizumab exceeds the initial postulated 30% to 40% of CSU thought to be caused by chronic autoimmune urticaria. Also, efficacy is fairly robust but heterogeneous with 34% of subjects in one trial achieving complete disease remission but with 66% with residual symptoms. Initial dose-ranging studies do not suggest that this is a dose-dependent effect and further study is warranted to better determine the patients most likely to respond to therapy.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is a polyvalent antibody product derived from pooled plasma of healthy donors that is thought to act through blockade of the Fc portion of IgG molecules.⁸⁴ It has also been suggested that IVIG may have direct inhibitor effects on B-cell and T-cell function.^{85,86} One study evaluated the efficacy of IVIG 2 g/kg over 2 days in 6 subjects (aged 16–72 years) with recurrent severe CSU with daily symptoms requiring high-dose corticosteroids. Infusions were given every 4 to 6 weeks. Five of the 6 subjects had a significantly improved Urticaria Activity Score after the first 3 cycles.

O'Donnell and colleagues⁸⁴ also studied the effect of IVIG in 10 patients (aged 24–75 years) with CSU. All subjects had severe CSU that was poorly responsive to conventional treatment with antihistamines. Subjects all had evidence of serum histamine-releasing activity, as shown by a positive autologous intradermal serum test. Subjects were treated with 0.4 g/kg of IVIG over 5 days. Although subjects had a varied response to therapy, 9 subjects had improvement of urticaria. The mean Urticaria Activity Score improved from baseline of 24.6 to 12.6 at 2 weeks and 7.8 at 6 weeks after treatment. These data suggest a possible benefit of IVIG in patients with refractory urticaria. There are insufficient data to classify which patients will best respond or to identify a unique phenotypes. Nonetheless, the varied response of patients to IVIG suggests a potential underlying phenotype of responders (Table 2).

Rituximab

Rituximab is a chimeric murine/human recombinant monoclonal antibody that binds to CD20. Rituximab treatment results in B-cell depletion with a resultant decrease in the

Table 2 The mechanism of action of intravenous immunoglobulin	
Drug Name	Mechanism of Action
IVIG	Circulating immune globulin G binds to act the Fc portion of IgG molecules ⁸⁴

production of IgG antibodies. Application in CSU is targeted at reducing antibody binding to the FcεR1. The use of rituximab in patients with CSU is limited to case reports.^{87,88} In a case report by Chakravarty and colleagues,⁸⁷ the investigators evaluated the use of rituximab in a patient in whom other causes of urticaria had been excluded and who had positive IgG autoantibodies to FcεR1 on skin biopsy of an urticarial lesion. The patient had been previously treated with oral antihistamines, cyclosporine, mycophenolate mofetil, and even oral steroids. Four weekly infusions of rituximab were given at 375 mg/m² concurrently with methotrexate administration of 15 to 25 mg/wk subcutaneously. Resolution of symptoms was seen within 6 weeks of completion of rituximab therapy. A case report by Steinweg and Gaspari⁸⁸ evaluated a 38-year-old woman with a 1-year history of CSU refractory to fexofenadine, ranitidine, hydroxyzine, and even high-dose (60-mg) prednisone therapy. During a breakthrough episode requiring hospitalization the subject was infused with 1 g of rituximab followed by 1 g of rituximab 2 weeks later with complete remission of symptoms for 10 months.

Insufficient data are available at this time for any recommendations involving rituximab therapy. It may be considered in patients who are refractory to other, more established therapies.

Tumor Necrosis Factor-Alpha

TNF-α promoter polymorphisms have been associated with susceptibility to CSU.⁸⁹ Despite the recognition of genetic polymorphisms, conflicting data exist regarding the significance of a correlation between TNF-α levels and CSU.^{90,91} Excluding physical urticarias and urticarial vasculitis, a total of 21 documented cases exist in which TNF-α inhibitors were used in cases of refractory chronic autoimmune urticaria or CSU.^{92,93} The course of disease in the case series by Wilson and colleagues⁹³ was varied but there was a generalized improvement with initial treatment, although further pulses of therapy were occasionally needed for relapse. Sand and Thomsen⁹² reported the results of TNF-α inhibitor therapy using adalimumab or etanercept in patients who had failed high-dose antihistamines with the addition of an immunosuppressive agent. Improvement was noted in 15 of the 18 patients studied with a diagnosis of CSU or chronic autoimmune urticaria. Complete resolution was seen in 12 of these 15 patients. Response to therapy was frequently seen in the first month but patients generally relapsed within a few weeks following discontinuation.

This group needs much more research to aid in determining the best phenotypes for therapy. There seems to be some indication of efficacy of TNF-α in patients with autoimmune disease. When the practice parameter for urticaria was examined, investigators concluded that the best data regarding biologic agents were for omalizumab.^{94–116} However, there is a paucity of data regarding the group most likely to respond to therapy.

SUMMARY

Most biologics currently approved and in phase II and III clinical trials for use in asthmatics have shown benefit in a common Th2 high phenotype. Studies with these biologics have suggested that response can be predicted based on surrogate biomarkers of Th2 activity, including serum periostin levels, total IgE, sputum and blood eosinophil count, as well as FeNO. Further data are required to determine the optimal biologic based on clinically individualized patterns of these markers. There remains a lack of therapeutic options for patients with neutrophilic asthma expressing a Th2 low, Th-1, or Th-17 phenotype. The mixed results of both brodalumab and the TNF-α

inhibitors suggests there is a phenotype that may benefit from these options but this population is yet to be characterized. In the case of urticaria and atopic dermatitis, there are much less robust data regarding phenotypic discriminators of the patients most likely to benefit from therapy. It is anticipated that further phenoendotypes may be identified as the underlying mechanism of these diseases becomes better understood. The population that benefits from biologic therapy in hereditary angioedema is well characterized but the subpopulations that may respond best to respective treatments remain to be identified.

Determining those patients most likely to benefit from therapy is of critical importance because clinicians must consider the pharmacoeconomic and societal costs of these new therapeutics. Average wholesale prices vary from tens to more than \$100,000 per year. Regardless of indication, there is a surprising paucity of data regarding the pharmacoeconomics of these therapies. Although clinicians focus on controlling their patients' disease, often their response to lack of disease control can be simply to add further medicines. It can easily be seen that, in a health care system that has limits, clinicians must begin to take into account costs and try to optimize less expensive medicines and institute biologic agents only in patients who are most likely to benefit from their use.

The cost of long-term prophylaxis with C1 inhibitor concentrate in patients with hereditary angioedema has been estimated to be as high as €182,000 per year in Denmark.¹¹⁷ In contrast, the cost of treating attacks with icatibant on an as-needed basis would be approximately €93,000 euros per year assuming an average of 4 attacks per month. Furthermore, the price of long-term prophylaxis with danazol has been estimated to be as much as 370 times less than C1 inhibitor concentrate. On-demand therapy does not necessarily equate to cost-effective care in America, with icatibant carrying a cost of approximately \$6800 per dose and other therapies for acute attacks priced similarly.¹¹⁸ Prophylactic treatment of hereditary angioedema with C1-esterase inhibitor is estimated to cost approximately \$487,000 per year in the United States. Estimating 6000 patients with this diagnosis actively seeking treatment per year in the United States prices the annual societal cost of therapy at \$2.9 billion dollars.

Although hereditary angioedema therapy raises significant concerns regarding cost-effectiveness of therapy, the diagnosis affects a fairly small number globally. The current and anticipated use of biologics in asthma, atopic dermatitis, and urticaria do not benefit from a similar low prevalence of disease. Despite omalizumab being approved in the United States for use in asthma since 2003 and for use in urticaria since 2014, few data are available regarding cost-effectiveness in America. The estimated direct cost of omalizumab prescriptions is between \$15,000 and \$44,000 in asthmatics.¹¹⁹ Most studies regarding omalizumab cost-effectiveness are model based and do not represent material cost savings.^{120,121}

It has never been of greater importance to correctly estimate patient outcome before starting therapy based on cost analysis. The significant cost of therapy combined with the growing indications for biologics implies that a trial-by-error model would be unsustainable. Treatment decisions need to be guided by appropriate patient stratification based on an understanding of each individual's underlying phenotype.

REFERENCES

1. Boyman O, Kaegi C, Akdis M, et al. EAACI IG Biologicals Task Force paper on the use of biologic agents in allergic disorders. *Allergy* 2015; 70(7):727–54.

2. Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for U.S. adults: National Health Interview Survey, 2012. National Center For Health Statistics. Vital Health Stat 10 2014;260.
3. Akinbami L, Moorman J, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 2012;(94):1-8.
4. Barnett S, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. J Allergy Clin Immunol 2011;127(1):145-52.
5. Global strategy for asthma management and prevention. Available at: www.ginaasthma.org. Accessed January 20, 2017.
6. Expert Panel Report 3. Guidelines for the Diagnosis and Management of Asthma – summary report 2007. J Allergy Clin Immunol 2007;120:S94-138.
7. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. Am J Respir Crit Care Med 2004;170(8):836-44.
8. Meltzer EO, Blaiss MS, Nathan RA, et al. Asthma burden in the United States: results of the 2009 Asthma Insight and Management survey. Allergy Asthma Proc 2012;33(1):36-46.
9. Williams SA, Wagner S, Kannan H, et al. The association between asthma control and health care utilization, work productivity loss and health-related quality of life. J Occup Environ Med 2009;51(7):780-5.
10. Kaijoka EH, Itoman EM, Li ML, et al. Pediatric prescription pick-up rates after ED visits. Am J Emerg Med 2005;23(4):454-8.
11. Feehan M, Ranker L, Durante R, et al. Adherence to controller asthma medications: 6-month prevalence across a US community pharmacy chain. J Clin Pharm Ther 2015;40:590-3.
12. Melani A, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med 2011;105(6):930-8.
13. Press VG, Arora VM, Shah LM, et al. Misuse of respiratory inhalers in hospitalized patients with asthma or COPD. J Gen Intern Med 2011;26(6):635-42.
14. Patel MR, Leo HL, Baptist AP, et al. Asthma outcomes in children and adolescents with multiple morbidities: findings from the National Health Interview Survey. J Allergy Clin Immunol 2015;135(6):1444-9.
15. Vernon MK, Wiklund I, Bell JA, et al. What do we know about asthma triggers? A review of the literature. J Asthma 2012;49(10):991-8.
16. Se Wenzel, Busse WW. Severe asthma: lessons from the Severe Asthma Research Program. J Allergy Clin Immunol 2007;119(1):14-21.
17. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;42(2):343-73.
18. Cisternas M, Blanc P, Yen I, et al. A comprehensive study of the direct and indirect costs of adult asthma. J Allergy Clin Immunol 2003;111(6):1212-8.
19. Menzies-Gow A, Fan Chung K. Omalizumab for the treatment of severe allergic asthma. Expert Rev Clin Immunol 2008;4(5):543-8.
20. Gibeon D, Chung KF. The investigation of severe asthma to define phenotypes. Clin Exp Allergy 2012;42(5):678-92.
21. Hekking PP, Bel EH. Developing and emerging clinical asthma phenotypes. J Allergy Clin Immunol Pract 2014;2(6):671-80.
22. Chung KF, Adcock IM. Clinical phenotypes of asthma should link up with disease mechanisms. Curr Opin Allergy Clin Immunol 2015;15(1):56-62.

23. Nair P, Dasgupta A, Brightling CE, et al. How to diagnose and phenotype asthma. *Clin Chest Med* 2012;33(3):445–57.
24. Baines KJ, Simpson JL, Wood LG, et al. Transcriptional phenotypes of asthma defined by gene expression profiling of induced sputum samples. *J Allergy Clin Immunol* 2011;127(1):153–60.
25. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178(3):218–24.
26. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181(4):315–23.
27. Bourdin A, Molinari N, Vachier I, et al. Prognostic value of cluster analysis of severe asthma phenotypes. *J Allergy Clin Immunol* 2014;134(5):1043–50.
28. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999;54:236–72.
29. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: the next steps toward personalized care. *J Allergy Clin Immunol* 2015;135(2):299–310.
30. Fingleton J, Braithwaite I, Travers J, et al. Serum periostin in obstructive airways disease. *Eur Respir J* 2016;47(5):1383–91.
31. 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(1):98–104.
32. Shiobara T, Chibana K, Watanabe T, et al. Dipeptidyl peptidase-4 is highly expressed in bronchial epithelial cells of untreated asthma and it increases cell proliferation along with fibronectin production in airway constitutive cells. *Respir Res* 2016;17:28.
33. Mumtazi SR, Hahn PY. Topics in practice management: update on exhaled nitric oxide in clinical practice. *Chest* 2015;149(5):1340–4.
34. Woodruff PG, Modrek B, Choy DF, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009;180(5):388–95.
35. Haldar P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973–84.
36. Parulekar AD, Diamant Z, Hanania NA. Role of T2 inflammation biomarkers in severe asthma. *Curr Opin Pulm Med* 2016;22(1):59–68.
37. Trevor JL, Deshane JS. Refractory asthma: mechanisms, targets, and therapy. *Allergy* 2014;69(7):817–27.
38. Chung KF. Asthma phenotyping: a necessity for improved therapeutic precision and new targeted therapies. *J Intern Med* 2016;279(2):192–204.
39. McKinley L, Alcorn JF, Peterson A, et al. TH17 cells mediate steroid-resistant airway inflammation and airway hyperresponsiveness in mice. *J Immunol* 2008;181(8):4089–97.
40. Shaw DE, Berry MA, Hargadon B, et al. Association between neutrophilic airway inflammation and airflow limitation in adults with asthma. *Chest* 2007;132(6):1871–5.
41. Cui J, Pazdziorko S, Miyashiro JS, et al. TH1-mediated airway hyperresponsiveness independent of neutrophilic inflammation. *J Allergy Clin Immunol* 2005;115(2):309–15.
42. Fu JJ, Baines KJ, Wood LG, et al. Systemic inflammation is associated with differential gene expression and airway neutrophilia in asthma. *OMICS* 2013;17(4):187–99.

43. St-Laurent J, Bergeron C, Page N, et al. Influence of smoking on airway inflammation and remodeling in asthma. *Clin Exp Allergy* 2008;38(10):1852–9.
44. Thomson NC. Novel approaches to the management of noneosinophilic asthma. *Ther Adv Respir Dis* 2016;10(3):211–34.
45. Rasmussen F, Hancox RJ. Mechanisms of obesity in asthma. *Curr Opin Allergy Clin Immunol* 2014;14(1):35–43.
46. Omalizumab [Package Insert] Novartis AG. © 2016 Genentech USA, Inc. Available at: https://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed January 20, 2017.
47. Licari A, Marseglia A, Caimmi S, et al. Omalizumab in children. *Paediatr Drugs* 2014;16(6):491–502.
48. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108(2):184–90.
49. Soler M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18(2):254–61.
50. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics* 2001;108(2):E36.
51. 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(8):804–11.
52. Clavenna MJ, Turner JH, Samuelson M, et al. Differential effect of omalizumab on pulmonary function in patients with allergic asthma with and without chronic rhinosinusitis. *Allergy Asthma Proc* 2016;37(1):23–6.
53. Teach SJ, Gill MA, Togias A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;136(6):1476–85.
54. Flood-Page PT, Menzies-Gow AN, Kay AB, et al. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med* 2003;167(2):199–204.
55. Flood-Page P, Swenson C, Faierman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007;176(11):1062–71.
56. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicenter, double-blind, placebo-controlled trial. *Lancet* 2012;380(9842):651–9.
57. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized: placebo-controlled study. *Am J Respir Crit Care Med* 2011;184(1):1125–32.
58. 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(5):355–66.
59. Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomized dose-ranging study. *Lancet Respir Med* 2014;2(11):879–90.
60. Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011;365(12):1088–98.

61. Brightling CE, Saha S, Hollins F. Interleukin-13: prospects for new treatments. *Clin Exp Allergy* 2010;40(1):42–9.
62. Li W, Gao P, Zhi Y, et al. Periostin: its role in asthma and its potential as a diagnostic or therapeutic target. *Respir Res* 2015;16:57.
63. 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(3):567–74.
64. 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(8):748–56.
65. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013;368(26):2455–66.
66. Busse WW, Holgate S, Kerwin E, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. *Am J Respir Crit Care Med* 2013;188(11):1294–302.
67. Eric 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(7):753–62.
68. 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(1):76–80.
69. Wenzel SE, Barnes PJ, Bleecker ER, et al. A randomized, double-blind, placebo-controlled study of tumor necrosis factor-alpha blockage in severe persistent asthma. *Am J Respir Crit Care Med* 2009;179(7):549–58.
70. Zuberbier T, Aberer W, Asero R, et al. European Academy of Allergy and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum, World Allergy Organization. The EAACI LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014;69(7):868–87.
71. Cooke A, Bulkhi A, Casale TB. Role of biologics in intractable urticarial. *Biologics* 2015;9:25–33.
72. Saini SS. Chronic spontaneous urticarial: etiology and pathogenesis. *Immunol Allergy Clin North Am* 2014;34(1):33–52.
73. Mekori YA, Giorno RC, Anderson P, et al. Lymphocyte subpopulations in the skin of patients with chronic urticarial. *J Allergy Clin Immunol* 1983;72(6):681–4.
74. Caproni M, Giomi B, Volpi W, et al. Chronic idiopathic urticarial: infiltrating cells and related cytokines in autologous serum-induced wheals. *Clin Immunol* 2005;114(3):284–92.
75. Vietri J, Turner SJ, Tian H, et al. Effect of chronic urticarial on US patients: analysis of the National Health and Wellness Survey. *Ann Allergy Asthma Immunol* 2015;115(4):306–11.
76. Kikuchi Y, Kaplan AP. Mechanisms of autoimmune activation of basophils in chronic urticarial. *J Allergy Clin Immunol* 2001;104(6):1056–62.
77. Hide M, Francis DM, Grattan CEH, et al. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticarial. *N Engl J Med* 1998;328:1599–604.
78. Sabroe RA, Fiebiger E, Francis DM, et al. Classification of anti-FcεpsilonRI and anti-IgE autoantibodies in chronic idiopathic urticarial and correlation with disease severity. *J Allergy Clin Immunol* 2002;110(3):492–9.

79. Alyasin S, Hamidi M, Karimi AA, et al. Correlation between clinical findings and results of autologous serum skin test in patients with chronic idiopathic urticarial. *South Med J* 2011;104(2):111–5.
80. Cugno M, Marazano AV, Asero R, et al. Activation of blood coagulation in chronic urticaria: pathophysiological and clinical implications. *Intern Emerg Med* 2010;5:97–101.
81. Saini S, Rosen KE, Hseigh HJ, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol* 2011;128(3):537–73.e1.
82. Maurer M, Rosen K, Hsieh H, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticarial. *N Engl J Med* 2013;368:924–35.
83. Kaplan A, Ledford D, Asthby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticarial despite standard combination therapy. *J Allergy Clin Immunol* 2013;132(1):101–9.
84. O'Donnell BF, Barr RM, Black AK, et al. Intravenous immunoglobulin in autoimmune chronic urticarial. *Br J Dermatol* 1998;138(1):101–6.
85. Dwyer JM. Manipulating the immune system with immune globulin. *N Engl J Med* 1992;326:107–16.
86. Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? *Nat Rev Immunol* 2013;13(3):176–89.
87. Chakravarty SD, Yee AF, Paget SA. Rituximab successfully treats refractory chronic autoimmune urticarial caused by IgE receptor autoantibodies. *J Allergy Clin Immunol* 2011;128(6):1354–5.
88. Steinweg SA, Gaspari AA. Rituximab for the treatment of recalcitrant chronic autoimmune urticarial. *J Drugs Dermatol* 2015;14(12):1387.
89. Tavakol M, Amirzargar AA, Movahedi M, et al. Interleukin-6 and tumor necrosis factor-alpha gene polymorphisms in chronic idiopathic urticarial. *Allergol Immunopathol (Madr)* 2014;42(6):533–8.
90. Piconi S, Trabattoni D, Iemoli E, et al. Immune profiles of patients with chronic idiopathic urticarial. *Int Arch Allergy Immunol* 2002;128(1):59–66.
91. Tedeschi A, Lorini M, Suli C, et al. No evidence of tumor necrosis factor-alpha release in blood of patients with chronic urticarial. *Allergy* 2006;61(4):510–1.
92. Sand FL, Thomsen SF. TNF-alpha inhibitors for chronic urticaria: experience in 20 patients. *J Allergy (Cairo)* 2013;2013:130905.
93. Wilson LH, Eliason MJ, Leiferman KM, et al. Treatment of refractory chronic urticarial with tumor necrosis alfa inhibitors. *J Am Acad Dermatol* 2011;64(6):1221–2.
94. Bernstein J, Lang D, Khan D, et al. The diagnosis and management of acute and chronic urticarial: 2014 update. *J Allergy Clin Immunol* 2014;133(5):1270–7.e66.
95. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C1-esterase. *Am J Sci* 1963;31:37–44.
96. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy* 2014;69(5):602–16.
97. Zuraw BL, Bernstein JA, Lang DM, et al. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol* 2013;131(6):1491–3.

98. Pappalardo E, Cicardi M, Duponchet C, et al. Frequent de novo mutations and exon deletions in the *C1inhibitor* gene of patients with angioedema. *J Allergy Clin Immunol* 2000;106(6):1147–54.
99. Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun* 2006;343(4):1286–9.
100. Bygum A. Hereditary angioedema in Denmark: a nationwide survey. *Br J Dermatol* 2009;161(5):1153–8.
101. Bork K, Frank J, Grundt B, et al. Treatment of acute attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol* 2007;119(6):1497–503.
102. Craig T, Aygoren-Pursun E, Bork K, et al. WAO guideline for the management of hereditary angioedema. *World Allergy Organ J* 2012;5(12):182–99.
103. Zanichelli A, Vacchini R, Badini M, et al. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients. *Allergy* 2011;66(2):192–6.
104. Prematta M, Gibbs JG, Pratt EL, et al. Fresh frozen plasma for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol* 2007;98:383–8.
105. Gelfand JA, Sherins RJ, Alling DW, et al. Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. *N Engl J Med* 1976;295(26):1444–8.
106. Du-Thanh A, Raison-Peyron N, Drouet C, et al. Efficacy of tranexamic acid in sporadic idiopathic bradykinin angioedema. *Allergy* 2010;65:793–5.
107. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010;363(6):532–41.
108. Lumry WR, Li HH, Levy RJ, et al. Randomized placebo-controlled trial of the bradykinin B2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. *Ann Allergy Asthma Immunol* 2011;107(6):529–37.
109. Sheffer AL, Campion M, Levy RJ, et al. Ecallantide (DX-88) for acute hereditary angioedema attacks: integrated analysis of 2 double-blind, phase 3 studies. *J Allergy Clin Immunol* 2011;128(1):153–9.
110. Levy RJ, Lumry WR, McNeil DL, et al. EDEMA4: a phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. *Ann Allergy Asthma Immunol* 2010;104(6):523–9.
111. Lumry WR, Bernstein JA, Li HH, et al. Efficacy and safety of ecallantide in treatment of recurrent attacks of hereditary angioedema: open-label continuation study. *Allergy Asthma Proc* 2013;34(2):155–61.
112. Crag TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol* 2009;124(4):801–8.
113. Craig TJ, Wasserman RL, Levy RJ, et al. Prospective study of rapid relief provided by C1 esterase inhibitor in emergency treatment of acute laryngeal attacks in hereditary angioedema. *J Clin Immunol* 2010;30(6):823–9.
114. Craig TJ, Bewtra AK, Bahna SL, et al. C1 esterase inhibitor concentrate in 1085 hereditary angioedema attacks – final results of the IMPACT2 study. *Allergy* 2011;66(12):1604–11.
115. Zuraw BL, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. *Am J Med* 2012;125(9):938.

116. Lumry W, Manning ME, Hurewitz DS, et al. Nanofiltered C1-esterase inhibitor for the acute management and prevention of hereditary angioedema attacks due to C1-inhibitor deficiency in children. *J Pediatr* 2013;162(5):1017–22.
117. Rasmussen ER, Aagaard L, Bygum A. Real-life experience with long-term prophylactic C1 inhibitor concentrate treatment of patients with hereditary angioedema: effectiveness and cost. *Ann Allergy Asthma Immunol* 2016;116(5):476–7.
118. Tilles SA, Borish L, Cohen JP. Management of hereditary angioedema in 2012: scientific and pharmacoeconomic perspectives. *Ann Allergy Asthma Immunol* 2013;110(2):70–4.
119. Belliveau PP, Lahoz MR. Evaluation of omalizumab from a health plan perspective. *J Manag Care Pharm* 2005;11(9):735–45.
120. 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(1):120–9.
121. Wu AC, Paltiel AD, Kuntz KM, et al. Cost-effectiveness of omalizumab in adults with severe asthma: results from the Asthma Policy Model. *J Allergy Clin Immunol* 2007;120(5):1146–52.