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ABSTRACT

**Introduction:** Allergic conditions such as asthma and atopic dermatitis have a high prevalence but represent a heterogeneous group of diseases despite similar clinical presentation and underlying pathophysiology. A better understanding of the phenotypes and endotypes of these diseases has driven rapid development of biologic medications targeting many steps of the inflammatory pathways.

**Areas Covered:** There are 2 major inflammatory pathways that drive allergic diseases: Type-2 (Th-2) inflammation and non-type 2 inflammation. All of the biologic medications currently approved for use, and most of the biologic medications under development for allergic diseases have focused on the Th-2 inflammatory pathway. Biologic targets along this pathway include Anti-Immunoglobulin E (IgE), Anti-Interleukin -5 (IL-5), Anti-IL 4, and Anti-IL-13. Although the most study has been done in the realm of severe asthma, biologic targets for other allergic diseases including atopic dermatitis, chronic rhinosinusitis with nasal polyposis, chronic idiopathic urticaria, eosinophilic esophagitis, and eosinophilic granulomatosis with polyangiitis are also discussed.

**Expert Commentary:** Novel biologic therapies have emerged over the last several years that have revolutionized the management of patients with refractory allergic disease.

**KEY WORDS:** Endotype, Biologic medication, Allergic diseases, Type 2-inflammation, Non-Type 2 inflammation
1. INTRODUCTION

Allergic conditions including asthma and atopic dermatitis are among the most common diseases throughout the world. Despite wide-spread clinical therapies, many patients continue to have uncontrolled symptoms and it has become clear that these entities may have a heterogeneous presentation. As more is understood regarding the underlying mechanisms of these diseases, it is now more evident than ever that, although some patients may present with a similar clinical picture, the drivers of disease can be quite diverse between patients. This has brought the concept of endotyping to the forefront of our understanding of asthma and other allergic diseases with resultant implications for novel therapy. In contrast to phenotype- a clinical description of a patient or disease entity- an endotype is defined as a sub-classification of a particular disease that is based on a particular pathophysiologic mechanism and associated clinical biomarkers. As we have gained more understanding regarding the pathophysiologic drivers in asthma and other allergic diseases, targeted therapies have become available based on specific endotypes. Targeted therapies hold the expectation and promise of precision, personalized medicine. In this article we will review the current landscape of the use of biologics in severe asthma and other allergic diseases.

2. SEVERE ASTHMA

Asthma is a chronic, heterogeneous inflammatory disease of the airways, characterized by recurrent episodes of bronchoconstriction, airway hyper-responsiveness and mucus hypersecretion. It affects approximately 300 million people worldwide and 24 million people in the United States [1, 2]. While asthma outcomes have improved over the last few decades with increased use of controller therapies, there remains a large unmet need for improved therapies in severe asthma. Severe asthma is a subset
of difficult-to-treat asthma that occurs in patients who remain uncontrolled despite high doses of inhaled corticosteroids (ICS) combined with long acting beta agonists (LABA), leukotriene modifiers, or theophylline [3]. Severe asthma affects 5%-10% of the adult asthma population and is associated with increased mortality, increased hospitalizations, significant burden of symptoms, significant health care costs (higher than type 2 diabetes, stroke, and COPD [4]), significant missed work and school, and even lower likelihood for employment [1].

The first step in management of severe asthma is to confirm the diagnosis of severe asthma. A clinical history should focus on symptoms of dyspnea, cough, wheeze, chest tightness, and nocturnal symptoms. Diseases that can mimic asthma should be excluded. These can include chronic obstructive pulmonary disease (COPD), bronchiolitis obliterans, bronchiectasis, tracheobronchomalacia, vocal cord dysfunction, and hypersensitivity pneumonitis [3]. Appropriate clinical testing such as full pulmonary function testing with evidence of reversibility of airflow obstruction, and/or methacholine challenge showing evidence of airway hyper-responsiveness assist in making the diagnosis of asthma. Once a diagnosis of asthma is confirmed and comorbidities including gastroesophageal reflux disease, rhinosinusitis, obstructive sleep apnea, cardiovascular comorbidities and infections have been addressed, initiation of appropriate first-line therapies, such as short acting beta agonists and ICS, should be implemented. Avoidance of precipitating exposures and mitigation of seasonal and environmental allergens should also be addressed. Immunotherapy can be considered in appropriate patients. If the patient remains symptomatically uncontrolled, the addition of higher dose ICS/LABA inhaled medications should be considered. Special attention to inhaler technique and adherence is important, and addressing these can improve symptoms in 50-80% of severe asthmas [5]. Because administration of biologic agents may be costly and time-intensive, other adjunctive therapies should be considered. The use of tiotropium, a long-acting inhaled anti-cholinergic, was approved for the use in asthma in 2015 and has been demonstrated to reduce asthma exacerbations [6]. More recently, chronic
macrolide therapy has been shown to decrease number of exacerbations in asthma, regardless of underlying eosinophilia [7]. Bronchial thermoplasty is a bronchoscopic procedure that reduces airway smooth muscle and has effects on airway nerves. It has also been shown to reduce asthma exacerbations out to 5 years [8].

There are 2 major inflammatory pathways in asthma, Type 2 (Th2)-driven inflammation and non-Type 2-driven inflammation. Type 2 pathway inflammation is characterized by activation of cytokines from T helper 2 cells and innate lymphoid cells (ILC) 2 that result in the atopy and eosinophilia characteristic of asthma. The inflammatory cascade of both type 2 and non-type 2 pathways start at the epithelial cells of the airways. Cytokines, such as IL-23, IL-33, and thymic stromal lymphopoietin (TSLP) are released from the epithelial cells in response to pollutants, allergens, and infectious agents. These cytokines then signal downstream cells, such as eosinophils, basophils, mast cells, and lymphocytes, which, in turn, produce and are effected by cytokines that characterize the asthmatic response [1]. Biologic medications, thus far, have predominantly targeted specific downstream cytokines of the Type 2 pathway. These biologic targets are Interleukin (IL)-4, IL-5, and IL-13. Most clinical biomarkers developed for monitoring response to therapy (e.g. eosinophils in blood or sputum, exhaled nitric oxide) represent activation of these pathways [9] (FIGURE 1). IL-4 and IL-13 work to promote Immunoglobulin E (IgE) isotype-switching in B cells; when IgE binds to its receptor on mast cells and basophils, cellular activation and degranulation occurs with recruitment of other inflammatory cells to the airways.

Another type 2 cytokine is IL-5. It is critical in eosinophilic proliferation, maturation, and chemotaxis. Eosinophils release eosinophil cationic protein, eosinophil derived neurotoxin and major basic protein that cause local tissue inflammation on the airways. More recently, TSLP, which is required for Type 2 differentiation, has been recognized as an important mediator of inflammation and is being evaluated as an important biologic target [10].

- 2.1 IgE
Omalizumab

Asthma had long been considered a disease of atopy, driven by allergen specific IgE reactions. Omalizumab targets circulating IgE and in 2003 became the first FDA-approved biologic medication for use in severe asthma. Omalizumab is a recombinant humanized anti-IgE antibody that blocks IgE from binding to its high affinity receptor. The high affinity IgE receptor (FcεRI) is found on mast cells and basophils, and blocking of IgE binding blunts the allergic response driven by histamines, leukotrienes, prostaglandins, and other mediators.

Early studies of the anti-IgE monoclonal antibody examined early and late asthmatic responses to inhaled allergens. In a small parallel-group, randomized, double blind, placebo-controlled study of 19 asthmatics, those patients in the anti-IgE antibody group showed a reduced free serum IgE level, increased dose of allergen needed to provoke an early asthmatic response, and reduction in the mean maximal fall in FEV₁ during the early and late response when compared to the placebo group [11].

Subsequent larger trials showed that omalizumab reduced asthma exacerbations in patients with allergic asthma during a stable inhaled corticosteroid phase followed by a corticosteroid reduction phase [12, 13]. Both studies recruited asthmatic patients on inhaled corticosteroid therapy with a serum IgE level between 30-700 IU/mL and skin prick testing positive for at least 1 common allergen. These large clinical trials, with greater than 500 patients each, demonstrated that the omalizumab group reported significantly fewer asthma exacerbations compared to placebo group during both the stable steroid phase and the steroid reduction phase [12, 13].

A subsequent large prospective, multicenter, double-blind, placebo controlled trial showed that omalizumab also improves exacerbation rate in patients with more severe asthma [14]. In a study of 850 patients with severe asthma (17% of whom were on stable dose oral corticosteroids), the omalizumab group (at 48 weeks) showed a 25% reduction in exacerbations, improved AQLQ(S) scores, reduced mean daily albuterol puffs, and decreased asthma symptom scores compared to placebo [14].
Interestingly, a post hoc analysis of this study showed that those patients with high levels of specific type 2 biomarkers, including blood eosinophils, serum periostin levels, and Fractional exhaled Nitric Oxide (FeNO) levels, demonstrated the greatest reduction in asthma exacerbations [15]. The most recent Cochrane Review included 25 trials of omalizumab in severe asthma and concluded that omalizumab reduced exacerbations and hospitalizations in patients with severe persistent Ig-E mediated allergic asthma who require oral corticosteroids [16].

While omalizumab was first approved for use in severe allergic asthma in patients aged 12-75 by the FDA in 2003, it was approved for children aged 6-12 with uncontrolled moderate to severe persistent allergic asthma in 2016. Additionally, Omalizumab is approved in Europe in patients with allergic asthma with IgE levels up to 1500 IU/ml based on safety data which showed that dosing of omalizumab above the initial recommended dosing table had consistent pharmacokinetics and pharmacodynamics without an increase in adverse events [17].

2.2 IL-5

IL-5 is a cytokine secreted predominantly by T lymphocytes, mast cells, eosinophils and ILC2 cells [18]. IL-5 is a potent eosinophilic cytokine [10] and is responsible for cellular differentiation and maturation of eosinophils in the bone marrow, as well as survival and activation of eosinophils at peripheral sites of allergic inflammation. This has made IL-5 and its receptor, found on eosinophils and basophils, a biologic target in Type 2 and hyper-eosinophilic, intrinsic asthma. IL-5 is also important in B-cell survival and maturation, and therefore can promote IgE production and subsequent mast cell and basophil activation [1]. Because of its role in this pathway, it was thought to be a potential target for extrinsic, allergic asthma as well. Blocking IL-5 activity with monoclonal antibodies has revolutionized the management of severe eosinophilic asthma. To date, there are 3 biologics targeting IL-5 activity: mepolizumab, reslizumab and benralizumab.

_Mepolizumab_
Mepolizumab is a humanized monoclonal anti IL-5 antibody. Mepolizumab was first studied in several trials in a general asthma population that was not enriched for eosinophilia [19, 20, 21]. Although it was shown that even a single dose of mepolizumab decreases both blood and sputum eosinophils [21], it did not have an effect on airway hyper-responsiveness, FEV₁, nor on peak expiratory flow rates (PEFR) [20]. It wasn’t until study populations were enriched for eosinophilic asthma that mepolizumab began to show improvement in clinical outcomes. In 2009, Nair, et al., published a small double-blind, randomized parallel study with patients with persistent sputum eosinophilia (more than 3%) despite at least 4 weeks of oral corticosteroid therapy [22]. They showed a significant improvement in asthma exacerbations in the mepolizumab group compared to the placebo group. The mepolizumab group was also able to more aggressively titrate down the dose of oral corticosteroid. A larger, longer (1 year vs 5 weeks) trial published the same year, showed mepolizumab was associated with an approximately 57% relative reduction in exacerbations compared to placebo as well as an improvement in Asthma Quality of Life Questionnaire (AQLQ) scores [23].

Mepolizumab was subsequently studied in eosinophilic patients in large trials with continued promising results. The DREAM study showed that the safety and efficacy of 3 different doses of intravenous mepolizumab (75 mg, 250 mg, or 750 mg) were equally effective at significantly reducing asthma exacerbations [24]. Given the expense and time burden of administering an IV infusion of the drug on a monthly bases, Ortega et al., (MENSA) compared intravenous vs subcutaneous administration of the drug [25] in a phase 3 trial of 576 patients with eosinophilic asthma (defined by a peripheral eosinophilia of least 300 cells/µL) on high dose ICS with or without oral corticosteroid use. Patients were randomized to monthly mepolizumab administration of 75 mg IV, 100 mg subcutaneous, or placebo for 32 weeks; both intravenous and subcutaneous dosing schemes reduced asthma exacerbations by approximately 50% when compared to placebo and there were no significant differences in adverse events [25]. Another phase 3 studied also demonstrated that eosinophilic
Asthma patients treated with systemic corticosteroids could benefit from mepolizumab use [26]. Subjects receiving mepolizumab had improved FEV₁ even though they were able to reduce systemic corticosteroid dose by approximately 50%. In a more recent phase 3b study, mepolizumab was associated with significant improvements in health-related quality of life in patients with severe eosinophilic asthma, and had a safety profile similar to that of placebo [27]. Finally, the most recent Cochrane Review looking at mepolizumab in asthma reviewed 8 trials, but only one included the now-approved subcutaneous route of administration. That review concluded that measures of quality of life and reduction in exacerbation rates were only noted in severe eosinophilic asthma, and more studies were needed to clarify which subgroups of severe asthma may benefit from mepolizumab [28]. Mepolizumab was approved for use by monthly injection via the subcutaneous route in severe asthma for patients 12 years or older by the FDA on November 4, 2015.

Reslizumab

Similar to mepolizumab, reslizumab is also a humanized monoclonal antibody directed at IL-5, but is administered in the intravenous form and dosed in a weight-based fashion, 3.0 mg/kg. An early, double-blind, placebo-controlled study of 106 patients with severe asthma that were poorly controlled on high-dose ICS in combination with at least one other agent, and with sputum eosinophils of 3% or more were randomized to reslizumab infusion vs placebo. The reslizumab group was found to have significant improvement in Asthma Control Questionnaire (ACQ), reduction in sputum eosinophils, and reduction in asthma exacerbations (8% vs 19%) when compared to the placebo group [29]. Given this promising result, larger randomized control phase III clinical trials were then conducted. Castro, et al, enrolled patients with inadequately controlled asthma on medium to high dose ICS with at least 1 exacerbation in the prior year, with at least 3% sputum eosinophils. The reslizumab group showed a significant reduction in asthma exacerbations (50-59%), improvement in FEV₁, and improvement in asthma quality of life scores [30]. More recent studies have demonstrated that reslizumab produced larger reductions.
in asthma exacerbations and larger improvements in lung function in patients with late versus early-onset asthma [31]. Further trials have recently been completed investigating reslizumab administered via the subcutaneous route. These phase III clinical trials, which are not yet published (NCT02452190 and NCT02501629), looked at reduction of clinical asthma exacerbations (CAEs) and reduction of daily oral corticosteroids dose, respectively. Teva Pharmaceuticals announced in January 2018 that these trials did not meet their primary endpoints, but no new safety concerns were identified with subcutaneous administration of the medication [32].

Reslizumab was approved by the FDA for use in severe eosinophilic asthma in patients 18 years and older on March 23, 2016. It was approved for intravenous infusion every 4 weeks at a dose of 3.0 mg/kg.

Benralizumab

As of November 2017 a third anti-IL-5 biologic agent, benralizumab, has been approved for add-on maintenance for severe eosinophilic asthma. In contrast to mepolizumab and reslizumab, benralizumab targets the IL-5Rα that is found on the surface of eosinophils and basophils. When benralizumab is bound to the receptor, it induces apoptosis of the bound cell through activity of natural killer cells [18]. Initial studies showed that a single dose of intravenous benralizumab administration decreased airway, sputum, bone marrow, and peripheral blood eosinophil counts [18], and subcutaneous dosing of both 20 gm and 100 mg decreased asthma exacerbations [33]. Subsequently, 2 large phase III trials were conducted. Bleecker, et al, (SIRROCO) [34], and FitzGerald, et al, (CALIMA) [35], both looked at annual rate of asthma exacerbation in poorly-controlled asthmatics on high dose ICS and LABA. Patients were stratified into high (at least 300 cells/µl) and low (less than 300 cells/µl) peripheral eosinophilia groups. They found that in the high eosinophil group, both Q4 week dosing and Q8 week dosing, significantly
reduced annual asthma exacerbation rate and improved FEV₁. Additionally, both studies found that the Q8 week dosing also improved asthma quality of life outcomes.

In a more recent study of benralizumab at a dose of 30 mg administered subcutaneously either every 4 weeks or every 8 weeks versus placebo was done to evaluate its efficacy on the reduction in oral glucocorticoid dose in adult patients with severe eosinophilic asthma [36]. The two benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75%, as compared with a reduction of 25% in the oral glucocorticoid doses in the placebo group (P<0.001). The odds of a reduction in the oral glucocorticoid dose were more than 4 times as high with benralizumab than with placebo. Benralizumab administered every 8 weeks resulted in an annual exacerbation rate that was 70% lower than the rate with placebo (0.54 vs. 1.83, P<0.001). These effects occurred without a sustained effect on FEV₁.

Benralizumab was approved by the FDA on 11/15/17 for patients 12 years old or older in inadequately controlled severe asthma with an eosinophil phenotype. It is the first biologic to be approved with a Q8 week subcutaneous dosing (after Q4 week dosing for the first 3 doses). In addition to adding a third IL-5 agent to the biologic market, the unique mechanism of action of benralizumab, when compared to mepolizumab and reslizumab, may offer additional benefits to patients who have failed previous therapy. Additionally, benralizumab would potentially minimize cytokine production associated with anti-cytokine antibodies, as can occur with use of both mepolizumab and reslizumab [35].

2.3 IL-4 and IL-13

Interest in biologic agents in asthma extends beyond IgE and IL-5 targeted therapy. IL-4 and IL-13 are also key components of the Th-2 pathway and pathogenesis of asthma. IL-4 is important in CD4+ lymphocyte differentiation and the production of IgE. IL-13 drives airway hyper-responsiveness, mucus
production, and subepithelial fibrosis [37]. These two interleukins also share a receptor complex (IL-4Rα/IL-13Rα1). Several agents that target IL-4 and/or IL-13 are being studied.

**Dupilumab**

Dupilumab is a fully humanized monoclonal antibody to the α-subunit of the IL-4 receptor, and thereby inhibits both IL-4 and IL-13 activity. Dupilumab has FDA approval for atopic dermatitis but has yet to be approved for use in severe asthma. Phase II studies have been completed and are promising. In a phase 2a study, Wenzel, et al, enrolled patients with moderate-to-severe asthma and elevated eosinophil levels who were also on ICS and LABAs. They were randomized to dupilumab therapy vs. placebo. The dupilumab group had fewer asthma exacerbations when LABAs and ICS were withdrawn, improved lung function, and reduced levels of Th2-associated inflammatory markers [38]. In the Phase 2b study, Wenzel, et al, enrolled 769 patients with severe asthma with uncontrolled symptoms on medium-to high dose ICS plus LABA. They found the dupilumab groups showed improvement in lung function and reduced severe exacerbations compared to placebo. This was irrespective of baseline peripheral eosinophil count; however, the subgroup with at least 300 eosinophils/µl had the greatest improvement in FEV1 and reduction in annualized severe exacerbation rates [39].

While phase III dupilumab trials have yet to be published, a press release by Regeneron Pharmaceuticals, Inc. and Sanofi on 9/11/17 revealed that the phase III trial (QUEST) enrolled 1902 asthmatics with uncontrolled, persistent asthma and met its two primary outcomes. Dupilumab had reduced severe asthma exacerbations at week 52 and had improved lung function compared to placebo by week 12. Outcomes were more pronounced in the patients with higher (at least 300 cells/µl) peripheral eosinophilia [40].

**Lebrikizumab and Tralokinumab**
Two IL-13 antibodies, lebrikizumab and tralokinumab, are also being studied for their use in severe asthma. Lebrikizumab and tralokinumab are both humanized monoclonal antibodies that inhibit the function of IL-13. Lebrikizumab was looked at in replicate phase III trials (LAVOLTA I and LAVOLTA II) after phase II studies showed it improved lung function and exacerbation rate in asthmatics with high blood eosinophil or periostin levels [41]. Periostin is an extracellular protein that is secreted by airway epithelial cells when exposed to IL-4 or IL-13 [37]. The LAVOLTA trials enrolled over 2000 patients with uncontrolled asthma on ICS, who were stratified based on asthma medications, history of exacerbations, and serum periostin levels. Although both studies enrolled the same patient population, the LAVOLTA 1 study met its primary outcomes of reduced exacerbation rates in the lebrikizumab group in the high biomarker subgroups, whereas the LAVOLTA II did not. Additionally, there was a high number of adverse events in both treatment and placebo groups [41]. No other clinical trials of the use of lebrikizumab in severe asthma are currently ongoing.

• Tralokinumab is currently being studied in phase III clinical trials; although the preliminary data suggest it may not be beneficial in the general severe asthma population. After an early study demonstrated improvement in asthma control score in those patients with high sputum IL-13 levels [42], a phase IIb study in 452 patients with severe and uncontrolled asthma who had at least 2-6 exacerbations per year was conducted [43]. They found that the tralokinumab group did not show significant reduction in annualized asthma exacerbation rate, the study’s primary endpoint. However, the patients in the tralokinumab group (when dosed every two weeks) did show significant improvement in FEV₁. Additionally, in post-hoc sub-group analyses, a trend toward improvement in annualized asthma exacerbation rate was noted in two biomarker groups: those that showed high levels of serum dipeptidyl peptase-4 (DPP-4), a gene that is highly induced by IL-13, and periostin. Two Phase III studies (NCT02281357, NCT02194699) have been recently completed, but the data are not yet published. AstraZeneca released a statement
in November 2017 indicating that these two trials did not meet their respective primary endpoints of reduction in annualized asthma exacerbation rate (AAER) and reduction in daily, average, oral corticosteroid dose [44].

- **2.4 Prostaglandin D$_2$ Receptor**

  *Fevipiprant*

  The prostaglandin D$_2$ receptor 2 (DP$_2$ receptor) has also become a targeted area of interest in asthma given its role in the Th2 pathway. The DP$_2$ receptor (also known as CRTH2) mediates migration of Th2 cells, stimulates production of IL-4, IL-5, and IL-13, and delays apoptosis of the Th2 cell. The DP$_2$ receptor is also found on the surface of eosinophils and mediates degranulation and chemotaxis of the eosinophil. Fevipiprant (QAW039) is a selective and potent antagonist of the DP$_2$ receptor. Fevipiprant was looked at in a small, single center, randomized trial of 61 asthma patients with at least 2% sputum eosinophils and 1 severe exacerbation requiring systemic corticosteroids [45]. When administered orally on a daily basis, the fevipiprant group was noted to have significant reduction in sputum eosinophil levels, 4.5 times the reduction than in the placebo group. Fevipiprant also significantly improved post-bronchodilator FEV1 and had a favorable safety profile; further phase III studies are underway.

- **2.5 Thymic Stromal Lymphopoietin (TSLP)**

  *Tezepelumab*

  There is also interest in thymic stromal lymphopoietin (TSLP) as a target for biologic therapy in asthma. TSLP is an epithelial-cell-derived cytokine that drives allergic inflammatory responses by acting through the innate immune system. Among others, it activates dendritic cells and mast cells, and levels of TSLP protein found the airway of asthmatics are higher when compared to normal [46]. Tezepelumab (AMG 157) is a humanized monoclonal antibody that binds TSLP and prevents interaction with its
receptor. A small, proof-of-concept study randomized 31 patients with mild allergic asthma to receive tezepelumab or placebo. The authors looked at attenuation of the late asthmatic response. The late asthmatic response is a well-defined phenomenon in asthmatics who note a delayed episode of decreased lung function approximately 3-8 hours after exposure to an aeroallergen to which they are sensitized. The study did find that tezepelumab did attenuate the degree of bronchoconstriction in the late asthmatic response, as well as reducing markers of airway inflammation, namely FeNO and sputum eosinophils, throughout the duration of the study [46].

More recently, Corren and colleagues conducted a phase 2, randomized, double-blind, placebo-controlled trial, comparing subcutaneous tezepelumab at three dose levels with placebo over a 52-week treatment period [47]. The use of tezepelumab at a dose of 70 mg every 4 weeks, 210 mg every 4 weeks, or 280 mg every 2 weeks resulted in a statistically significant reduction in annualized asthma exacerbation rates at week 52 when compared to placebo. The pre-bronchodilator FEV₁ at week 52 was also higher in all tezepelumab groups compared with placebo. Overall, those who received tezepelumab had lower rates of clinically significant asthma exacerbations than those who received placebo, independent of baseline blood eosinophil counts, exhaled nitric oxide levels or TH2 status.

- **2.6 Non-Th2 inflammation targets**

All of the approved biologics and most of the biologics currently in development focus on Th2 inflammatory pathway. This has left a large unmet need for patients with severe asthma without significant Th2 inflammation. These patients have alternate endotypes of asthma, including neutrophilic, mixed inflammatory, or pauci-granulocytic asthma. The non-Th 2 pathway also begins at the epithelial lining of the airways. Infectious agents and irritants activate cytokines such as IL-33 and IL-25 which, in turn, activate ILC2, Th-17 lymphocytes, and Th-1 lymphocytes. Th-1 and Th-17 lymphocytes activate neutrophilic inflammation through IL-6, IL-17, interferon-gamma (INF-γ) and tumor necrosis
factor-alpha (TNF-\(\alpha\)) [4]. A randomized control trial looking at Brodalumab, an IL-17 receptor antagonist, failed to show clinical benefit based on asthma symptoms scores [48]. CXCR2 is another target being investigated. CXCR2 is a potent chemoattractant for neutrophils, and a small trial looking at Navarixin, a CXCR2 receptor antagonist, did show a reduction in sputum and blood neutrophils and trend toward better asthma control based on ACQ, but no significant change in FEV\(_1\) [49].

3. ATOPIC DERMATITIS (AD)

Atopic dermatitis (AD) is a pruritic, chronic inflammatory disorder of the skin. It often has onset in childhood but can persist to adulthood. It is frequently diagnosed in conjunction with asthma and allergic rhinitis, implicating Th2 inflammation in this disease [50]. The pathogenesis of atopic dermatitis is driven by an imbalance of Th2 inflammation due to both environmental and genetic factors. Just like asthma, elevated levels of circulating Th2 cells lead to high levels of IL-4, IL-5, and IL-13. These cytokines then attract eosinophils and basophils and promote B-cell production of IgE. Unique to atopic dermatitis is the presence of these cytokines in the dermis and epidermis. When present in the skin, these cytokines act on keratinocytes to disrupt the barrier function of the skin. This allows for penetration of allergens and pathogens into the skin, which leads to release of TSLP, IL-33, and IL-25, thus promoting the scratch-itch cycle. Furthermore, TSLP, IL-33 and IL-25 activate innate lymphoid cells (ILC), which subsequently promote further Th2 inflammation [50]. Just as in asthma, there has been significant interest in targeting the Th2 inflammatory pathway with biologic targets (FIGURE 2).

• 3.1 IL-4 and IL-13

Many patients with AD have elevated levels of both IL-4 and IL-13. As noted above, the signaling pathways of these two interleukins merge at a common receptor, IL-4R\(\alpha\). Because of this, both the IL-4 and IL-13 pathways have become targets for biologic therapies. Dupilumab antagonizes the IL-4R\(\alpha\),
thereby, blocking both pathways simultaneously. After a phase II trial showed that dupilumab improved Eczema Area and Severity Index (EASI) score and pruritus scores [51], while maintaining a favorable side effect profile, 2 simultaneous phase III trials (SOLO I and SOLO II) were completed and published in 2016 [52]. The two studies enrolled nearly 1400 patients with moderate-to-severe AD inadequately controlled on topical therapies to receive 16 weeks of subcutaneous dupilumab or placebo. The dupilumab groups reported significant improvements in the Investigator’s Global Assessment (IGA, one of the most commonly used disease severity scales in atopic dermatitis), improvement in EASI scores, as well as improvement in other validated measures of pruritus, anxiety and depression, and quality of life [52]. Subsequently, a large phase III trial showed ongoing safety and efficacy of the use of long term dupilumab (1 year) in adults with moderate-to-severe atopic dermatitis inadequately controlled on topical corticosteroids[53]. Dupilumab was approved by the FDA on March 28, 2017 for use in moderate-to-severe atopic dermatitis when symptoms are inadequately controlled on topical therapy.

Tralokinumab and Lebrikizumab, both IL-13 monoclonal antibodies, are also under investigation in atopic dermatitis. A multi-center phase IIb has been completed but not yet published examining tralokinumab in AD, with a primary outcome of identifying the proportion of patients achieving IGA assessment of 0 (clear) or 1(almost clear) (NCT02347176). Simultaneous phase III trials also underway (NCT03131648, NCT03160885). Additionally, a phase II study evaluating lebrikizumab and reduction in EASI score has been completed but not yet published (NCT02340234).

- **3.3 IgE, IL-5, and other targets**

Other cytokines in the cascade of inflammation have also been evaluated in atopic dermatitis. Omalizumab was initially shown to improve pruritus scores but not overall disease severity. However, when looking specifically at patients with AD who do not have mutations in filaggrin, which is important in maintaining skin barrier protection, omalizumab did improve skin disease severity when compared to
patients with filaggrin mutations [54]. Mepolizumab, an IL-5 antibody, has also been investigated for use in AD, although in small studies did not show any significant clinical benefit despite reduction in peripheral eosinophil levels [55]. Finally, an IL-31 antagonist is currently in phase I and II clinical trials. IL-31 is a cytokine that is produced by Th2 cells, keratinocytes, and mast cells in response to exposure to microbial peptides. It has been found in high levels in skin of patients with AD, and in murine models, overexpression of IL-31 resulted in AD-like symptoms [50].

4. **CHRONIC RHINOSINUSITIS with NASAL POLYPOSIS (CRSwNP)**

   Chronic rhinosinusitis with nasal polyps (CRSwNP) frequently occur in patients with asthma, atopic dermatitis, and chronic sinusitis. Polyps are often associated with tissue eosinophilia and can lead to significant symptoms, such as chronic headache and anosmia, both of which can significantly affect quality of life. The Th2 inflammatory pathway is thought to mediate nasal polyps [56]. Currently, there are no biologics available for the indication of nasal polyposis.

   • **4.1 IgE**

   Omalizumab has been found to improve nasal symptoms based on endoscopic polyp scores, but this has only been looked at in patients with comorbid asthma [57].

   • **4.2 IL-5**

   Anti IL-5 antibodies, mepolizumab and reslizumab, have both been studied in proof-of-concept CRSwNP studies. Mepolizumab showed improvement in nasal polyp scores and a trend toward improvement in clinical symptoms [58]. Based on these findings, a phase III clinical trial for mepolizumab in severe nasal polyposis refractory to topical steroids is underway (NCT03085797). Reslizumab has been shown to reduce nasal and serum eosinophils [59], but no further trials are underway. It should be
noted, however, in patients with nasal polyps and comorbid asthma, reslizumab may be an effective option. In a subgroup analysis from the reslizumab trials in severe asthma [30], patients with asthma with CRwNP showed an 83% decrease in asthma exacerbations, compared to a 70% decrease in patients with asthma and chronic sinusitis without nasal polyps

• 4.3 IL-4 and IL-13

Dupilumab improved endoscopic nasal polyp scores, as well as improved sense of smell and other clinical markers when added to intranasal corticosteroids in 60 patients with severe chronic sinusitis with nasal polyposis [56]. A phase III clinical trial is currently underway (NCT02912468).

5. CHRONIC IDIOPATHIC URTICARIA (CIU)

Chronic idiopathic urticaria (CIU) is defined as itchy hives that last for at least 6 weeks and come about without obvious cause. Due to the severity and duration of bothersome symptoms, the disease has a significant effect on a patient’s quality of life [60]. Histamine release from mast cells and basophils is known to play a key role in the pathogenesis of urticaria. Until 2014, anti-histamines were the mainstay of therapy, however, many patients with chronic idiopathic urticaria remained symptomatic despite anti-histamine usage.

• 5.1 IgE

IgE, when bound to its high affinity receptor (FcεRI), found on mast cells and basophils, leads to activation and de-granulation of these cells, thus leading to urticaria. After promising phase II trials, 2 large phase III trials (ASTERIA I and II) evaluating omalizumab in CIU investigated the improvement in itch-severity score and safety profile of omalizumab in patients with moderate-to-severe chronic idiopathic urticaria who remained symptomatic despite H₁-antihistamine therapy [60, 61]. The
omalizumab groups in both studies showed a significant improvement in itch-severity scores following 12 weeks (ASTERIA I) and 24 weeks (ASTERIA II) of omalizumab therapy. Both studies reported favorable side effect profiles. On March 21, 2014 the FDA approved omalizumab for the indication of chronic idiopathic urticaria for patients 12 years of age or older who remain symptomatic despite treatment with antihistamines.

• 5.2 Other targets

Although omalizumab is the only biologic approved for use in chronic idiopathic urticaria, intravenous immunoglobulin infusion (IVIG), and rituximab are also used in an off-label manner. IVIG is thought to be most beneficial in the subset of patients with urticaria who develop autoantibodies to the FcεRI or to IgE itself. IVIG promotes the clearance of these auto-antibodies [62]. In small case series, there have been mixed responses to IVIG therapy. In addition to this, cost and need for IV access has limited wide-spread IVIG use in chronic idiopathic urticaria. Rituximab, a chimeric murine/human monoclonal antibody against CD20+ B-cells, is also thought to have an inhibitory effect on the production of auto-antibodies in chronic urticaria. In several case reports, rituximab has showed more benefit in auto-immune driven urticaria and other urticarial vasculitis syndromes [62].

6. EOSINOPHILIC ESOPHAGITIS (EoE)

Eosinophilic esophagitis (EoE) is an allergic disease of the esophagus which affects as many as 1-5 people out of every 10,000 in the United States [63]. It is characterized by infiltration of eosinophils (>15/high-power field) into the esophagus. The eosinophilic infiltration is driven predominantly by Th2 inflammatory response triggered by food and environmental allergens. Presenting symptoms include feeding difficulty and failure to thrive in children. In teenagers and adults, dysphagia and food
impaction are more common. Acid-suppressing medications, swallowed corticosteroids, and elimination of offending foods are currently the mainstays of therapy.

- **6.1 IL-5**

  Anti IL-5 biologics have been studied, but neither mepolizumab nor reslizumab, has demonstrated improvement in meaningful clinical outcomes in children and adults, despite reduction in blood and esophageal eosinophilia [64, 65]. Phase II clinical trials with mepolizumab in eosinophilic esophagitis in both adults (NCT00274703) and children (NCT00358449) have been completed but not yet published.

- **6.2 IL-4 and IL-13**

  Dupilumab has also been investigated in the treatment of EoE. A phase 2 trial was recently completed assessing the safety and efficacy of dupilumab in this population (NCT02379052). Dellon, Hiriano, et al, randomized 47 patients with EoE to dupilumab vs placebo. Presentation of the data from the trial at the recent World Congress of Gastroenterology at American College of Gastroenterology meeting in October, 2017 showed significant improvement in dysphagia scores, peak eosinophil counts, EoE Endoscopic reference scores, and EoE histological scoring [66].

7. **EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)**

   Eosinophilic granulomatosis with polyangiitis (EGPA, previously called Churg-Strauss Syndrome) is a small vessel vasculitis characterized by asthma and peripheral eosinophilia. Pulmonary manifestations include severe asthma and pulmonary infiltrates, while non-pulmonary manifestations include cardiomyopathy, neuropathy, and nephropathy.

- **7.1 IL-5**
A recent phase III multi-center trial enrolled 168 patients with EGPA on a stable dose of oral corticosteroid and randomized them to mepolizumab vs placebo for 52 weeks. The study’s primary endpoints, accrued weeks of remission and percentage of patients who achieved remission, were both achieved. 28% of patients in the mepolizumab group achieving remission compared to 3% in the placebo group (OR 5.91, with statistical significance) and subjects treated with mepolizumab were able to reduce corticosteroid dosing by 50% [67]. Following publication of these results, in December 2017, mepolizumab became the first drug approved by the FDA for the indication of EGPA. Phase IIa pilot studies with other Anti IL-5 agents for EGPA, including reslizumab (NCT02947945), and benralizumab (NCT0301043), are underway.

8. HOW TO CHOOSE A BIOLOGIC MEDICATION

With the introduction of such a plethora of medications in a short period of time, the clinical question of how clinicians should choose a biologic still remains largely unanswered. The new biologic medications are expensive and cost prohibitive for some patients. Most of the biologics also require administration in the clinic or hospital setting. This increases cost, time, and inconvenience for patients, particularly for those who live at a distance from centers with the capability of administering these medications but this must be evaluated in the context of the significant clinical benefits that these therapies offer. Cost, convenience, frequency and delivery of dosing regimen should all be considered when choosing a biologic for each patient. With currently available therapies, clinical phenotypes and biomarkers should also be used in choosing biologics. Current clinically available biomarkers include serum IgE level when considering omalizumab, or peripheral blood and sputum eosinophils when considering anti IL-5 therapies. Ongoing research continues to work toward novel biomarkers such as periostin, DPP4, exhaled nitric oxide, and other targets.
9. **5 YEAR VIEW**

The research boom in the realm of allergic diseases, and particularly along the Th2 inflammation pathway, is expected to continue as more biologic targets are being studied and become more thoroughly understood. There is an increasing gap in the knowledge of non-th2 pathways in allergic diseases when compared to Th2 pathways. This will likely be a shifting focus of research in the future. Further articulation of clinically available biomarkers will also be a focus, so that these medications can be used to further direct personalized, precision medicine. This includes using blood periostin levels when deciding on anti-IL-13 therapy in a patient with severe asthma. Although serum periostin has been shown to correlate nicely with airway markers of eosinophilia, elevated levels of periostin are not specific to type 2 asthma. They can be found in adults with osteoporosis and children with high rate of bone turnover [68]. In the future, how and when to look for filaggrin mutations when considering omalizumab for patients with atopic dermatitis or galectin-3 levels when considering omalizumab in severe asthma may be clinically important. In a small study of 8 patients, Galectin-3, an inflammatory protein, was found in higher levels in the airways of asthma patients who responded to omalizumab therapy compared to patients who did not respond.[69] Thus, more research is needed in the understanding of these biomarkers before they can be used in a widespread clinical setting. Eventually, it is hoped that genetic testing will allow for an even more personalized approach. Additionally, given the expense and time required for administration of the currently available biologic medications, a focus on orally available medications is likely to become a priority.

10. **CONCLUSIONS**

Significant research and clinical interest in biologic medications in allergic diseases has evolved over the last decade. While most research has been conducted in severe asthma, there is increasing
knowledge about other allergic diseases, including even rare diseases such as EGPA. Despite the rapid evolution of knowledge in this area, there still remains a significant amount that needs to be understood regarding long term safety and efficacy of these biologic medications.

11. EXPERT COMMENTARY

Patients with asthma and other allergic conditions continue to suffer despite current therapies. Novel biologic therapies have emerged over the last several years that have revolutionized the management of patients with refractory disease. Novel biomarkers have allowed for a personalized targeted approach to therapy but newer biomarkers and therapies are still needed to achieve disease remission in more patients. A major focus of current and future research is gaining a better understanding of the underlying pathophysiology and genetics of allergic diseases. Novel biomarkers will undoubtedly capitalize on increased understanding of disease mechanisms to identify those patients with allergic disease most likely to respond to new novel targeted therapies.

12. KEY ISSUES

- Biologic medications for allergic diseases have predominantly targeted the Th-2 inflammatory pathway.
- Biologic medications approved for severe asthma include anti-IgE and anti-IL 5 therapies.
- Biologic medications approved for atopic dermatitis include anti-IL 4/IL-13 therapy.
- No biologic medications have been approved for chronic rhinosinusitis with nasal polyposis, but anti-IgE and anti-IL 5 therapies are under investigation.
- Biologic medications approved for chronic idiopathic urticaria include anti-IgE therapy.
- No biologic medications have been approved for eosinophilic esophagitis, but anti-IL 5 therapies are under investigation.
• Biologic medications approved for eosinophilic granulomatosis with polyangiitis include anti-IL 5 therapy.

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Declaration of interest

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Figure 1: Biologics and their targets in asthma. Adapted from [70].

![Biologics and their targets in asthma](image1.png)

**Pathophysiological features of asthma**

**Inflammation**
- AHR & bronchoconstriction
- MSC hyperplasia & hypersecretion
- Tissue remodelling

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>Omalizumab</td>
<td>O</td>
</tr>
<tr>
<td>IL-5</td>
<td>Mepolizumab, Reslizumab, Benralizumab</td>
<td>MRB</td>
</tr>
<tr>
<td>IL-4/IL-13</td>
<td>Dupilumab</td>
<td>D</td>
</tr>
<tr>
<td>IL-13</td>
<td>Lebrikizumab, Tralokinumab</td>
<td>LT</td>
</tr>
<tr>
<td>PD2</td>
<td>Feviflortant</td>
<td>F</td>
</tr>
<tr>
<td>TSLP</td>
<td>Tezepelumab</td>
<td>F</td>
</tr>
</tbody>
</table>

Figure 2: Biologics and their targets in atopic dermatitis. Adapted from [71].

![Biologics and their targets in atopic dermatitis](image2.png)
Table 1: Summary of biologics in clinical trials and their indications

<table>
<thead>
<tr>
<th>Biologic medication</th>
<th>Mechanism Of Action</th>
<th>Patients enrolled</th>
<th>Outcomes</th>
<th>Admin</th>
<th>Study</th>
<th>Status*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>IgE 30-700 SPK (+)</td>
<td>↓ Exacerbations ↓ ICS Use</td>
<td>SC</td>
<td>EXTRA</td>
<td>APPROVED</td>
</tr>
<tr>
<td>Mepolizumab</td>
<td>IL-5</td>
<td>Blood Eos &gt;300 Sputum Eos &gt;3%</td>
<td>↓ Exacerbations ↑ lung function</td>
<td>SC</td>
<td>DREAM, MENSA</td>
<td>APPROVED</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>IL-5</td>
<td>Sputum Eos &gt;3%</td>
<td>↓ Exacerbations ↑ lung function</td>
<td>IV</td>
<td></td>
<td>APPROVED</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>IL-5Rα</td>
<td>Severe asthmatics, &gt;1 exacerbation</td>
<td>↓ Exacerbations ↑ lung function</td>
<td>SC</td>
<td>CALIMA, SIRROCO</td>
<td>APPROVED</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>IL-4Rα</td>
<td>Severe asthmatics, &gt;1 exacerbation</td>
<td>↓ Exacerbation ↑ lung function</td>
<td>SC</td>
<td>QUEST</td>
<td>P3</td>
</tr>
<tr>
<td>Lebrikizumab</td>
<td>IL-13</td>
<td>Severe asthmatics</td>
<td>↓ Exacerbations in high</td>
<td>SC</td>
<td>LAVOLTA I</td>
<td>P3</td>
</tr>
<tr>
<td>Biologic</td>
<td>Biomarker</td>
<td>Disease</td>
<td>Action</td>
<td>Route</td>
<td>Status</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tralokinumab IL-13</td>
<td>Severe asthmatics, Recurrent exacerbations</td>
<td>↓ Exacerbations ↑ lung function</td>
<td>SC</td>
<td>TROPOS</td>
<td>P2/3^</td>
<td></td>
</tr>
<tr>
<td>Fevipiprant PD1 receptor</td>
<td>&gt;2% sputum eos</td>
<td>↓ sputum eos</td>
<td>oral</td>
<td></td>
<td>P2/3^</td>
<td></td>
</tr>
<tr>
<td>Tezepelumab TSLP</td>
<td>Mild allergic asthmatics</td>
<td>↓ bronchoconstriction /LAR</td>
<td>IV</td>
<td></td>
<td>P3^</td>
<td></td>
</tr>
<tr>
<td>Navarixin CXCR2 receptor antagonist</td>
<td>Sputum neutrophils &gt;40%</td>
<td>↓ sputum and blood neutrophils</td>
<td>Oral</td>
<td></td>
<td>P2</td>
<td></td>
</tr>
</tbody>
</table>

**Atopic Dermatitis (AD)**

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Biomarker</th>
<th>Disease</th>
<th>Action</th>
<th>Route</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupilumab IL-4Rα</td>
<td>Mod to severe AD</td>
<td>↓ disease severity ↑ QOL</td>
<td>SC</td>
<td>SOLO I and II</td>
<td>APPROVED</td>
</tr>
<tr>
<td>Lebrikizumab IL-13</td>
<td>Mod to severe AD</td>
<td></td>
<td>SC</td>
<td></td>
<td>P2^</td>
</tr>
<tr>
<td>Tralokinumab IL-13</td>
<td>Mod to severe AD</td>
<td></td>
<td>SC</td>
<td>ECZTRA</td>
<td>P2/3^</td>
</tr>
<tr>
<td>Omalizumab IgE</td>
<td>Mod to severe AD</td>
<td>↓ Pruritus ↓ disease severity in biomarker subgroup</td>
<td>SC</td>
<td></td>
<td>P2</td>
</tr>
<tr>
<td>Mepolizumab IL-5</td>
<td>AD</td>
<td>↓ Blood eos, but no clinical benefit</td>
<td>SC</td>
<td></td>
<td>P2</td>
</tr>
</tbody>
</table>

**Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)**

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Biomarker</th>
<th>Disease</th>
<th>Action</th>
<th>Route</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab IgE</td>
<td>CRSwNP with asthma IgE 30-700</td>
<td>↓ nasal polyp scores</td>
<td>SC</td>
<td></td>
<td>P2</td>
</tr>
<tr>
<td>Mepolizumab IL-5</td>
<td>Severe CRSwNP</td>
<td>↓ nasal polyp scores</td>
<td>SC</td>
<td></td>
<td>P2/P3^</td>
</tr>
<tr>
<td>Reslizumab IL-5</td>
<td>“massive” NP</td>
<td>↓ nasal and serum Eos. Good safety profile ↓ asthma exacerbations in comorbid asthma</td>
<td>IV</td>
<td></td>
<td>P1</td>
</tr>
</tbody>
</table>

**Chronic Idiopathic Urticaria (CIU)**

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Biomarker</th>
<th>Disease</th>
<th>Action</th>
<th>Route</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab IgE</td>
<td>Mod to severe CIU</td>
<td>↓ clinical symptoms, itch severity score</td>
<td>SC</td>
<td>ASTERIA I and II</td>
<td>APPROVED</td>
</tr>
</tbody>
</table>

**Eosinophilic esophagitis (EoE)**

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Biomarker</th>
<th>Disease</th>
<th>Action</th>
<th>Route</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab IL-5</td>
<td>Adults with EoE, Dysphagia, &gt;20 eos/hpf</td>
<td>↓ blood and esophageal eos, but no clinical benefit</td>
<td>SC</td>
<td></td>
<td>P2^</td>
</tr>
<tr>
<td>Reslizumab IL-5</td>
<td>Children and Adolescents EoE &gt;24 eos/hpf</td>
<td>↓ blood and esophageal eos, but no clinical benefit</td>
<td>IV</td>
<td></td>
<td>P2</td>
</tr>
</tbody>
</table>

**Eosinophilic Granulomatosis with Polyangiitis (EGPA)**

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Biomarker</th>
<th>Disease</th>
<th>Action</th>
<th>Route</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mepolizumab IL-5</td>
<td>EGPA on stable oral steroids</td>
<td>↓ clinical remission rates</td>
<td>SC</td>
<td></td>
<td>APPROVED</td>
</tr>
<tr>
<td>Reslizumab IL-5</td>
<td>EGPA</td>
<td></td>
<td>IV</td>
<td></td>
<td>P2^</td>
</tr>
<tr>
<td>Benralizumab IL-5Rα</td>
<td>EGPA</td>
<td></td>
<td>SC</td>
<td></td>
<td>P2^</td>
</tr>
</tbody>
</table>

Table 1 Legend: Summary of biologic medications in allergic diseases in order of discussion in the article. *(P3=completed phase III clinical trials; P3^=phase III clinical trials underway, not yet completed; P2=completed Phase II clinical trials; P2^=phase II clinical trials underway, not yet completed; P1: completed, phase I clinical trial; SPK=skin prick testing; LAR=late asthmatic response.)*
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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.


44. AstraZeneca provides update on tralokinumab Phase III programme in severe, uncontrolled asthma. 2017.


