**Biologic targeted therapy in allergic asthma**

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**Objective:** To review the structure, function, clinical utility, and safety of current biologic targeted therapies being used for the treatment of asthma.

**Data Sources:** Medical literature obtained from PubMed and OVID searches from June to November 2013.

**Study Selections:** Studies were selected based on article impact, relevance, and clinical significance. Particular emphasis was placed on articles discussing therapies targeted at IgE, interleukin (IL)-4, IL-4 receptor, IL-5, IL-13, tumor necrosis factor-α, CRTh2, and toll-like receptors 7 and 9.

**Results:** Since the approval of omalizumab in 2003, the development of biologic asthma therapies has grown at a remarkable pace. With approximately 30 drugs currently in clinical trials and dozens more in development, the future of asthma biologic therapies is promising. Despite several well-publicized setbacks, researchers remain focused on elucidating the complex pathophysiology of asthma. The hope is that asthma biologic therapies will eventually be tailored to an individual's asthma phenotype. With more than 300 million people worldwide affected by asthma and with roughly 5% to 10% of this population living with severe, uncontrolled asthma, the need for new biologic therapies is great.

**Conclusion:** The introduction of each new biologic therapy into clinical trials has been associated with great anticipation, but the outcome of these trials, in many cases, has led to disappointment. Given the lack of overwhelming positive responses, these results have emphasized that asthma is a complex clinical syndrome with multiple underlying genotypes and clinical phenotypes. It has become abundantly clear that it is very unlikely that there is one “magic bullet” to cure all patients with asthma.

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The naming of these monoclonal antibodies has been a source of great confusion to practitioners worldwide. The World Health Organization and the American Medical Association have convened groups that have established naming guidelines. Although there are no fully mouse-derived monoclonal antibodies (mab) used in asthma, they are designated by an o preceding the mab name. Chimeric antibodies (combining human and nonhuman proteins) such as rituximab have the xi preceding the mab. Partially humanized antibodies such as omalizumab have a zu before the mab. Fully humanized monoclonal antibodies such as tralokinumab have a u preceding the mab. A k or ki precedes the mab for interleukin agents and l or ll in immunomodulatory agents such as infliximab. These guidelines help clinicians understand the origins of these antibodies but do little to explain their mechanism of action in many cases.

Individual Agents

IgE-Targeted Therapies

Omalizumab (Xolair, Genentech, South San Francisco, California; Novartis, New York, New York) was first approved for use in Australia in 2002 and is currently the only Food and Drug Administration (FDA)—approved biologic used in the treatment of asthma. It is a recombinant DNA-derived, humanized antibody that selectively binds the Cε3 domain of the free IgE heavy chain. In addition, it has been reported, rather fortuitously, that omalizumab functions to decrease FcεRI receptor density on mast cells and basophils. Through these 2 mechanisms—blockage of free IgE and downregulation of FcεRI receptors—omalizumab acts to interrupt the allergic cascade of asthma. This cascade is characterized by mast cell degranulation; the release of preformed granule-associated mediators, such as histamine, tryptase, chymase, and heparin; and further secretion of chemokines and cytokines from inflammatory cells. Together, these chemical mediators play a role in the eosinophilia, tissue inflammation, hyper-responsiveness, and airway structural changes often seen in patients with asthma.

In human studies, omalizumab has been shown to lower free serum levels of IgE by 96% to 99%, suppress new IgE production, and decrease airway inflammation. However, the effects on airway remodeling remain relatively uncertain. Researchers are currently investigating the role of omalizumab on transforming growth factor-β and endothelin-1, which are involved in bronchial airway maintenance.
In multiple phase III trials, patients receiving omalizumab had fewer asthma exacerbations, improvements in asthma symptoms and quality of life, and decreased requirements for inhaled corticosteroids (ICSs) and rescue bronchodilators. The most important of these studies was a large (N = 419) 28-week trial demonstrating that omalizumab as an add-on therapy could decrease clinically significant asthma exacerbation rates by 26% compared with placebo and lower emergency department visit rates by 44% compared with placebo. Importantly, this study was able to show these benefits without an increase in side effects. In the recent EXTRA study (N = 850) Hanania et al. evaluated the difference in exacerbation frequency between omalizumab and placebo with respect to 3 biomarkers: fraction of exhaled nitric oxide (FeNO), blood eosinophils, and serum periostin. As expected, decreases in asthma exacerbations were most pronounced in those groups with high periostin levels (Table 2). For the high-FeNO phenotype, asthma exacerbations decreased by 53% vs 16% with placebo; for the high-periostin phenotype, exacerbation frequency between omalizumab and placebo with respect to these studies in 1 long-term study of 154 patients. In a review of 39,510 patients conducted by the American Academy of Allergy, Asthma, and Immunology, only 41 episodes of anaphylaxis were reported (rate 0.09%) and all patients responded to standard treatment. Furthermore, a recent systematic review study of 8 trials (N = 3,429) did not detect an increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms with omalizumab. It is important to note that the FDA has yet to formally approve omalizumab as a therapy in children 6 to 11 years old with severe persistent asthma. In 2012, a FDA safety subcommittee voted (19 to 1) in favor of recommending omalizumab for use in children 6 to 11 years old and the National Institute for Health and Clinical Excellence in the United Kingdom voted similarly in 2013.

Despite the favorable recommendations by the FDA subcommittee and the National Institute for Health and Clinical Excellence, some concern exists as to whether the clinical effectiveness of omalizumab in children can justify the high cost of such treatment. This may explain why omalizumab has yet to receive a formal approval by the FDA for use in children.

**Interleukin-4—Targeted Therapies**

Because of the central role T-helper type 2 (Th2) cells play in coordinating allergic and asthmatic responses, their receptors and the cytokines that stimulate them have become key therapeutic targets. Although interleukin (IL)-13 and IL-4 contribute to B-cell isotype switching to IgE, it is IL-4 that plays the key role in maintaining the Th2 phenotype. Furthermore, IL-4 has been shown to induce fibronectin, a key component of airway remodeling in the human lung.

The earliest humanized anti–IL-4 antibody to be developed was pascolizumab. Initially, it was shown to be well tolerated in primates and humans. However, phase II trials for pascolizumab on a larger scale were discontinued after the drug showed little benefit to patients with asthma not taking corticosteroids (NCT00024544).

The next drug to target the IL-4 pathway was pitrakinra, a mutant IL-4 protein that inhibits the binding of IL-4 and IL-13 to IL-4 receptor α (IL-4Rα). In 1 small-scale study (N = 24) published in 2007, patients with atopic asthma were administered 25 mg of pitrakinra subcutaneously after an allergen challenge and showed a 17.1% maximum percentage decrease in forced expiratory volume in 1 second (FEV1) compared with a maximum decrease of 23.1% in the placebo group.

The same study also evaluated 60 mg of pitrakinra administered by nebulization and reported a 4.4% decrease in FEV1; for the pitrakinra group compared with a 15.9% decrease for placebo after the challenge. Furthermore, no significant changes in hematologic, biochemical, urinalysis, or electrocardiographic tests were seen. Moreover, there

**Table 1**

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<th>Target Drug</th>
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<th>Effect/notes</th>
<th>Development</th>
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<td>Free IgE</td>
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<td>IL-4</td>
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Abbreviations: ACQ, Asthma Control Questionnaire; DP1, D-prostanoid; FDA, Food and Drug Administration; FENO, fractional exhaled nitric oxide; FEV1, forced expiration volume in 1 second; ICS, inhaled corticosteroid; IL, interleukin; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α.
were no significant differences in safety outcomes between those who received pitrakinra and those who received placebo.23 Another recent phase II trial (N = 294) testing the therapeutic agent AMG-317, a human monoclonal antibody to IL-4Ra, did not demonstrate significant clinical efficacy after weekly subcutaneous injections of 75, 150, or 300 mg. A subset of patients with higher overall Asthma Control Questionnaire (ACQ) scores showed an 87% decrease in asthma exacerbations for the treatment group compared with the placebo group after 3 months after the final injection of IL-13 antibody and that 23.2% of participants taking lebrikizumab reported musculoskeletal side effects compared with 5.4% in the placebo group. In a similar study (N = 212), Noonan et al. found no statistically significant increase in FEV1 in patients with a low-periostin phenotype and only a minor increase in those with a high-periostin phenotype.36 Further research is needed to evaluate the mechanism and importance of this interaction.

Two recently published phase II trials have shown positive results for lebrikizumab, an IgG4 humanized monoclonal antibody that binds IL-13. A study by Corren et al.33 showed improvement of FEV1 in patients with a high-periostin phenotype. However, it is important to point out that although the improvement in FEV1 was significant, there was still considerable airway obstruction in patients. Two important observations from this study were that FEV1 improvement persisted for 3 months after the final injection of IL-13 antibody and that 13.2% of participants taking lebrikizumab reported musculoskeletal side effects compared with 5.4% in the placebo group. In a similar study (N = 212), Noonan et al. found no statistically significant or clinically significant increase in FEV1 in patients with a high-periostin phenotype.39 Furthermore, unlike Corren et al, Noonan et al reported fewer adverse events and none involving the musculoskeletal system. One key difference between the 2 studies is that Corren et al enrolled participants with asthma inadequately controlled by ICSs, long-acting β-adrenergoreceptor agonists, and the most common adverse event.29 These early results are promising but more data are needed to establish the efficacy of this therapy.

IL-13—Targeted Therapies

Interleukin-13, which is secreted primarily by Th2 cells, is involved in the regulation of IgE production, eosinophilic inflammation, airway smooth muscle contraction, and the recruitment of monocytes, macrophages, and T cells into airway spaces.30 Because of these diverse functions, IL-13 is a key therapeutically target in the treatment of allergy and asthma. IL-13 binds to a low-affinity IL-13Rα1 receptor and a high affinity complex of IL-13Rα1 and IL-4Rα.31 In human studies, IL-13—producing cells outnumbered IL-4—producing cells in the lung.32 Also, there was a subset of patients who show elevated IL-13 levels in sputum despite the use of ICSs.33 Interestingly, in a genetic analysis study by Woodruff et al.,34 the group reported that only half the patients with mild asthma had an IL-13 gene expression signature,35 furthering the belief that asthma genotype characterization is essential to tailoring effective asthma treatment. The current IL-13—dependent blood biomarkers are IgE, eosinophils, the chemokines CCL11 and CCL17, and the cytokine periostin.36 Recently, periostin was shown to be the best predictor of airway eosinophilia among these biomarkers.37 One potential complication to IL-13 studies is the finding that corticosteroids have been shown to inhibit IL-13 activity.38 Further research is needed to evaluate the mechanism and importance of this interaction.

IL-4R—Targeted Therapies

The soluble, recombinant, human IL-4R antibody altrakincept (Nuvance, Immunex-Amgen, Thousand Oaks, California) is composed solely of the extracellular domain of the IL-4R. Early promise for the IL-4R antibody altrakincept was shown during an allergen challenge experiment in a murine model in which the drug inhibited eosinophil infiltration and late-phase lung inflammation.24 In a follow-up to this experiment, 2 clinical trials tested the response of patients with moderate asthma to altrakincept.25,26 The first trial showed that a single inhalation of a nebulized form of the drug, given once a week at 1,500 µg, but not 500 µg, could improve lung function and decrease airway inflammation as demonstrated by decreased FeNO.25 The second trial confirmed these results with a longer study (12 weeks) in which ICS was gradually withdrawn from patients while taking nebulized altrakincept at a dose of 1,500 µg once a week without signs of relapse.26 Despite the promise of these 2 early-phase studies, asthma exacerbations, symptoms, and FEV1 did not show improvement in a follow-up phase II trial (NCT00001909). However, concerns were raised by investigators regarding the bioavailability of nebulized altrakincept because of the potential for its proteolysis in patients with asthma. In all trials of altrakincept, the drug has been shown to be well tolerated by patients, with the number of adverse events comparable in the placebo and active groups.

Another recent phase II clinical trial (N = 294) testing the therapeutic agent AMG-317, a human monoclonal antibody to IL-4Ra, did not demonstrate significant clinical efficacy after weekly subcutaneous injections of 75, 150, or 300 mg. A subset of patients with higher overall Asthma Control Questionnaire (ACQ) scores (>2.86) did respond slightly better to treatment with AMG-317, as measured by FEV1, but overall the results were inconclusive. The most recent phase II trial involving an IL-4Ra—targeted monoclonal antibody, dupilumab, was recently completed in patients with moderate to severe asthma and elevated eosinophil levels (NCT01312961). This study (N = 104) showed an 87% decrease in asthma exacerbations for the treatment group compared with the placebo group after long-acting β-adrenergoreceptor agonists and ICSs were gradually withdrawn.28 The safety profiles also were similar between the treatment and placebo groups, with injection site reactions being

### Table 2

Asthma biomarkers used in biologic trials

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Strengths</th>
<th>Weaknesses</th>
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<tr>
<td>Total IgE</td>
<td>easy to obtain; inexpensive; sensitive</td>
<td>not specific for all asthma types</td>
</tr>
<tr>
<td>Specific IgE</td>
<td>easy to obtain; good correlation with atopic</td>
<td>not specific for all asthma types</td>
</tr>
<tr>
<td>Exhaled nitric oxide</td>
<td>easy to obtain; correlated with airway eosinophil inflammation and IL-13 production</td>
<td>expensive, not specific to lower airway inflammation, not specific for all asthma types</td>
</tr>
<tr>
<td>Sputum eosinophilia</td>
<td>correlates with airway inflammation, decreased FEV1, and increased BHR, correlates with treatment responses</td>
<td>difficult to obtain</td>
</tr>
<tr>
<td>Blood eosinophils</td>
<td>inexpensive; easy to obtain; responds to multiple therapies</td>
<td>not sensitive or specific for asthma or atopy</td>
</tr>
<tr>
<td>Serum periostin</td>
<td>Sensitive indicator of Th22 airway inflammation; best indicator of eosinophilic inflammation in persistent uncontrolled asthma</td>
<td>expensive, not readily available</td>
</tr>
</tbody>
</table>

Abbreviations: BHR, bronchial hyper-responsiveness; FEV1, forced expiratory volume in 1 second; IL-13, interleukin-13; TH2, T-helper type 2.
leukotriene inhibitors, whereas Noonan et al recruited participants who had no previous exposure to ICSs.

Tralokinumab, a humanized anti–IL-13 monoclonal antibody, has been shown to attenuate airway eosinophilia and bronchial hyper-responsiveness in murine models. In a recent study conducted by Piper et al [54, 55] (N = 194), varying doses (150, 300, or 600 mg) of tralokinumab were administered subcutaneously every 2 weeks to adults with moderate to severe uncontrolled asthma despite controller therapies. The primary end points of the study were ACQ score, lung function before using a bronchodilator, rescue β2-agonist use, and safety. Although no change in ACQ score was reported, lung function was improved in each of the tralokinumab groups. The FEV1 improved 16.1% for the group receiving 600 mg of the drug, 13.3% for 300 mg, 8.1% for 150 mg, and 4.3% for the placebo group. These data suggest that neutralizing IL-13 may result in a therapeutic benefit in uncontrolled moderate to severe asthma. However, larger studies of longer duration are needed to fully understand the role of IL-13 blockade in uncontrolled asthma.

Anrukinumab is a fully humanized IgG monoclonal antibody that binds to IL-13 and neutralizes IL-13 bioactivity. This antibody allows IL-13 interaction with IL-13Rα1 or IL-13Rα2 but blocks recruitment of IL-4Ra to the IL-13–IL-13Rα1 complex. Excitement for this biologic therapy was generated during an early experiment in which the antibody was shown to attenuate early-phase bronchoconstriction in a sheep model. In a recent phase II clinical trial in patients with mild toophic asthma (N = 56), anrukinumab significantly inhibited allergen-induced asthmatic responses within 14 days, as measured by FEV1 percentage of change. There was no effect on airway hyper-responsiveness to methacholine, blood or sputum eosinophils, or total IgE, suggesting IL-13 plays a prominent role in bronchoconstriction. The authors of this study noted that the degree to which anrukinumab decreases early and late asthmatic responses after an allergen challenge is similar to the degree of efficacy of leukotriene antagonists. In addition, there was no increase in adverse events reported by the treatment group over the placebo group and hematologic, biochemical, and urinalysis test results were similar across all groups.

**IL-5–Targeted Therapies**

Interleukin-5 plays an important role in the activation and maturation of eosinophils at sites of inflammation. Clinical studies have demonstrated an increase in IL-5 in bronchial biopsies from patients with asthma. In addition, the level of IL-5 in bronchial mucosa has been linked to disease severity. Therefore, IL-5 has been targeted in patients with a strong eosinophilic component to their asthma and whose ICS treatment has failed. In studies of mice and nonhuman primates, TRFK-5, an early-generation monoclonal anti–IL-5 antibody, has been shown to inhibit eosinophil migration into airways.

Mepolizumab (BoSsartia, GlaxoSmithKline, Philadelphia, Pennsylvania) is a humanized monoclonal antibody against free IL-5. Several studies have shown mepolizumab to effectively decrease eosinophil numbers in airways and blood of patients with asthma for 3 months without side effects, but, disappointingly, there was no improvement in asthma symptoms, FEV1, or bronchial hyper-responsiveness. One explanation for these findings may be that there are eosinophils in the airways of patients that lack the IL-5 receptor. Recently, 2 trials were reported that considered more specific subtypes of patients with asthma. Patients with asthma with high eosinophilia and decreased responses to ICS were treated with mepolizumab and showed clinically significant decreases in asthma exacerbations and improvements in respiratory function and ACQ score. The latest mepolizumab trial, the Dosing Ranging Efficacy And safety with Mepolizumab (DREAM) study (N = 621), supported the finding that patients with severe asthma and elevated eosinophils can respond well to anti–IL-5 treatment. In this trial, there was no change reported in serum IgE levels. Recently, a meta-analysis of 7 trials of mepolizumab involving 1,131 patients with asthma was reported. The analysis found mepolizumab to significantly lower blood and sputum eosinophil counts, decrease asthma exacerbation frequency, and improve scores on the Asthma Quality of Life Questionnaire compared with placebo. Furthermore, this analysis determined that mepolizumab had no clinically significant effects on functional airway outcomes, including FEV1, peak expiratory flow, and airway hyper-responsiveness to methacholine. Overall, clinical studies have reported that mepolizumab is well tolerated by patients. Although several serious adverse events, such as cerebrovascular disorder, asthma exacerbation, and gastrointestinal disturbance, have been reported, investigators have determined these were unrelated to the study medication.

Reslizumab (Cinquil, Teva Pharmaceutical Industries, Petach Tikva, Israel) is a humanized monoclonal anti–IL-5 antibody originally raised in rats. In the earliest small-scale clinical trial of reslizumab, the antibody was given in a single dose of 0.1, 0.03, or 1.0 mg/kg to patients (N = 32) with severe, uncontrolled asthma. The outcome showed little improvement in asthmatic symptoms (ACQ scores) and lung function (FEV1) between treatment and placebo groups but did show a marked decrease in eosinophil levels, from 22.9% to 5.5%, in the reslizumab group compared with no change in the placebo group. A more recent phase II trial (N = 53) showed that reslizumab given at 3.0 mg/kg is most effective in a small subset of patients with the highest levels of eosinophilia (sputum eosinophils >3%) and the presence of nasal polyposis. These patients displayed improved lung function with a choline mean change in baseline FEV1 (compared with −8.0% in the placebo group) and decreased eosinophils (95.4% decrease from baseline sputum eosinophils in treated patients vs 38.7% in placebo group). The most common adverse events across all groups were nasopharyngitis, fatigue, and pharyngolaryngeal pain. Despite the adverse events, the overall positive results from these studies has led to the launch of several new phase III trials.

Benralizumab is currently being evaluated in 2 phase II trials (NCT00659659 and NCT00768079). Unlike the other 2 anti–IL-5 drugs, benralizumab targets the α-chain of the IL-5 receptor (CD125). Data are limited from this trial and it is too soon to judge its efficacy, safety, and selectivity. Recently, it has been reported that benralizumab (0.03–3.0 mg/kg) can decrease eosinophil and basophil counts for 2 to 3 months after injection, suggesting this antibody has the ability to cross into extravascular tissue.

**Anti–Tumor Necrosis Factor-α–Targeted Therapies**

Secreeted predominantly by T1 cells during the earliest stages of allergen-dependent asthma, tumor necrosis factor-α (TNF-α) is known to upregulate epithelial and endothelial adhesion molecules in airways in an effort to recruit neutrophils and eosinophils to sites of inflammation. In more severe asthma phenotypes, TNF-α and TNF-α receptor 1 tend to be elevated in the peripheral blood. There are multiple biologics available aimed at blocking the TNF-α response, including etanercept (a soluble fusion protein combining 2 p75 TNF-α receptors with an Fc fragment of human IgG1), infliximab (a chimeric mouse–humanized monoclonal antibody), and the human monoclonal antibodies adalimumab and golimumab.

The first excitement with respect to TNF-α treatment came from a study of etanercept (Enbrel, Amgen, Inc, Thousand Oaks, California) in which patients showed improvement in airway hyper-responsiveness, lung function, and ACQ scores over 12 weeks. Berry et al subsequently reported that the expression of membrane-bound TNF-α closely followed the clinical response, suggesting the use of TNF-α as a biomarker of responsiveness.
Furthermore, etanercept therapy had no effect on eosinophils or neutrophils but did decrease sputum histamine concentration. Two other studies of etanercept have shown little efficacy in the treatment of asthma. In 2006, Erin et al performed a study (N = 38) in patients with moderate asthma using the monoclonal antibody infliximab (Remicade, Janssen Biotech, Inc, Horsham, Pennsylvania). No improvement in morning peak flow occurred with infliximab over 12 weeks, but there was an improvement in peak flow variability and a 50% decrease in the number of mild exacerbations encountered. In 2011, after an investigation by several senior investigators at the Imperial College London, the American Journal of Respiratory and Critical Care Medicine issued a retraction of the 2006 journal article published by Erin et al on infliximab. The investigational group had questions regarding the veracity of the data and the validity of the article’s conclusions.

In a large-scale trial (N = 309) with golimumab (Simponi, Janssen Biotech, Inc, Horsham, Pennsylvania) designed to last 52 weeks, there was no clear improvement in lung functions or asthma exacerbations after 24 weeks. The study was terminated early because of serious adverse events, including pneumonia, sepsis, reactivation of tuberculosis, increased rate of malignancy, and 1 death. All future trials with golimumab have been suspended.

**CRTh2 Targeted Therapies**

The prostaglandin D2 chemotaxic receptor CRTh2, also known as the DP1 receptor, is expressed on Th2 cells, activated by prostaglandin D2, and is thought to play a significant role in the Th2-driven asthmatic response. Prostaglandin D2, a cyclooxygenase product formed by activated mast cells, binds to CRTh2 and D-prostanoid (DP1) receptors on mast cells, dendritic cells, and Th2 cells. CRTh2 signaling is involved in the chemotaxis of Th2 cells and eosinophils to inflammation sites, whereas DP1 signaling is involved in vasodilation. Because of this, CRTh2/DP2 and DP1 antagonists are being considered asthma therapeutic targets. Currently, there are more than 10 drug candidates targeting CRTh2 or CRTh2 and DP1.

AMG-853 is a selective and orally bioavailable antagonist of DP1 and CRTh2. In phase 1 trials, AMG-853 inhibited binding of prostaglandin D2 to human DP1 and CRTh2 cells and was well tolerated by patients. As part of a further study (N = 317), Busse et al. explored the use of AMG-853 as an add-on therapy to ICS in patients with mild asthma. The therapy displayed no associated risks but was ineffective at improving asthma symptoms or lung function. Another drug designed to target the prostaglandin D2 pathway is OC000459, a CRTh2-selective antagonist. In a trial of OC000459 as monotherapy in patients with moderate asthma, the drug showed a 22% improvement in symptom scores over placebo and a statistically significant change in FEV1 of 2.8% over placebo.

One rationale for the different results of AMG-853 and OC000459 is the tendency of patients with severe asthma who do not respond to ICSs to have a higher threshold for improvement than those patients with severe asthma who do not take ICSs. This could explain the higher efficacy of OC000459 as a monotherapy over AMG-853 as an add-on therapy. In addition to AMG-853 and OC000459, there have been some new therapies targeting the prostaglandin D2 pathway. Other agents in development affecting the prostaglandin D2 pathway are listed in Table 1.

**Therapies Targeted at Toll-like Receptors 7 and 9**

The Th12-mediated allergen-specific responses are thought to play a central role in the development of allergic asthma. It is theorized that the increase in Th12 activity in some patients with asthma may be caused by a suppression of the Th11 response. Investigators are currently working on ways to stimulate the Th11 response, and thus tilt the balance away from a Th12 response, through agonists of toll-like receptors (TLRs) 7 and 9. These TLRs are found on nearly every cell type, including immune cells, and are involved in innate immunity through recognition of pathogen-associated molecular patterns. Specifically, TLR-9 is known to recognize unmethylated CpG sequences of DNA molecules, which are commonly found in viral DNA. TLR-7 recognizes single-stranded RNA, another common feature of viral genomes. Together, TLR-7 and TLR-9 monitor the cytoplasm of cells for signs of foreign invasion. If stimulated, these TLRs secrete interferons and IL-12 and initiate a strong Th11 response.

QbG10 (bacteriophage Qbeta-derived virus-like particle with CpG-motif G10 inside) is a TLR-9 agonist packaged into virus-like particles. In a recent study by Behe et al (n = 63), patients were treated with a subcutaneous injection of 0.9 mg of QbG10 or placebo for 12 weeks as an add-on treatment while ICSs were gradually withdrawn. Those patients treated with QbG10 reported an improvement in ACQ score (change from 0.85 to 0.77 points, –9%), whereas the placebo group had increased ACQ scores from 0.92 to 1.68 (–61%) during the withdrawal of ICSs. At the completion of the study, two thirds of patients on QbG10 reported their asthma as “well controlled” compared with only one third of placebo-treated subjects. In addition, eosinophils in peripheral blood were reported to be significantly lower in the QbG10 group (data not shown). However, changes in FEV1 and FENO in the treatment and placebo groups were not statistically significant. Overall, QbG10 displayed a good safety profile during the study. The only adverse events reported involved injection site reactions occurring after QbG10 administration.

The synthetic TLR-7 agonists imiquimod (R837) and resiquimod (R848) also have generated interest as asthma therapy candidates for their ability to decrease the allergic Th12 response, act as immediate bronchodilators, and decrease eosinophilic inflammation in vitro and in vivo models. Although no clinical trials have been conducted, researchers are working on a nebulized form of the drug that could be ready for trials by 2014. It is important to note that the safety of these drugs has yet to be established for the treatment of asthma. In the treatment of hepatitis C and cancer, TLR-7 agonists have triggered several side effects ranging from fevers and myalgias to sepsis.

**Conclusion**

The past 2 decades have seen meteoric growth in the development of targeted immune-based biologics. Given the tremendous at-risk population with the immunologically mediated disease of asthma, it became a natural target disease for these medications. The introduction of each of these agents into clinical trials has been associated with great anticipation, but the outcome of these trials, in many cases, has led to disappointment. Given the lack of overwhelming positive responses, these results have emphasized that asthma is a complex clinical syndrome with multiple underlying genotypes and clinical phenotypes. It has become abundantly clear that it is very unlikely that there is 1 “magic bullet” to cure all patients with asthma.

Given the significant direct and indirect costs of these agents, it is likely that the use of these agents will be tightly controlled and focused on the patient with moderate to severe asthma whose use of conventional therapies has failed. Perhaps these agents will allow clinicians to desensitize, to environmental allergens, those patients for whom this form of therapy was previously unavailable because of their uncontrolled asthma. Furthermore, ultimately it will be critical to develop head-to-head trials with these agents to determine clinical superiority for particular asthma phenotypes. It is likely that the further study of these agents will explain how biomarkers can predict responses to therapeutic agents as clinicians try to preserve precious resources.
In the end, the mandate as clinicians and investigators is to improve the lives of all patients. It is likely that biologic therapies will allow clinicians to do precisely this in a subgroup of patients who have impaired quality of life and consume an inordinate amount of medical resources.

References


