Mechanisms and Practical Use of Biologic Therapies for Allergy and Asthma Indications

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KEYWORDS

• Biologic agent • Allergic rhinitis • Asthma • Anti-IgE • Anti–IL-5 • Anti–IL-4 • Anti–IL-13 • Anti-TSLP

KEY POINTS

- Currently available biologics for allergy and asthma are monoclonal antibodies that target specific cytokines or receptors in the type 2 inflammatory cascade.
- These agents have the potential to treat more than 1 disease process because of shared inflammatory pathways and downstream effects.
- Understanding the pathophysiology behind asthma and atopic disorders can help with patient selection for these agents.
- Practicalities, such as frequency of injection, disease endotype/phenotype, weight-based dosing, and other considerations, are also important when considering the use of monoclonal antibodies for allergy and asthma indications.

INTRODUCTION

Over the last 2 decades, the understanding of the immune mechanisms in inflammatory disorders has increased and the different atopic and nonatopic pathways that contribute to various endotypes of asthma and other allergic diseases have been further elucidated. Since the first biologic agent for asthma gained approval from the US Food and Drug Administration (FDA), interest in the development of additional agents to other potential immunologic targets has increased; with this peaked attention, further monoclonal antibodies have received FDA approval for asthma and other diseases. Because these novel therapeutics target different cytokines and cytokine receptors at different points in the inflammatory cascade, they have the potential to treat several different, and perhaps seemingly unrelated, disorders. The potential to treat more than 1 disorder with the same agent is appealing, but these therapies have

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significant costs or potential side effects. Understanding inflammatory biomarkers, patient profiles, and immunologic targets can assist physicians with patient and agent selection. This article presents a discussion of the current and some future biologic agents available for use in treating allergies and asthma.

DISCUSSION

Allergy is an immense subject, spanning diseases from food allergy to allergic contact dermatitis, and involving different types of hypersensitivity reactions. A discussion of all the available biologic agents for the scope of allergy is beyond this single article, and some of these disorders are addressed elsewhere in this issue. In this article, the subject of allergy is limited to addressing allergic rhinitis caused by type I immunoglobulin (Ig) E–mediated hypersensitivity, and does not include allergy caused by foods, medications, or other agents.

Allergic rhinitis is mediated by specific IgE directed against allergens. This process involves expression of cytokines, specifically interleukin (IL)-4, IL-5, and IL-13, associated with T-helper 2 (Th2) effector cells as well as infiltration of eosinophils, basophils, mast cells, and other inflammatory cells present in this type 2 inflammatory disease. Different types of inflammation are recognized and at least 3 different types of inflammation (type 1, type 2, and type 3) have been described, with type 2 immune mechanisms underlying most allergic disorders.[1–3] The presence of these type 2 cytokines in allergic rhinitis has led to the investigation of using biologics developed for other type 2 diseases, such as asthma and chronic rhinosinusitis with nasal polyposis, as treatment options in allergic rhinitis.

BIOLOGICS FOR ALLERGY

At present, there are no FDA-approved biologic options for the treatment of allergic rhinitis; however, there are biologics currently in the development pipeline, in phase III trials, or available for other FDA-approved indications that have been studied for the treatment of allergic rhinitis to environmental inhalants. In addition to current agents targeting cytokines, monoclonal antibodies targeting specific epitopes on certain allergens, such as cat or birch, are presently under investigation. However, because no specific agent is currently available for the treatment of allergic rhinitis alone, the practical applications of available therapeutics are limited and require the presence of a comorbidity that meets an FDA-approved biologic indication.

Omalizumab

Cross-linking of surface IgE and the resulting mast cell and basophil degranulation lead to the release of vasoactive and other proinflammatory mediators that result in the symptoms associated with allergic rhinitis, namely rhinorrhea, pruritus, sneezing, and so forth. The mechanism of action for omalizumab (tradename: Xolair) is further discussed later in the article, but, in summary, it is a humanized monoclonal anti-IgE antibody that binds to serum IgE molecules and has the subsequent downstream effect of reducing surface IgE cross-linking. Currently FDA approved for other indications, omalizumab has been studied for the treatment of allergic rhinitis both as a direct and as an add-on therapy.

A recent meta-analysis assessed the efficacy and safety of omalizumab in the treatment of allergic rhinitis.[4] Sixteen randomized controlled studies on the treatment of allergic rhinitis with omalizumab were identified by Yu and colleagues.[4] The results of this meta-analysis showed that there were statistically significant differences between the omalizumab group and the control group in the following aspects: daily

nasal symptom score (standardized mean difference [SMD] = −0.443; 95% confidence interval [CI], −0.538 to −0.347; *P*<.001); daily ocular symptom score (SMD = −0.385; 95% CI, −0.5 to −0.269; *P*<.001); daily nasal medication symptom scores (SMD = −0.421; 95% CI, −0.591 to −0.251; *P*<.001); proportion of days of emergency drug use (risk ratio [RR] = 0.488; 95% CI, 0.307–0.788; *P*<.005); and rhinoconjunctivitis-specific quality of life questionnaire score (SMD = −0.286; 95% CI, −0.418 to −0.154; *P*<.001). Importantly, there was no statistically significant difference in safety indicator: adverse events (RR = 1.026; 95% CI, 0.916–1.150; *P* = .655). The investigators concluded that omalizumab is effective and relatively safe in patients with allergic rhinitis.

Omalizumab has also been studied in patients on allergen immunotherapy. The hypothesis is that neutralization of IgE and reduction of IgE receptor expression on mast cells and basophils could eliminate, or at least reduce the severity of, allergen immunotherapy–related reactions, especially anaphylaxis. In the meta-analysis mentioned earlier, it was noted that omalizumab significantly improved redness and swelling at immunotherapy injection sites. Yu and colleagues[4] concluded that omalizumab used in conjunction with allergen-specific immunotherapy has shown promising results, especially in reducing adverse events.

In a randomized controlled trial, Casale and colleagues[5] evaluated the effectiveness of omalizumab in enhancing both safety and efficacy of rush immunotherapy.[6] Adult patients with ragweed allergic rhinitis were enrolled in a 3-center, 4-arm, double-blind, parallel-group, placebo-controlled trial. Patients received either 9 weeks of omalizumab or placebo, followed by 1-day rush or placebo immunotherapy, then 12 weeks of omalizumab or placebo plus immunotherapy. Patients receiving omalizumab plus rush immunotherapy had fewer adverse events than those receiving immunotherapy alone. The addition of omalizumab resulted in a 5-fold decrease in risk of anaphylaxis caused by rush immunotherapy (odds ratio, 0.17; *P* = .026).

As noted in the studies described here, omalizumab has been shown to be effective in reducing nasal symptom scores and improving quality of life in several studies of seasonal and perennial allergic rhinitis.[6] However, despite this demonstrated efficacy, omalizumab was not approved by the FDA for the treatment of allergic rhinitis. It was thought that the high cost of omalizumab precluded its chronic use for allergic rhinitis; however, its periodic use may be justified in treatment-resistant patients, especially those with seasonal disease.[7]

Other type 2 biologics have not been studied specifically in allergic rhinitis.

Dupilumab

Dupilumab is a human Ig4 monoclonal antibody directed against the IL-4 receptor subunit α (IL-4Rα), which is recognized by both IL-4 and IL-13. Although dupilumab has not completed studies specifically in allergic rhinitis, studies have assessed the efficacy of dupilumab for the treatment of allergic rhinitis in the setting of comorbid asthma. In patients with uncontrolled persistent asthma despite using medium-dose to high-dose inhaled corticosteroids plus long-acting β2-agonists with comorbid perennial allergic rhinitis, dupilumab's effect on the allergic rhinitis–associated items on the Sino-Nasal Outcome Test (SNOT-22) was studied. In patients with asthma with perennial allergic rhinitis, dupilumab 300 mg every 2 weeks versus placebo significantly improved all 4 allergic rhinitis–associated symptoms of the SNOT-22 (nasal blockage, −0.60; 95% CI, −0.96 to −0.25; runny nose, −0.67; 95% CI, −1.04 to −0.31; sneezing, −0.55; 95% CI, −0.89 to −0.21; postnasal discharge, −0.49; 95% CI, −0.83 to −0.16; all *P*<.01).[8]

Mepolizumab

Although allergic rhinitis is often thought of as exclusively an IgE-mediated disorder, eosinophilia is a hallmark of this disease process as well. IL-5 is a key mediator acting at many levels of eosinophil biology. Mepolizumab is a humanized anti–IL-5 antibody.

None of the IL-5/IL-5R biologics have been studied specifically in allergic rhinitis. However, a poster presented at the 2019 annual meeting of the American Academy of Allergy, Asthma and Immunology described a meta-analysis of patients with severe asthma from the mepolizumab phase 2b/3 clinical program (DREAM, MENSA, SIRIUS, and MUSCA) with self-reported history of comorbid upper airway disease including allergic rhinitis. Mepolizumab improved quality-of-life assessments in patients with severe asthma and self-reported upper airway disease.[9]

BIOLOGICS FOR ASTHMA

A simplified, streamlined overview of the type 2 inflammatory pathway and the immunologic targets for currently FDA-approved monoclonal agents for the treatment of certain endotypes of asthma is provided in **Fig. 1**. Familiarity with type 2 inflammation is helpful for the practical application because the currently FDA-approved biologic therapies target portions of the type 2 inflammatory cascade.

Recent updates to the Global Initiative for Asthma (GINA) and the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines have renewed focus

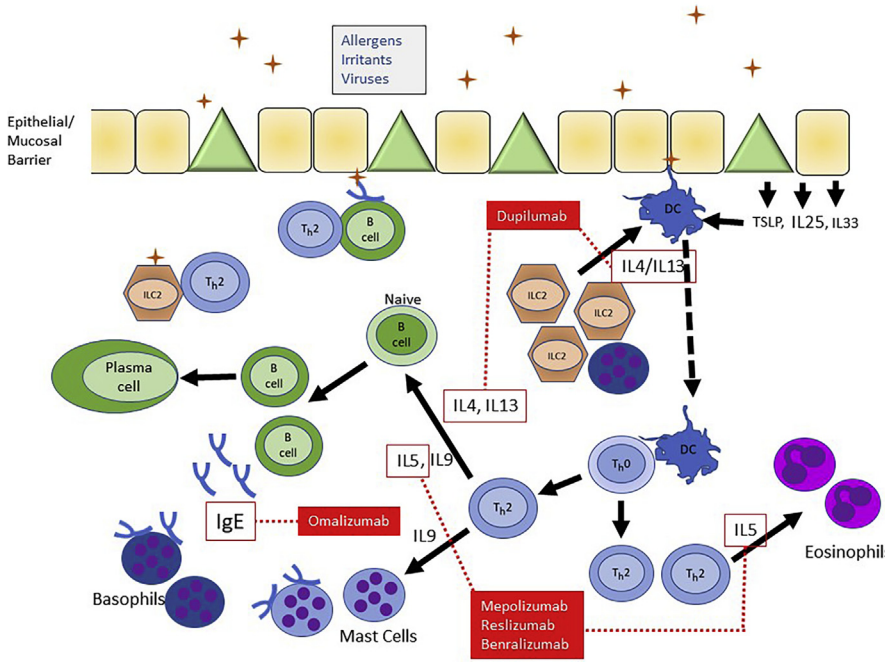

Fig. 1. A general overview of type 2 inflammation. B cell, B lymphocyte; DC, dendritic cell; ILC2, innate type 2 lymphoid cell; Th0, naive T-helper cell; TSLP, thymic stromal lymphopoietin. (*From* Franzese, C. Brief Immunology Review for Targeted Biologic Therapies in Allergic Disease. Curr Otorhinolaryngol Rep 8, 14–18 (2020). https://doi.org/10.1007/s40136-020-00263-0; with permission.)

on treating severe asthma. According to the GINA 2020 update, anti-IgE therapy should be considered as add-on therapy for adolescents, adults, and children (aged 6–11 years) with asthma poorly controlled on moderate-dose inhaled corticosteroids (ICS) and long-acting beta-agonist (LABA) (ie, step 5 treatment).[10] Anti–IL-5/5R therapy should be considered as add-on therapy for adults and adolescents (aged ≥12 years), with asthma poorly controlled on medium-dose ICS and LABA (ie, step 5 therapy).[10] There are currently 3 FDA-approved drugs to treat the IL-5 inflammatory pathway: mepolizumab, reslizumab, and benralizumab. Anti–IL-4R therapy should be considered as add-on therapy for adults and adolescents (aged ≥12 years) with asthma poorly controlled on moderate-dose ICS and LABA (ie, step 5 therapy).[10]

All but 1 of the following listed biologic agents has an FDA approval for an asthma indication. **Table 1**provides a summary of the pivotal trials supporting the approved asthma indications.

Omalizumab

Omalizumab is a humanized monoclonal antibody that functions as an IgE antagonist, binding to free-floating IgE, specifically to the Cε3 domain; however, cell surface–bound IgE is unaffected.[11,12] Binding of IgE to cell surface receptors depends on exposure to the Cε3 domain. When omalizumab attaches to the Cε3 domain of serum IgE, it inhibits binding to the FcεRI high-affinity IgE receptor and the CD23 receptor.[12] This process diminishes release of inflammatory mediators and upregulates the replacement of FcεRI high-affinity IgE receptors with FcεRII low-affinity IgE receptors.[12] Omalizumab cannot bind to or displace bound IgE because it requires exposure of Cε3 domain and, thus, is unable to bind directly to any IgE receptors itself. In theory, this prevents omalizumab from triggering mediator release and anaphylaxis.

Omalizumab is currently indicated for the treatment of poorly controlled or uncontrolled moderate to severe persistent asthma despite ICS in patients 6 years of age and older with a positive skin test or specific IgE reactivity to a perennial allergen, as add-on maintenance treatment of nasal polyps in patients 18 years of age and older with inadequate response to nasal corticosteroids, and for chronic idiopathic urticaria in patients 12 years of age or older who remain symptomatic despite H1 antihistamine treatment.[13]

Omalizumab is administered via subcutaneous injection and is available as a prefilled syringe or lyophilized powder for reconstitution. Dosage for omalizumab is IgE and weight based. Injection-site pain is the most common adverse reaction seen with omalizumab. Additional warnings include malignancy, helminth infections, and cardiovascular disease, as well as a special black-box warning concerning anaphylaxis. The black-box warning was placed after adverse events were noted in postmarketing, with at least 0.2% of patients who received omalizumab reporting anaphylactic reactions.[14] The Omalizumab Joint Task Force published a report recommending that patients receiving omalizumab be prescribed an autoinjectable form of epinephrine and be observed for 2 hours after the first 3 injections and 30 minutes for all subsequent injections.[15,16]

A higher incidence of malignancies in the omalizumab-treated group compared with the control group (0.5% vs 0.2%) was reported in the initial pooled analysis of phase I and II trials.[17] These malignancies were heterogeneous in tumor type and organ involvement.[18] In the EXCELS observational study, there was no significant difference found in the adjusted malignancy rate in patients treated with omalizumab.[19]

Mepolizumab

Mepolizumab is a humanized monoclonal antibody that functions as an IL-5 antagonist by binding directly to IL-5 and preventing it from binding to the IL-5 receptor α

Table 1
Pivotal trials supporting approved indications for asthma

Biologic Agent	Inclusion Criteria	Effects and Outcomes	Notable Findings
Omalizumab (IgE)	12–75 y old, asthma inadequately controlled with ICS + SPT to DF, DP, cockroach, dog, or cat and total IgE ≥30 IU/mL to 700 IU/mL	Reduced exacerbations (40% overall/60% if eos >300 cells/μL) Improved QOL Decreased ICS use Decreased asthma symptoms	Improved responses with ↑FeNO and eos> 300 cell/μL Improvement in FEV1 less consistent
Reslizumab (IL-5)	18–75 y old, asthma inadequately controlled with ICS + LABA, LTRA, or cromolyn ACQ at 1.5 or more Sputum eosinophils >3%	Reduced exacerbations (approximately 50%–60%) Improved FEV1 (0.100–0.160 L)	Greatest improvement in FEV1 of all 3 anti–IL-5 agents
Mepolizumab (IL-5)	18–82 y old, asthma inadequately controlled with ICS + 1 additional controller ≥2 exacerbations in past year treated with OCS Eosinophils>150 cells/μL at screening; >300 cells/μL within past year	Reduced exacerbations (47%–53% overall/79% if eos >500 cells/μL) Improved FEV1 (0.100 L overall/0.122 L if eos >500 cell/μL)	Most efficacious with eos >500 cell/μL
Benralizumab (IL-5)	12–75 y old, asthma inadequately controlled with ICS + LABA ≥2 exacerbations in past year	Reduced exacerbations (28%–51%) Improved FEV1 (0.100–0.160 L)	Efficacy correlates with increased eos
Dupilumab (IL-4/13)	>18 y old, asthma inadequately controlled on medium to high dose with ICS + LABA ≥ 1 exacerbation in past year	Reduced exacerbations (60%–80%) Improved FEV1 (0.150–0.160 L)	Most effective if eos> 300 cell/μL

Abbreviations: +, positive; ACQ, asthma control questionnaire; DF, *Dermatophagoides farinae*; DP, *Dermatophagoides pteronyssinus*; eos, eosinophils; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids;QOL, quality of life; SPT, skin prick test.

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subunit. It is currently indicated as add-on maintenance therapy for the treatment of patients with poorly controlled or uncontrolled severe asthma with an eosinophilic phenotype aged 6 years and older, patients aged 18 years or older with eosinophilic granulomatosis with polyangiitis (EGPA), and for treatment of patients aged 12 years and older with hypereosinophilic syndrome (HES) for greater than or equal to 6 months without an identifiable nonhematologic secondary cause.[20]

Because subjects in the mepolizumab trials had peripheral eosinophil counts greater than 150 cells/μL, this is often the minimum requirement from insurance companies for coverage. Mepolizumab is administered subcutaneously every 4 weeks with a dose of 40 mg for patients aged 6 years to 11 years and 100 mg for patients more than 12 years of age.[20] Its dosage is not weight based. Mepolizumab is available in a lyophilized powder that has to be reconstituted for administration in a health care setting and in a prefilled syringe form as well as an autoinjector, both for home administration. In the clinical trials, 2 mepolizumab-treated subjects and none of the placebo-treated subjects developed shingles in studies of more than 1300 subjects. The label states that clinicians should consider varicella vaccination in patients in whom such protection is medically appropriate before starting mepolizumab. The label also recommends treating patients with preexisting helminth infections before therapy with mepolizumab.[20]

Reslizumab

Reslizumab is also a humanized monoclonal antibody that functions as an IL-5 antagonist by binding directly to IL-5 and preventing its binding to the IL-5 receptor α subunit. It is currently indicated as add-on maintenance therapy for adult patients with poorly or uncontrolled severe asthma with an eosinophilic phenotype.[21]

Subjects in the reslizumab trials had peripheral eosinophil counts greater than 400 cells/μL; insurance companies often require levels greater than this for approval. Reslizumab's dosing is weight based at 3 mg/kg once every 4 weeks administered by intravenous infusion over 20 to 50 minutes, making it a good option for obese patients. Anaphylaxis was observed with reslizumab infusion in 0.3% of patients in placebo-controlled clinical studies. Anaphylaxis was reported as early as the second dose.[22] Also, 0.6% of patients in placebo-controlled clinical studies had at least 1 malignant neoplasm reported compared with 0.3% of patients in the placebo group. The observed malignancies in reslizumab-treated patients were diverse and without clustering of any particular tissue type.[21]

Benralizumab

Benralizumab is a humanized monoclonal antibody that is specifically engineered without a fucose molecule and binds directly to the IL-5 receptor α subunit.[23] When bound, it can trigger antibody-dependent cell cytotoxicity and apoptosis in eosinophils and mast cells.[23] Although benralizumab is in essence an IL-5 antagonist, its mechanism of action is technically different from mepolizumab and reslizumab, because it induces eosinophilic cell death, as opposed to binding to IL-5 itself. It is currently indicated as add-on maintenance therapy for the treatment of patients with poorly controlled or uncontrolled severe asthma with an eosinophilic phenotype aged 12 years and older.[23] It was also granted orphan drug status for adult patients with EGPA in November 2018, for hypereosinophilic syndrome (HES) in February 2019, and eosinophilic esophagitis in August 2019.[24]

Benralizumab is administered subcutaneously every 4 weeks with a fixed dose of 30 mg for patients aged 12 years of age and older for the initial 3 doses, then administered every 8 weeks thereafter. Given that, after the first 3 doses, the dosing interval is expanded to almost 2 months, this results in fewer injections and may be more

convenient for some patients with transportation difficulties or other lifestyle barriers. Similar to mepolizumab, benralizumab's dosing is not weight based. Benralizumab is available as a prefilled syringe for home administration or administration in a health care setting, as well as an autoinjector for home administration. Patients with preexisting helminth infections need to be treated before initiating therapy with benralizumab.[23]

Dupilumab

Dupilumab is a fully human monoclonal antibody that functions as an IL-4 receptor α-subunit antagonist. Although this agent only binds to the IL-4 receptor α subunit, it inhibits the signaling of both IL-4 and IL-13 because this particular subunit is present in both type I receptors, which bind IL-4, and type II receptors, which bind IL-4 and IL-13. It is currently approved as an add-on maintenance treatment in patients aged 18 years or older with inadequately controlled chronic rhinosinusitis with nasal polyposis, as well as the treatment of patients aged 6 years or older with moderate to severe atopic dermatitis uncontrolled by topical treatments, and as an add-on maintenance treatment in patients with moderate to severe asthma aged 12 years and older with eosinophilic phenotype and/or oral corticosteroid (OCS)-dependent asthma.[25]

In adults and adolescents (12 years of age and older) for moderate to severe asthma, an initial dose of 400 mg (2 200-mg injections) followed by 200 mg given every other week, or an initial dose of 600 mg (2 300-mg injections) followed by 300 mg given every other week, is administered subcutaneously either in a health care setting or at home via a prefilled syringe (for 200-mg and 300-mg options) or a prefilled pen (for 300 mg only). For patients requiring concomitant OCS or with comorbid moderate to severe atopic dermatitis, for which dupilumab is indicated, it is recommended to start with an initial dose of 600 mg followed by 300 mg given every other week.[25]

In the atopic dermatitis trials, dupilumab was associated with a higher incidence of conjunctivitis compared with subjects receiving placebo.[26] Dupilumab-treated subjects in the nasal polyp trials had a greater initial increase from baseline in blood eosinophil count compared with subjects treated with placebo, which is likely related to its underlying mechanism of action in blocking IL-4–mediated eosinophil migration out of the bloodstream.[27] Because the clinical significance of the transient increase in eosinophil level is unknown, it is recommended that clinicians be alert to vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially on reduction of OCS.

Tezepelumab

Tezepelumab is a subcutaneously administered humanized monoclonal antibody that blocks the action of thymic stromal lymphopoietin (TSLP), an epithelial cytokine.[28,29] TSLP sits at the top of multiple inflammatory cascades and plays a critical role in the initiation and persistence of allergic, eosinophilic, and other types of airway inflammation associated with severe asthma. TSLP is released in response to multiple triggers, including allergens, viruses, and other airborne particles, associated with asthma exacerbations. Blocking TSLP may prevent the release of proinflammatory cytokines by immune cells, resulting in the prevention of asthma exacerbations and improved asthma control.[30]

NAVIGATOR is a phase III, randomized, double-blinded, placebo-controlled trial in adults and adolescents (aged $\geq$12 years) with severe uncontrolled asthma who were receiving treatment with medium-dose or high-dose ICS plus at least 1 additional controller medicine with or without OCS. NAVIGATOR met the primary end point with tezepelumab added to standard of care, showing a statistically significant and clinically meaningful reduction in the annualized asthma exacerbation rate over 52 weeks compared with placebo.[31–33]

SOURCE is a phase III, multicenter, randomized, double-blinded, parallel-group, placebo-controlled trial for 48 weeks in adult patients with severe asthma who require continuous treatment with ICS plus LABA, and chronic treatment with maintenance OCS therapy. Patients were randomized to receive tezepelumab every 4 weeks or placebo as add-on therapy.[34] However, the SOURCE trial did not meet the primary end point of a statistically significant reduction in the daily OCS dose, without loss of asthma control, with tezepelumab compared with placebo.[35]

FUTURE DIRECTIONS

As additional trials continue for new biologic agents for asthma, an interesting shift seems to be occurring among potential biologic treatments for allergic rhinitis. Although cytokine-based or anti-IgE–based biologics seem to be helpful as add-on therapy to other treatments, none of them have been resoundingly successful as solo treatments for allergic rhinitis. Perhaps because of this, there has been interest in and development of monoclonal antibodies targeting specific epitopes on certain common allergens, such as cat and birch tree pollen.[36,37] Some of these trials involve investigating a single dosing treatment to a sustain an entire allergy season or whether there is blocking activity preventing symptomatic experience of pollen-food syndrome.[37] Whether any of these epitope-targeting monoclonal antibodies show efficacy remains to be seen, but their development opens up exciting possibilities for future treatment strategies.

SUMMARY

At present, monoclonal antibodies targeting type 2 inflammation are primarily indicated as add-on treatment to standard of care, maintenance therapy for patients with asthma and other approved disorders. However, because these agents target cytokines and cell surface receptors integral to type 2 inflammation, which is the underlying type of inflammation shared by several disease processes, they have the potential to treat more than 1 disorder and may change how patient care for atopic disorders is managed. Knowledge of the type 2 immunologic cascade will prove useful to agent selection, but practical matters such as frequency of injection, location (home vs office) of injection, weight based or not, and method (subcutaneous vs intravenous) of administration are important considerations as well.

CLINICS CARE POINTS

- Biologic therapies are add-ons to standard-of-care treatments. Ensuring patients have tried and been compliant with such therapy before starting a biologic agent is important.
- Dosing, route, and frequency of administration vary between different agents. Treating practitioners should consider these aspects when selecting a therapy.
- Patients who have not had the varicella vaccination may be at risk for shingles. Depending on the agent selected, a discussion with the patient regarding risks or consideration for a shingles vaccination may be necessary.

DISCLOSURE

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