

Biologics and Allergy Immunotherapy in the Treatment of Allergic Diseases



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KEYWORDS

- Allergy immunotherapy • Subcutaneous immunotherapy
- Sublingual immunotherapy • Rhinosinusitis with nasal polyps • Atopic dermatitis
- Biologics • Omalizumab • Mepolizumab

KEY POINTS

- Effective, safe, and inexpensive therapies for chronic allergic conditions remain a significant unmet need.
- Allergy immunotherapy through the sublingual and subcutaneous route has demonstrated clinical and cost efficacy in the treatment of allergic rhinitis and asthma, but adherence with both routes is problematic.
- Several biologics targeting specific components of the immune system have demonstrated efficacy in patient populations not responding to conventional medical treatment.
- Anti-immunoglobulin E therapy, omalizumab, has been shown to be effective in moderate to severe asthmatics not well controlled on inhaled corticosteroids and long-acting beta agonist, chronic urticaria, and allergic rhinitis.
- Agents targeting interleukin 5 (IL-5), mepolizumab, benralizumab, reslizumab have demonstrated efficacy and poorly controlled asthmatics with eosinophilic phenotype.
- Dupilumab, an agent targeting IL-4/IL-13 has been shown to be effective in moderate to severe atopic dermatitis and allergic asthma. In patients with severe chronic rhinosinusitis with polyps, dupilumab reduced polyp size, sinus opacification, and symptom severity.

INTRODUCTION

Allergic diseases, which include asthma, allergic rhinitis, chronic rhinosinusitis, atopic dermatitis, and food allergies, represent some of most common chronic pediatric and adult conditions worldwide. The 3 most common allergic diseases, asthma, allergic rhinitis, and atopic dermatitis often present during childhood and continue to be symptomatic through adulthood if they are not adequately managed. Medical management may include avoidance of known allergenic and nonallergenic triggers, pharmacotherapy, and immunomodulatory therapies. Ideally, complete avoidance of the

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offending allergen would be the optimal management approach, but this is rarely achievable. In addition, there are limited data indicating any single environmental control measure will result in improved outcomes. A Cochrane systematic review of randomized controlled trials that compared the effectiveness of several bedroom environmental control measures in dust mite (HDM) perennial allergic rhinitis found that isolated use of HDM impermeable bedding did not seem to be effective.¹ Similarly, there is little evidence indicating cat/dog removal from the household will improve allergic rhinitis or asthma symptoms.² This “failure to improve” after cat/dog removal may be due to the persistence of airborne animal dander long after removal³ or the ubiquitous presence of animal dander.⁴ It may be difficult to predict and avoid exposure to irritant triggers, such as fragrance/chemical odors and cold air. Pharmacotherapy is aimed at controlling symptoms and preventing exacerbations. Most allergy medications need to be administered one or more times a day even during asymptomatic periods. Adherence is as problematic as with any chronic condition.⁵ One study found that only 25% of asthmatic children were compliant with prescribed regimens.⁵ Concerns about medication adverse effects, costs, side-effects, and absence of active symptoms are likely contributing factors to the high rate of medication nonadherence in allergic conditions. These factors should be considered along with the risks and benefits of long-term therapy during the medical management decision-making process. Immunomodulators that target specific components of the immune system are another therapeutic option in the management of allergic disease. Compared with conventional pharmacotherapy, they offer the advantage of less frequent administration and potentially less adverse effects. The purpose of this paper is to review the efficacy and safety of biologics in the treatment of allergic rhinitis, chronic rhinosinusitis, asthma, and atopic dermatitis.

Allergy Immunotherapy

The oldest biological therapy for allergic disease that is still in current use is allergy immunotherapy (AIT). It entails administration of the identified allergen at repeated intervals over a 3- to 5-year period. The frequency of administration will vary with administration route. The treatment specific for the aeroallergen is identified during the allergy diagnostic evaluation. The allergen extracts are derived from natural sources (pollen) or cultures (mold/fungi and house dust mite). Influenced by the success of Jenner's work with the smallpox vaccine, physicians in the early 1900s theorized that they could induce a similar immunity by injecting “hay fever” patients with pollen extracts. Initial experiments were hampered with high rate of systemic allergic reactions.⁶ The first successful report of subcutaneous immunotherapy (SCIT) against “hay fever” was reported by Noon in a 1911 *Lancet* article.⁷ Patients were administered incrementally higher doses of a pollen extract, which Noon had prepared by extracting pollen in distilled water and freeze-thawing and boiling. Conjunctival allergen provocation test was used to confirm allergy sensitivity and monitor response to allergy immunotherapy. Noon noted that efficacy and safety were related allergen dose, which he summarized in the following statement: “an overdose can induce a severe attack of hay fever lasting 24 hours” and “sensibility of hay fever patients may be decreased by properly directed dosage.”⁷ Since Noon's report, numerous studies confirmed the safety and efficacy of SCIT in the treatment of allergic rhinitis and asthma.

However, it was not until many decades later that the mechanisms responsible for its efficacy began to be elucidated. AIT induces several immunologic changes that likely contribute to the sustained immune-specific tolerance associated with effective AIT. These include changes in allergen-specific T- and B-cell cytokine responses,

increase in allergen-specific immunoglobulin G4 (IgG4), production of antibodies capable of blocking allergen presentation, and reductions in mast cell, eosinophil, and basophil activation.⁸ The immunologic changes take place at different time points in the AIT course. Mast cell and basophil desensitization occurs early in the treatment course followed by induction of the generation of T and B regulatory cells producing IL-10 and other cytokines, which result in suppression of effector TH₁ and TH₂ cells.⁸ AIT is considered the only proven disease-modifying treatment of allergic disease. AIT's disease-modifying effects include altering the progression of the allergic disease, for example, development of asthma or new allergen sensitizations and the induction of long-term clinical tolerance, for example, preventing insect sting anaphylaxis. In contrast to pharmacotherapy, AIT can provide symptomatic improvement that may continue for years after therapy discontinuation.^{9,10}

SCIT continues to be prescribed in a manner largely unchanged from Noon's protocol of administering unmodified extracts in increasing doses over a period of weeks to months. The major disadvantage of SCIT is the relatively narrow margin between therapeutic efficacy and adverse side effects. Because of the risk of systemic allergic reactions that include rare life-threatening anaphylaxis, it is recommended that SCIT be administered in a medically supervised setting with an appropriate wait period.¹¹ Efforts to develop safer and more effective AIT led to investigations with modified allergens and alternate delivery routes.

Multiple randomized-controlled clinical trials demonstrated the safety and efficacy of sublingual immunotherapy, administered as a tablet or liquid extract. Although few studies have directly compared SCIT and sublingual immunotherapy treatment (SLIT), their efficacy seems comparable. However, SLIT clearly has the more favorable safety profile, which allows for home administration. Currently there are only 4 Food Drug Administration (FDA)-approved tablets in the United States (see [Table 1](#) for summary of approved products). In the United States, SLIT with liquid extracts is considered "off-label" treatment. "Off-label" treatment is not generally covered by third-party payers.

The recommended treatment duration for SLIT and SCIT is at least 3 years of monthly maintenance injections or daily tablet ingestion. There is little difference between the 2 routes in terms of adherence, which has been shown to be equally poor and comparable to adherence rates with long-term pharmacotherapy.⁵ In 3 retrospective claims-based analysis studies, the rate of premature discontinuation of treatment was 45% to 93% of SLIT and 41% to 77% of SCIT patients.¹² Cost and inconvenience were of the most commonly cited reasons for discontinuation.¹²

The other alternative AIT routes that have demonstrated efficacy in the treatment of allergic rhinitis/rhinoconjunctivitis are epicutaneous (EPIT) and intralymphatic immunotherapy (ILIT). In EPIT, the allergen is applied to skin in the form of a patch. A double-blind, placebo-controlled (DBPC) trial of 98 grass pollen allergic rhinoconjunctivitis patients examined the efficacy of one preseasonal EPIT course on 2 subsequent pollen seasons.¹³ Patients were randomized to receive 6 weekly grass pollen extract or placebo patches. The patches were applied to tape-stripped skin that remained on the skin for 8 hours 6-weekly. Allergen EPIT was associated with a median symptom improvement of 48% and 40% in the first and second treatment-free season, respectively as compared with 10% and 15% improvement after placebo ($P = .003$). Allergen EPIT was also associated with a significant decrease in conjunctival allergen reactivity and increase in allergen-specific IgG4 ($P < .001$). Adverse reactions were primarily eczema at the application site. One patient experienced a grade 2 systemic allergic reaction. EPIT also seems to be a promising treatment of food allergies.¹⁴ The FDA has granted Viaskin Peanut Patch Fast Track and Breakthrough Therapy Designation

Table 1
Federal Drug Administration–approved sublingual immuotherapy products

	<u>ORALAIR</u>	<u>RAGWITEK</u>	<u>GRASTEK</u>	<u>ODACTA</u>
Manufacturer	Stallergens	Merck & Co	Merck & Co	Merck & Co
Indications	Grass pollen–induced allergic rhinitis with or without conjunctivitis	Short ragweed pollen–induced allergic rhinitis with or without conjunctivitis	Timothy grass pollen–induced allergic rhinitis with or without conjunctivitis	Dust mite–induced allergic rhinitis with or without conjunctivitis
Ages	10–65 y	18–65 y	5–65 y	18–65 y
Dosage	100 IR, 300 IRA Age 10–17 y: Day 1: 100 IR Day2: 2 x 100 IR Day3 and following: 300 IR Age 18–65 y Day 1 and following: 300 IR	1 tablet daily, 12 Amb a 1-unit	1 tablet daily, 2800 bioequivalent allergy units (BAUs)	12 SQ-HDM, major allergen content not provided
First dose administration	Observe patients in the office for at least 30 min following the initial dose			
Instructions for dose administration	Place the tablet under the tongue for at least 1 min, until completely dissolved, then swallow			
Active ingredients	Grass pollen mix: Sweet Vernal, Orchard, Perennial Rye, Timothy, Kentucky Blue Grass	Short ragweed pollen	Timothy grass pollen	1:1:1:1 potency ratio of D. farinae group 1 allergen, D. farinae group 2 allergen, D. pteronyssinus group 1 allergen, and D. pteronyssinus group 2 allergen

Inactive ingredients	Mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, and lactose monohydrate	Gelatin NF (fish source) ^a , mannitol USP, and sodium hydroxide NF		
Initiation of therapy in relation to pollen season	Four months before the expected onset of each grass pollen season and continue throughout the season	At least 12 wk before the expected onset of ragweed pollen season and continue throughout the season	At least 12 wk before the expected onset of grass pollen season and continue throughout the season; for sustained effectiveness for one grass pollen season after cessation of treatment, GRASTEK may be taken daily for 3 consecutive years	Not specified/applicable
Contraindications	• Severe, unstable, or uncontrolled asthma • History of any severe systemic allergic reaction or any severe local reaction to SLIT • Hypersensitivity to any of the inactive ingredients contained in this product • A history of eosinophilic esophagitis			
Precautions	• Prescribe autoinjectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care on its use			

^a Gelatin is derived from a skin of cold-water fish source such as cod, pollock, or haddock. Gelatin constitutes a fraction of the 28 mg tablet weight. In one study, commercial, food-grade fish gelatin derived from the skins of codfish was evaluated in a double-blind, placebo-controlled food challenge. None of the 30 fish-allergic patients reacted adversely to the ingestion of cumulative dose of 3.61 g fish gelatin. Investigators concluded with a 95% certainty that 90% of fish-allergic consumers will not react to ingestion of a 3.61 g cumulative dose of fish gelatin.⁶¹

(DBV Technologies, Montrouge, France). The company submitted a Biologics License Application for Viaskin Peanut Patch for the treatment of peanut-allergic children aged 4 to 11 years to the FDA in October 2019. Questions regarding efficacy and the patch's adhesion to the skin prompted the FDA to cancel the Allergenic Products Advisory Committee meeting, which was convened to discuss approval for patch's approval.¹⁵

ILIT offers the advantage of a short treatment course that seems to have an efficacy similar to SCIT and SLIT. An open trial, ILIT with 3 injections of grass pollen administered at 4-week intervals resulted in significant improvement in nasal allergen challenge after 4 months and symptomatic improvement comparable to 3 years of SCIT.¹⁶ Subsequent DBPC ILIT trials have reported conflicting results. One DBPC trial of 36 patients with allergic rhinoconjunctivitis reported a significant improvement in seasonal allergy symptom with ILIT.¹⁷ Another DBPC trial of 45 patients with grass-pollen allergic rhinoconjunctivitis reported no improvement in clinical or immunologic parameters with ILIT.¹⁸ Another consideration with ILIT is that it may be difficult to locate inguinal lymph nodes in obese individuals.

At present, ILIT and EPIT are considered investigational and SCIT and SLIT are the only routes recommended in practice guidelines for the treatment of allergic rhinitis, asthma, and some cases of atopic dermatitis.^{11,19–21} Although, asthma is an indication for AIT, there have been no studies of SLIT or SCIT in poorly controlled severe asthma. In addition, "severe asthma uncontrolled by pharmacotherapy" is considered a relative contraindication for SCIT and SLIT.^{11,22}

TARGETED BIOLOGICAL THERAPIES

Omalizumab

Until the development of biologics targeting specific components of the immune system, management of severe asthma generally required multiple medications, that is, inhaled corticosteroids, long-acting beta-agonist, prednisone, etc. AIT is generally not an option because poorly controlled asthma has been identified as a risk factor for severe and fatal AIT reactions.²³ Management challenges related to polypharmacy adherence, suboptimal control despite adherence, and long-term medication adverse effects, for example, prednisone, prompted investigations of biological agents directed at specific components of the allergic inflammatory pathway.

The first biological agent for the treatment of moderate to severe asthma, omalizumab (Xolair; Genentech), was approved in the United States in 2003. It is a 95% humanized monoclonal antibody directed against the Fc portion of IgE. Omalizumab binds the Cε3 domain of the Fc, which prevents IgE binding to the high-affinity IgE receptor FcεR1 and subsequent effector cell activation.²⁴ Significant and rapid reductions in free serum IgE has been demonstrated after one dose of omalizumab.²⁵ In one study, mean serum IgE levels were decreased by 96% three days after omalizumab administration.²⁶ As serum IgE levels decreases, there is a reduction in the expression FcεR1 receptor on multiple cell types, for example, mast cells, basophils, dendritic cells, etc.^{26,27} In the study cited earlier, omalizumab treatment was also associated with a 73% reduction in basophil FcεR1 receptor expression within 7 days and a 90% reduction in basophil responsiveness at 90 days. In multiple clinical trials, omalizumab treatment resulted in reduced inhaled corticosteroid (ICS) dose and beta-agonist rescue inhaler use, fewer asthma exacerbations, and improved asthma symptoms.²⁴ Omalizumab has been shown to decrease the frequency of fall seasonal asthma exacerbations in adolescents and children.^{28,29} The major cause of fall seasonal asthma exacerbations is viral respiratory tract infections such as, rhinovirus. In a randomized-controlled trial comparing omalizumab

add-on treatment with guidelines-based asthma care, there was a reduced duration and frequency of rhinovirus infections in the omalizumab-treated group.³⁰ In another DBPC study, omalizumab resulted in a greater interferon-alpha responses to rhinovirus and fewer asthma exacerbations.²⁸ These studies provide evidence that omalizumab may decrease susceptibility to rhinovirus infections and subsequent asthma exacerbations.³⁰ This effect has not been demonstrated with any other asthma therapeutic agent.

According to the Global Initiative for Asthma 2020 update, anti-IgE therapy should be considered as add-on therapy for adolescents, adults, and children, aged 6 to 11 years, with asthma poorly controlled on moderate dose ICS and long-acting beta-agonist (ie, step 5 treatment).³¹

Omalizumab was later FDA approved for chronic urticaria. The speculated mechanisms for omalizumab's efficacy in chronic urticaria, a nonatopic condition, include reduced mast cell sensitivity, blockage of IgG autoantibodies directed against IgE or the FcεRI receptor or blockage of IgE autoantibodies directed against an antigen to be identified.³²

Omalizumab has also been studied in several other conditions. It was shown to be effective in reducing nasal symptom scores and improving quality of life and several studies of seasonal and perennial allergic rhinitis.²⁴ Despite demonstrated efficacy, omalizumab was not approved by the FDA for the treatment of allergic rhinitis. The cost of treatment may have been a factor in the FDA's decision.³³ Clinical trials investigating omalizumab as treatment of atopic dermatitis have yielded conflicting data. A recent systematic review and meta-analysis reported that only 43% of patients with atopic dermatitis responded to omalizumab.³⁴ A series of case reports suggest omalizumab may be effective in allergic bronchopulmonary aspergillosis, systemic mastocytosis, and eosinophilic granulomatosis with polyangiitis.²⁴ Pretreatment with omalizumab has been shown to improve the safety of rush and cluster aeroallergen immunotherapy and oral food immunotherapy.^{35–38} Omalizumab added to AIT provided an additional 48% improvement compared with AIT alone.³⁹

The most common adverse reaction from omalizumab is injection-site pain and bruising. The package insert contains additional warnings regarding malignancies, geohelminth infections, cardiovascular diseases, and a "black box" warning concerning anaphylaxis. A "black box" is the most serious type of warning mandated by the US Food and Drug Administration (FDA) in pharmaceutical package inserts.⁴⁰ The warning was based on a review of spontaneous postmarketing adverse events submitted to the FDA suggesting that at least 0.2% of patients who received Xolair (omalizumab) experienced anaphylaxis.⁴¹ The review also noted that many of the cases were delayed in onset and characterized by a protracted progression. Based on the anaphylaxis warning, a Joint Task Force of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology (omalizumab Joint Task Force) published a report recommending omalizumab patients be prescribed an epinephrine autoinjector and be observed for 2 hours after the first 3 injections and 30 minutes for all subsequent injections.^{42,43}

Initial pooled analysis of phase I and II trials reported a higher incidence of malignancies in omalizumab-treated group compared with the control group (0.5% vs 0.2%).⁴⁴ The malignancies were heterogeneous in tumor type and organ and most of the cases (60%) were diagnosed within 6 months of treatment.⁴⁵ Subsequently, multicenter, prospective, observational cohort study entitled Evaluating the Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma found no significant difference in the adjusted malignancy rate between the omalizumab-treated (n = 5007) and nonomalizumab group (n = 2829).

Biologics Targeting Interleukin 5

Interleukin 5 (IL-5) is a TH2 cytokine that plays a key role in eosinophil activation. Since 2017, the FDA has approved 3 anti-IL-5 therapies as add-on therapy for severe asthma with an eosinophilic phenotype: benralizumab (Fasenra; AstraZeneca), a humanized monoclonal antibody directed against IL-5R α ; mepolizumab (Nucala; GalxoSmithKline), a neutralizing anti-IL-5 antibody; and reslizumab (Cinqair), an IgG4 κ monoclonal antibody targeting circulating IL-5. The pivotal trials differed in how they defined an eosinophilic phenotype and asthma exacerbation. Mepolizumab and benralizumab trials required that patients have eosinophil counts greater than 150 cells/ μ L and reslizumab required that patients have an eosinophil count greater than or equal to 400 cells/ μ L. This has practical implications as clinical trial's inclusion criteria can influence health insurance coverage policies. Other differences between the agents include administration route, dosing frequency, and safety warnings. Mepolizumab and benralizumab are administered subcutaneously and reslizumab is administered intravenously. Reslizumab and mepolizumab are administered every 4 weeks. Benralizumab is also administered every 4 weeks for the first 3 infusions and thereafter every 8 weeks. Reslizumab has an additional "black box" safety warning regarding anaphylaxis that states "healthcare professionals should be prepared to manage anaphylaxis that can be life-threatening that and must be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis."⁴⁶ However, the product information for reslizumab and mepolizumab indicate that it should be administered by a health care professional. A systematic review and meta-analysis of biological agents targeting eosinophilic inflammation in type 2 asthma found that all 3 anti-IL-5 associated with significant reductions in asthma exacerbation with no superiority of one biological over the others.⁴⁷ As no anti-IL-5 agent demonstrated superior clinical efficacy, it is likely that benralizumab would be a preferred agent due to its less frequent dosing requirement.

Dupilumab

Dupilumab (Dupixent; Regeneron) is a humanized monoclonal antibody directed at IL-4 α , which blocks the signaling of IL-4 and IL-13, which are key cytokines involved in the differentiation of TH2 lymphocytes from naïve T cells.⁴⁸ It was initially approved in 2017 for treatment of moderate to severe atopic dermatitis. It was subsequently approved in 2018 for the treatment of moderate to severe asthma and in 2019 for the treatment of chronic rhinosinusitis with nasal polys. It is administered subcutaneously every 2 weeks. Administration can be performed at home or in the clinic setting.

Atopic dermatitis is a chronic relapsing inflammatory skin condition effecting approximately 15% to 20% of children and 1% to 3% of adults worldwide.⁴⁹ The incidence of atopic dermatitis has increased 2- to 3-fold in industrialized nations since the 1970s. Before dupilumab approval, topical corticosteroids and hydration were the mainstay of atopic dermatitis treatment and safe and effective treatment of severe atopic dermatitis was a significant unmet need. The FDA granted the application for dupilumab Priority Review and Breakthrough Therapy Designation because of this unmet need.⁵⁰

A systematic review and meta-analysis evaluated the safety and efficacy of dupilumab for the treatment of moderate to severe atopic dermatitis and reviewed 6 randomized-controlled trials involving 2447 patients.⁵¹ Compared with placebo, dupilumab treatment resulted in significant improvements in Eczema Area and Severity Index score (standardized mean difference [SMD] = -0.89 , 95% confidence interval [CI] -1.0 to -0.78), greater reduction in percentage of body surface area affected

(SMD = -0.83 , 95% CI -0.90 to -0.75), pruritus numeric rating scale scores (SMD = -0.81 , 95% CI -0.96 to -0.66), and Dermatology Life Quality Index scores (SMD = -0.78 , 95% CI -0.89 to -0.66). Dupilumab resulted in greater proportion of patients achieving Investigator's Global Assessment response (relative risk = 3.82 ; 95% CI 3.23 – 4.51), which was the primary outcome in the pivotal clinical trials.⁵¹

In a large DBPC of 1902 patients 12 years of age or older with uncontrolled asthma that compared add-on dupilumab with placebo, dupilumab resulted in 47.7% reduction in asthma exacerbations compared with placebo.⁵² Dupilumab treatment was also associated with a significant increase in FEV(1) (0.32 L vs 0.14 L in matched placebo group; $P < .001$).⁵²

Dupilumab was the first biological approved for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP).⁵³ CRSwNP is a chronic inflammatory condition associated with significant morbidity and decreased quality of life with an estimated prevalence of 4.2% in the United States and 4.3% in Europe.⁵⁴ Approximately 25% to 30% of patients with chronic rhinosinusitis have CRSwNP.⁵⁵ There are limited effective medical treatment options for CRSwNP, for example, nasal corticosteroids, nasal saline irrigation, and oral corticosteroids. Patients failing medical therapy may require sinus surgery and repeated courses of oral corticosteroids. In addition, nasal polyps may reoccur despite sinus surgery and appropriate postoperative medical management. Patients with both CRSwNP and asthma require, on average, significantly more sinus surgeries than patients with CRSwNP alone.⁵⁵

Two multinational, multicenter, randomized DBPC parallel-group studies evaluated the efficacy of dupilumab as add-on therapy to standard of care in 728 adults with severe CRSwNP.⁵⁴ Severe CRSwNP inclusion criteria were based on symptoms, medical/surgical history, and examination findings. Included patients had to have bilateral nasal polyps, symptoms of chronic rhinosinusitis despite intranasal corticosteroid use, and a bilateral endoscopic nasal polyp score of at least 5 (maximum 8). Inclusion criteria also required a history of received systemic corticosteroids in the preceding 2 years or previous sinonasal surgery.

Dupilumab significantly improved the coprimary endpoints in both studies. At 24 weeks, least squares mean difference in NPS of dupilumab treatment versus placebo was -2.06 (95% CI -2.43 to -1.69 ; $p < 0.0001$) i difference in nasal congestion or obstruction score was -0.89 (-1.07 to -0.71 ; $p < 0.0001$) i; and difference in Lund-Mackay CT scores was -7.44 (-8.35 to -6.53 ; $p < 0.0001$).

There were no significant safety issues in the dupilumab asthma and CRSwNP trials. However, in atopic dermatitis trials, dupilumab associated with a higher incidence of conjunctivitis (8.6%–22.1%) compared with those receiving placebo (2.1%–11.1%).⁵⁶ The pathogenesis of dupilumab-induced conjunctivitis is unknown. Management depends on the symptoms severity but should include an ophthalmology consultation for new-onset conjunctivitis. In most case, patients are able to continue dupilumab with medical management of their conjunctivitis. Dupilumab is available as a prefilled syringe or pen that can be self-administered at a dosing frequency of every 4 weeks.

SUMMARY: PRACTICAL CONSIDERATIONS AND UNMET NEEDS

One of the most significant unmet need in the management of chronic allergic diseases such as asthma, chronic rhinosinusitis, and atopic dermatitis is the availability of safe, effective, inexpensive, and convenient therapies. Ideally, such therapies would be disease modifying and potentially curative. Until this past decade, allergy immunotherapy was the only immune modifying treatment. However, for several reasons, which include

convenience and safety, SCIT has only been prescribed to a small percentage of allergic patients (2%–9% in the United States).¹² SLIT offers the advantage of a better safety profile and home administration, but adherence has been shown to be equally as poor as SCIT and pharmacotherapy with other chronic conditions. In addition, neither immunotherapy route has been studied in severe allergic asthma. Biologics targeting IL-5, IgE, and IL-4/IL-13 have expanded the therapeutic options for allergic asthma and other refractory allergic conditions. Dupilumab offers the advantage of home administration and has an indication for 3 conditions: atopic dermatitis, asthma, and rhinosinusitis with nasal polyps. SCIT is relatively inexpensive and has shown to significantly reduce health care costs compared with standard drug treatment.^{57–59} Single-allergen SLIT has also been shown to be cost-effective, but multiallergen SLIT could be cost-prohibitive.⁶⁰ All of the biologics have substantial monetary costs, which can amount to thousands of dollars a month. Although these expenses are often covered by third-party payers, obtaining authorization approval can be challenging.

In summary, the armamentarium for chronic allergic disease management includes pharmacotherapy, SLIT, SCIT, and several biological agents targeting specific components of the immune system. There continues to be a need for less expensive and more effective therapies that could potentially lead to long-term remissions after discontinuation.

CLINICS CARE POINTS

- AIT is the only treatment of allergic asthma and allergic rhinitis with proven post-treatment clinical efficacy and favorable immunologic changes. There have been limited studies examining the optimal duration of AIT, but it seems that at least 3 years is necessary for persistent posttreatment efficacy. Studies have demonstrated that adherence with SCIT and SLIT is equally poor. Indications for AIT include allergic asthma, allergic rhinitis, atopic dermatitis, and peanut allergy.
- Omalizumab is a biological agent that targets IgE. It was initially approved for moderate to severe allergic asthma and later approved for chronic urticaria. Dosage for allergic asthma depends on IgE level and body weight. Patients with IgE levels that do not fall within the product information range (30 to 700 IU/ml for adults/adolescents 12 and older and 30–1300 IU/ml in children 6 to <12 years old) product information dosing guide would generally not. The product information includes a warning about anaphylaxis. Thus, it is recommended that omalizumab be administered in medically supervised setting.
- Three biological agents targeting IL-5 have been approved for the treatment of severe asthma with an eosinophilic phenotype: benralizumab, a humanized monoclonal antibody directed against IL-5R α ; mepolizumab, a neutralizing anti-IL-5 antibody; and reslizumab, an IgG4 κ monoclonal antibody targeting circulating IL-5. There are no direct studies comparing these products but a systematic review and meta-analysis found no evidence that one product was superior to another in reducing asthma exacerbations. Product preference may depend on the administration guidelines. The products differ in their product information warnings and administration route and frequency. Benralizumab and mepolizumab are administered subcutaneously at 8- and 4-week intervals, respectively. Reslizumab is administered intravenously at 4-week intervals and has a “black-box” warning regarding anaphylaxis. The product information for all 3 indicate they should be administered by a health care provider.
- Dupilumab is a biological agent that targets IL-4/IL-13. It offers the advantage of treating 3 allergic conditions. It was initially approved for atopic dermatitis and

later for allergic asthma and chronic rhinosinusitis with nasal polyps. Another advantage is that it can be self-administered in the home setting.

- All of the biological agents are relatively expensive, and the treatment duration is indefinite. None to date have demonstrated persistent posttreatment efficacy. It is likely that their use will be limited to patients with more severe and difficult-to-treat allergic disease.

CONFLICT OF INTEREST

None.

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