

Future Horizons in Allergy

Michael J. Marino, MD, Amber U. Luong, MD, PhD^{*}

KEYWORDS

- Allergic rhinitis • Aspirin-exacerbated respiratory disease • Allergen immunotherapy
- Immunoglobulin E

KEY POINTS

- Testing of local immunoglobulin E (IgE) in the nasal mucosa using mucosal brush biopsy may improve diagnostic accuracy.
- Urinary leukotriene E4 may be useful in identifying patients with aspirin sensitivity.
- Recombinant allergens and alternative approaches to allergen immunotherapy may offer disease-modifying treatment with improved safety and dosing compared with subcutaneous immunotherapy.

INTRODUCTION

There have been numerous advances in the diagnosis and management of atopy relevant to the allergy-treating otolaryngologist. These include emerging technologies, new devices, and refinement of existing methods, and in many ways reflect an overall trend in health care toward personalized medicine.¹ At the diagnostic level, these advances will help to identify specific allergic conditions in a clinically useful way, and even differentiate these from nonallergic diseases with shared symptomatology. Improved diagnostic precision is in turn fundamental to delivering targeted therapies.

Several developments in the diagnosis of allergy and related nonallergic conditions may aid the otolaryngologist in identifying and differentiating specific entities. Local immunoglobulin E (IgE) in the nasal mucosa can be useful in the diagnosis of allergic rhinitis, and mucosal brush biopsy may make this a practical test.^{2–4} Urinary leukotriene E4 (LTE4) can identify aspirin sensitivity among patients with different respiratory diagnoses.^{5–9} Lipidomics^{10–12} and microRNA expression in extracellular microvesicles^{13,14} allow for the identification of extracellular allergic biomarkers, and may complement the traditional identification of intracellular proteins. Furthermore,

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Department of Otorhinolaryngology–Head and Neck Surgery, McGovern Medical School at the University of Texas Health Science Center, 6431 Fannin Street, MSB 5.036, Houston, TX 77030, USA

^{*} Corresponding author.

E-mail address: amber.u.luong@uth.tmc.edu

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nasal provocation testing with optical rhinometry may help to differentiate allergic and nonallergic rhinitis.^{15–17}

The management of allergy may be improved through the introduction of targeted therapeutics as well as the refinement of existing treatments. Intranasal steroids and antihistamines are part of the traditional management of allergic rhinitis, and the use of these drugs is supported by clinical guidelines.¹⁸ New delivery systems and formulations may improve the efficacy of intranasal steroids and antihistamines by enhancing bioavailability.^{19,20} Recombinant allergens offer the potential to be a targeted therapy with modifications for increased immunologic properties and decreased allergenic activity.^{21–23} Meanwhile, alternative administration routes for allergen immunotherapy, such as epicutaneous,²⁴ intralymphatic,²⁵ and sublingual,²⁶ may allow for enhanced patient convenience, dose reduction, and improved safety. Monoclonal antibodies, such as omalizumab and dupilumab, may be useful in managing allergic rhinitis, and might be particularly useful in patients with comorbid conditions.^{27,28} Finally, intranasal capsaicin may represent a treatment option for a subgroup of patients with nonallergic irritant rhinitis.^{29–31} The various advances in allergy diagnosis and management are summarized in **Table 1**.

DIAGNOSIS

Local Immunoglobulin E and Mucosal Brush Biopsy

Allergen-specific IgE is defining of the pathophysiology of allergic disease, and is, therefore, used as a marker for these conditions. Typically, serum IgE levels have been used in clinical practice. Testing for IgE in the nasal mucosa may improve diagnostic accuracy when assessing for conditions such as allergic rhinitis.⁴ Furthermore, there is a subgroup of patients with detectable allergen-specific IgE localized in the nasal mucosa, but who have negative skin prick testing and serum allergen-specific IgE.³² Obtaining nasal mucosal tissue biopsy from patients for the diagnosis of allergic rhinitis is a significant barrier to the routine use of local IgE levels.⁴

Mucosal brush biopsy has been described as a technique for the collection of epithelial cells, monocytes, neutrophils, and eosinophils in the nasal mucosa as early as 1988.³³ In that study, Pipkorn and colleagues³³ indicated that mucosal brush biopsy might also be useful for biochemical analysis. More recently, Reisacher³ demonstrated that antigen-specific IgE could be detected via nasal mucosal brush biopsy, including patients for whom skin prick testing was negative. Cells are collected from the mucosal surface of the inferior turbinates with a cytology brush and IgE is harvested from the lysed cells. Microarray analysis of nasal mucosal brush biopsy are more sensitive at detecting IgE levels than standard in vitro IgE assays, and may improve diagnostic accuracy.² A limitation of this technique, however, is the rate at which IgE is detectable in nonallergic patients has not been well-defined. Overall, testing the nasal mucosal for local IgE using a minimally invasive technique such as mucosal brush biopsy may improve the clinical diagnosis of allergic rhinitis, particularly among patients with negative skin prick testing and normal serum IgE levels.

Urinary Leukotriene E4

Several recent studies have described urinary LTE4 as potentially useful in the diagnosis of allergic disease,^{5–8} particularly for identifying aspirin sensitivity.^{5–7} In 2006, Micheletto and colleagues⁹ demonstrated that urinary LTE4 excretion increased in aspirin intolerant-asthmatics who underwent nasal provocation testing with lysine aspirin. A systematic review and metaanalysis by Hagan and colleagues⁵ examined publications pertaining to the use of urinary LTE4 as a diagnostic testing for aspirin

Table 1
Summary of advances in the diagnosis and management of allergy

Technology	Application	Clinical Benefits
Diagnosis		
Nasal mucosa IgE	Quantification of nasal mucosa local IgE using mucosal brush biopsy	Detection of antigen-specific IgE in patients with negative skin prick and serum testing
Urinary leukotriene E4	Detection of increased urinary leukotriene E4 in patients with aspirin sensitivity	Reliable, safe, and objective identification of patients with aspirin sensitivity
Lipidomics and extracellular vesicle microRNA	Detection of immunogenic nonprotein species	Diagnosis through the identification of immunologically active species that have not been routinely tested
Optical rhinometry	Detect changes in nasal blood flow to specific challenges	Objective diagnosis of nonallergic irritant rhinitis with intranasal capsaicin challenge
Management		
Intranasal delivery systems	Liposomal topical steroid and antihistamine formulations, and exhalational delivery systems	Improve the distribution and bioavailability of medications delivered to the nasal cavity
Recombinant allergens	Allergens generated from engineered DNA templates	Selection for improved immunologic activity and safety
Alternative administration of allergen immunotherapy	Epicutaneous immunotherapy, intralymphatic immunotherapy, and sublingual immunotherapy	Improve dosing regimens to enhance patient convenience and compliance
Monoclonal antibodies	Targeted blockade of immunogenic proteins	Disease-modifying treatment of allergic disease and comorbid disease, such as asthma, nasal polyposis, and atopic dermatitis
Intranasal capsaicin	Blockade of TRPV1-SP signaling	Inhibition of a potential mechanism for nonallergic irritant rhinitis

Abbreviation: TRPV1-SP, transient receptor potential cation subfamily V, receptor 1 – substance P.

sensitivity. When urinary LTE4 was quantified by a radioimmunoassay technique, the sensitivity and specificity for the diagnosis of aspirin intolerant asthma were 81 % and 79%, respectively.⁵ A simple and accurate test for aspirin sensitivity would allow for the identification of patients whose management would benefit from medication avoidance, aspirin desensitization, and multidisciplinary treatment of respiratory and sinonasal disease. Furthermore, urinary LTE4 testing may be safer and faster than the current gold standard diagnostic test of aspirin challenge.

Lipidomics and Extracellular Microvesicle microRNA

The biochemical diagnosis of allergy has traditionally been focused on the identification of intracellular or cell surface proteins. MicroRNA contained within extracellular

microvesicles and lipids, however, may be involved in cellular immune responses.^{10,13} To this extent, lipids and extracellular microRNA could be alternative biomarkers in the diagnosis of allergy. Lipidomics is the technique of profiling cellular lipids for identification purposes, and has potential application for the identification of allergenic lipid molecule species. Bashir and colleagues¹⁰ profiled lipids in 22 common allergenic plant species using gas chromatography–mass spectrometry and identified 106 molecular lipid species, which were compiled into a database. This library in turn can serve in the identification of lipid antigens. Furthermore, that study demonstrated that these lipid molecules stimulated cytokine expression in dendritic cells and natural killer T cells, affirming the role of lipids in the immune response.¹⁰ Asthma patients were also accurately identified by profiling eicosanoids in exhaled breath condensate¹¹ and lipid species in bronchoalveolar lavage fluid.¹² Analysis of exhaled breath condensate in asthmatics demonstrated increased 5-, 12-, and 15-hydroxysteicosatenoic acid and prostaglandin D₂ and E₂ levels.¹¹ Similarly, bronchoalveolar lavage in asthmatics (not treated with corticosteroids) demonstrated increased prostaglandin, lysophosphatidylcholine, phosphatidylcholine, sphingomyelin, and triglyceride species compared with normal controls.¹² Exhaled breath condensate eicosanoid profiling was also able to discriminate aspirin intolerant patients with 92% accuracy.¹²

Extracellular vesicles, which are present in most bodily fluids, may contain RNA and even allow for the transfer of genetic material between cells.¹³ This transfer of RNA, through extracellular vesicles in the nasal mucus, may contribute to the local immune response in allergic rhinitis, and therefore be a novel diagnostic target. In a study of patients with allergic rhinitis, extracellular vesicle microRNA sequences were compared with those in healthy controls. Certain sequences were found to be increased in allergic rhinitis patients, whereas other sequences were decreased.¹³ Similar findings were also demonstrated in a mouse model of allergic rhinitis, and extracellular vesicle microRNA levels were found to modulate interleukin-10 expression.¹⁴ Both extracellular vesicle microRNA and lipidomics may represent alternative approaches in the diagnosis of allergy, and are contrasted from the traditional biochemical identification of proteins.

Optical Rhinometry

Optical rhinometry offers a method for objectively measuring nasal patency by using optical spectroscopy to quantify visible and near-infrared light absorption in the tissue. The optical rhinometer is, therefore, able to measure the volume of blood within the nasal cavity, and in turn the degree of nasal congestion.¹⁷ Optical rhinometry has been able to detect changes in nasal patency after nasal provocation testing with histamine, oxymetazoline, *Dermatophagoides farinae*, and capsaicin challenges.^{15–17} Nonallergic irritant rhinitis was accurately assessed using optical rhinometry with intranasal capsaicin challenge.¹⁶ This may offer an objective diagnostic test for nonallergic irritant rhinitis, and aid in differentiating these patients from those with allergic rhinitis, despite overlapping symptoms.

MANAGEMENT

Intranasal Delivery Systems

Intranasal steroids and antihistamines have been central in the management of allergic rhinitis, and their use is outlined in clinical guidelines.¹⁸ Alternative drug formulations for intranasal steroids and antihistamines have been developed using liposomal particles, with the purported advantage of improved bioavailability.^{19,20} These types of

formulations have been described for budesonide¹⁹ and fexofenadine.²⁰ New delivery mechanisms are becoming available for traditional intranasal steroids. This includes exhalation delivery systems, which may have improved distribution of medication to the turbinates and osteomeatal complex.^{34,35} New formulations and delivery systems offer the potential for increased efficacy for traditional drugs used in the management of allergic rhinitis.

Recombinant Allergens

Recombinant allergens offer the potential to increase immunologic activity, while decreasing the side effects of traditional immunotherapy. There are several advantages to recombinant allergens that are directed at certain deficiencies in the preparation and administration of natural allergen extracts. Recombinant allergens can be tailored precisely to the patient's sensitization profile and avoid contamination with unwanted allergens that can occur in the preparation of natural allergen extracts.²¹ Unwanted allergens in natural extract preparations can lead to new cross-reactions. Dosing can also be closely controlled, because recombinant allergens are generated from a DNA template, allowing for exact quantities of the recombinant molecule.²¹ This process also allows for modifications to enhance desired immunologic activity of the allergen, while suppressing unwanted allergenic activity. Overall, these features make recombinant allergens a more targeted therapy over traditional allergen extracts.

Recombinant allergen vaccines have been studied for the treatment of allergic rhinitis in randomized, controlled trials among patients sensitive to birch and grass.^{22,23} Patients treated with a recombinant birch allergen vaccine demonstrated improved symptoms and decreased rescue medication use.²² Increased specific IgG levels were also observed in the group treated with recombinant birch allergen, and there were not any unwanted cross-reactions.²² In a comparison group treated with traditional birch allergen extract, 3 of 29 patients developed new IgE sensitivities.²² In a study of recombinant grass allergen, patients in the treatment group also demonstrated improved symptom scores and increased allergen-specific IgG.²³ These studies indicate that recombinant allergens may be an efficacious alternative to traditional allergen extracts, and be targeted to specific allergy profiles.

Allergen Immunotherapy Administration Routes

Allergen immunotherapy has typically been delivered through a subcutaneous route. Alternative routes of administration have been studied and entered into clinical practice, including intralymphatic immunotherapy, epicutaneous immunotherapy (EIT), and sublingual immunotherapy (SLIT). These other routes have been developed to address disadvantages to subcutaneous immunotherapy (SCIT), primarily related to SCIT dosing schedules. Shorter administration routines or more convenient approaches would improve patient compliance and the number of patients that can consider allergen immunotherapy as a treatment option.

EIT has been suggested as an alternative administration route to shorten the treatment duration by targeting antigen-presenting cells in the skin.³¹ A study by Senti and colleagues²⁴ found EIT to be an effective treatment for grass pollen-induced allergic rhinitis, with improvement in patient symptoms for the 2 seasons after administration. In this study, the patients only received 6 weekly patches for EIT delivery, substantially shorter treatment duration than SCIT. There were, however, local adverse events at the epicutaneous site, including pruritus, erythema, and eczema.²⁴ Intralymphatic immunotherapy has also been suggested as a route with decreased treatment duration, and was

demonstrated to have improved patient-reported symptoms, decreased serum IgE, fewer adverse events, and better patient compliance than SCIT.²⁵

SLIT has entered clinical practice as an alternative to SCIT for patients seeking a disease modifying treatment approach. In 2014, the US Food and Drug Administration approved 3 sublingual formulations for use in allergen immunotherapy.^{26,31} These include Grastek for timothy grass, Ragwitek for short ragweed, and Oralair directed at 5 grass pollens.³¹ Recently, Odactra was approved by the US Food and Drug Administration for use in house dust mite allergy. The approved SLIT formulations have been demonstrated to be safe and efficacious in large, randomized, controlled clinical trials.^{36–38} SLIT offers patients the advantage of at-home dosing after initial observation in the office for adverse events. Up to 75% of patients experience a local oral or gastrointestinal reaction; however, systemic reactions are rare and thought to be as low as 0.06% of administered doses.²⁶ Preseasonal and coseasonal administration is preferred for SLIT because this regimen may have the same clinical effect as year-round dosing, while minimizing exposure to adverse events.³¹

Monoclonal Antibodies

Monoclonal antibodies may have a role in the management of allergic disease, particularly in patients with comorbid asthma. Omalizumab is a monoclonal antibody against IgE and is indicated in the United States for the treatment of moderate to severe asthma. In a pilot study of patients with severe asthma and comorbid allergic rhinitis, symptoms of nasal obstruction, rhinorrhea, sneezing, and itching were reduced.²⁷ Of the patients in that study, 73% were also able to discontinue the use of medications for the symptomatic treatment of allergic rhinitis.²⁷ Furthermore, omalizumab may have efficacy in desensitization for multiple food allergies, including children with peanut allergy.^{28,39,40}

Dupilumab, a fully human monoclonal antibody directed at the α subunit of interleukin-4 receptor (IL-4R α), has been investigated in the treatment of atopic dermatitis and asthma. IL-4R α blockade inhibits the activity of IL-4 and IL-13, and has reduced IgE levels in mouse models.²⁸ Dupilumab has reduced exacerbations in patients with moderate to severe asthma, and improved symptoms in patients with moderate to severe atopic dermatitis.²⁸ Furthermore, IL-5-blocking antibodies, such as mepolizumab, reslizumab, and benralizumab, have been investigated in severe asthma, eosinophilic esophagitis, nasal polyposis, and Churg-Strauss syndrome.²⁸ Overall, monoclonal antibodies offer patients the potential for targeted and disease-modifying treatments for different allergic conditions in the head and neck.

Intranasal Capsaicin

Nonallergic irritant rhinitis can mimic allergic rhinitis symptomatically, and be a source of treatment frustration for patients without identifiable allergy and failing traditional therapies. Patients with nonallergic irritant rhinitis may have an increase in the expression of transient receptor potential cation subfamily V, receptor 1 (TRPV1).³⁰ Intranasal capsaicin seems to block the TRPV1-substance P (SP) signaling pathway in the nasal mucosa, and therefore may be a treatment for patients with nonallergic irritant rhinitis.³⁰ A recent Cochrane review²⁹ examined the usefulness of intranasal capsaicin in the treatment of nonallergic irritant rhinitis from the available published evidence. Intranasal capsaicin was found to be a treatment option, and that symptomatic benefits may last up to 36 weeks.²⁹ The current evidence, however, was based on several small, generally low-quality studies, and larger randomized controlled trials are needed to firmly establish the role of intranasal capsaicin in the treatment of nonallergic irritant rhinitis.²⁹

SUMMARY

The otolaryngologist treating allergy can expect several advances in the diagnosis and management of this and related diseases. These advancements in both diagnosis and management will parallel broader trends in health care toward personalized medicine. Microarray analysis of nasal mucosal brush biopsies offers the potential to improve the diagnostic yield for allergy as the cause of rhinitis symptoms. In contrast, optical rhinometry may be a useful tool in differentiating patients with nonallergic irritant rhinitis. Urinary LTE4 levels can help to identify the subset of patients with aspirin sensitivity. Lipidomics and extracellular vesicle microRNA represent an entirely different approach to the diagnosis of allergic conditions, and uncover diagnostic gaps in the traditional identification of cellular proteins. Collectively, these advances would improve precision in the diagnosis of allergic diseases, the foundation for targeted therapies.

Management of allergy will be improved by the refinement of existing techniques, including improved delivery systems and formulations for intranasal medications. Furthermore, alternative routes of allergen immunotherapy may improve the efficacy, safety, and convenience of this option for patients selecting disease-modifying treatment. In keeping with trends for personalized medicine, multiple target therapies are becoming available to patients. These options include recombinant allergens selected to meet a patient's specific allergic profile, and developed for maximal immunogenicity. Monoclonal antibodies can also offer targeted therapies for a diverse array of allergic and related conditions including allergic rhinitis, food allergy, asthma, and atopic dermatitis. Last, intranasal capsaicin can be a specific treatment for patients with nonallergic irritant rhinitis, and allow for the successful management of these patients with related symptomatology.

There are multiple exciting developments in the treatment of allergy, and these promise to aid the otolaryngologist in treating these patients. Diagnostic techniques promise to bring improved precision, which in turn allows for directed therapies. To this extent otolaryngologists will be able to precisely diagnosis patients and offer treatments targeted for the specific allergic condition.

REFERENCES

1. Anaya JM, Duarte-Rey C, Sarmiento-Monroy JC, et al. Personalized medicine. Closing the gap between knowledge and clinical practice. *Autoimmun Rev* 2016;15:833–42.
2. Reisacher WR. Detecting local immunoglobulin E from mucosal brush biopsy of the inferior turbinates using microarray analysis. *Int Forum Allergy Rhinol* 2013;3:399–403.
3. Reisacher WR. Mucosal brush biopsy testing of the inferior turbinate to detect local, antigen-specific immunoglobulin E. *Int Forum Allergy Rhinol* 2012;2:69–74.
4. De Schryver E, Devuyst L, Derycke L, et al. Local immunoglobulin e in the nasal mucosa: clinical implications. *Allergy Asthma Immunol Res* 2015;7:321–31.
5. Hagan JB, Laidlow TM, Divekar R, et al. Urinary leukotriene E4 to determine aspirin intolerance in asthma: a systematic review and meta-analysis. *J Allergy Clin Immunol Pract* 2017;5(4):990–7.e1.
6. Divekar R, Hagan J, Rank M, et al. Diagnostic utility of urinary LTE4 in asthma, allergic rhinitis, chronic rhinosinusitis, nasal polyps, and aspirin sensitivity. *J Allergy Clin Immunol Pract* 2016;4:665–70.
7. Yamaguchi T, Ishii T, Yamamoto K, et al. Differences in urinary leukotriene E4 levels and distribution of eosinophils between chronic rhinosinusitis patients with aspirin-intolerant and -tolerant asthma. *Auris Nasus Larynx* 2016;43:304–8.

8. Chiu CY, Tsai MH, Yao TC, et al. Urinary LTE4 levels as a diagnostic marker for IgE-mediated asthma in preschool children: a birth cohort study. *PLoS One* 2014;9:e115216.
9. Micheletto C, Tognella S, Visconti M, et al. Changes in urinary LTE4 and nasal functions following nasal provocation test with ASA in ASA-tolerant and -intolerant asthmatics. *Respir Med* 2006;100:2144–50.
10. Bashir MEH, Lui JH, Palnivelu R, et al. Pollen lipidomics: lipid profiling exposes a notable diversity in 22 allergenic pollen and potential biomarkers of the allergic immune response. *PLoS One* 2013;8:e57566.
11. Sanak M, Gielicz A, Bochenek G, et al. Targeted eicosanoid lipidomics of exhaled breath condensate provide a distinct pattern in the aspirin-intolerant asthma phenotype. *J Allergy Clin Immunol* 2011;127:1141–7.
12. Kang YP, Lee WJ, Hong JY, et al. Novel approach for analysis of bronchoalveolar lavage fluid (BALF) using HPLC-QTOF-MS-based lipidomics: lipid levels in asthmatics and corticosteroid-treated asthmatic patients. *J Proteome Res* 2014;13: 3919–29.
13. Wu G, Yang G, Zhang R, et al. Altered microRNA expression profiles of extracellular vesicles in nasal mucus from patients with allergic rhinitis. *Allergy Asthma Immunol Res* 2015;7:449–57.
14. Luo X, Han M, Liu J, et al. Epithelial cell-derived micro RNA-146a generates interleukin-10-producing monocytes to inhibit nasal allergy. *Sci Rep* 2015;5: 15937.
15. Luong A, Cheung EJ, Citardi MJ, et al. Evaluation of optical rhinometry for nasal provocation testing in allergic and nonallergic subjects. *Otolaryngol Head Neck Surg* 2010;143:284–9.
16. Lambert EM, Patel CB, Fakhri S, et al. Optical rhinometry in nonallergic irritant rhinitis: a capsaicin challenge study. *Int Forum Allergy Rhinol* 2013;3:795–800.
17. Cheung EJ, Citardi MJ, Fakhri S, et al. Comparison of optical rhinometry to acoustic rhinometry using nasal provocation testing with *dermatophagoides farinae*. *Otolaryngol Head Neck Surg* 2010;143:290–3.
18. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis. *Otolaryngol Head Neck Surg* 2015;152:S1–43.
19. Kim JE, Cho HJ, Kim DD. Budesonide/cyclodextrin complex-loaded lyophilized microparticles for intranasal applications. *Drug Dev Ind Pharm* 2014;40:743–8.
20. Qiang F, Shin HJ, Lee BJ, et al. Enhanced systemic exposure of fexofenadine via the intranasal administration of chitosan-coated liposome. *Int J Pharm* 2007;430: 161–6.
21. Valenta R, Niederberger V. Recombinant allergens for immunotherapy. *J Allergy Clin Immunol* 2007;119:826–30.
22. Pauli G, Larsen TH, Horak F, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009;122:951–60.
23. Jutel M, Jaeger L, Suck R, et al. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol* 2005;116:608–13.
24. Senti G, von Moos S, Tay F, et al. Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: a double-blind, placebo-controlled dose escalation study. *J Allergy Clin Immunol* 2012;129:128–35.
25. Senti G, Prinz Vavricka BM, Erdmann I, et al. Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. *Proc Natl Acad Sci U S A* 2008;105:17908–12.

26. Li JT, Bernstein DI, Calderon MA, et al. Sublingual grass and ragweed immunotherapy: clinical considerations—a PRACTALL consensus report. *J Allergy Clin Immunol* 2016;137:369–76.
27. Masieri S, Cavaliere C, Begvarfaj E, et al. Effects of omalizumab therapy on allergic rhinitis: a pilot study. *Eur Rev Med Pharmacol Sci* 2015;20:5249–55.
28. Ozdemir C. Monoclonal antibodies in allergy; updated applications and promising trials. *Recent Pat Inflamm Allergy Drug Discov* 2015;9:54–65.
29. Gevorgyan A, Segboer C, Gorissen R, et al. Capsaicin for non-allergic rhinitis. *Cochrane Database Syst Rev* 2015;(7):CD010591.
30. Van Gerven L, Alpizar YA, Wouters MM, et al. Capsaicin treatment reduces nasal hyperreactivity and transient receptor potential cation channel subfamily V, receptor 1 (TRPV1) overexpression in patients with idiopathic rhinitis. *J Allergy Clin Immunol* 2014;133:1332–9, 1339.e1–3.
31. Ricketti PA, Alandijani S, Lin CH, et al. Investigational new drugs for allergic rhinitis. *Expert Opin Investig Drugs* 2017;26:279–92.
32. Rondón C, Doña I, López S, et al. Seasonal idiopathic rhinitis with local inflammatory response and specific IgE in absence of systemic response. *Allergy* 2008;63:1352–8.
33. Pipkorn U, Karlsson G, Enerbäck L. A brush method to harvest cells from the nasal mucosa for microscopic and biochemical analysis. *J Immunol Methods* 1988;112:37–42.
34. Palmer J, Jacobson K, Messina J, et al. Exhance-12: a one year study of safety and efficacy of opn-375, a fluticasone exhalation delivery system (FLU-EDS), in patients with chronic rhinosinusitis with and without polyps. Poster presented at: American Rhinologic Society Annual Meeting. San Diego (CA), September 16, 2016.
35. Optinose. Technical overview. Available at: <http://www.optinose.com/optinose-platform/technical-overview>. Accessed June 27, 2017.
36. Creticos PS, Esch RE, Couroux P, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2014;133:751–8.
37. Durham SR, Yang WH, Pederson MR, et al. Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:802–9.
38. Didier A, Malling HJ, Worm M, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;120:1338–45.
39. Bégin P, Dominguez T, Wilson SP, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using omalizumab. *Allergy Asthma Clin Immunol* 2014;10:7.
40. Schneider LC, Rachid R, LeBovidge J, et al. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *J Allergy Clin Immunol* 2013;132:1368–74.