

Advances in upper airway diseases and allergen immunotherapy in 2011

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The purpose of this review is to highlight recently published important articles on upper airway diseases and allergen immunotherapy. We review articles on rhinitis, sinusitis, conjunctivitis, and immunotherapy. New insights into epidemiology, pathophysiology, diagnosis, and therapy are described for each of the above diseases. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

Key words: Rhinitis, sinusitis, nasal polyps, conjunctivitis, allergen immunotherapy

The purpose of this review is to highlight important articles on upper airway diseases and allergen immunotherapy published in 2011. We start with the key advances in upper airway diseases, which are summarized in [Table I](#).¹⁻¹⁶

RHINITIS

Epidemiology

Epidemiologic studies continue to delineate factors predisposing to allergic rhinitis. In the European Community Respiratory Health Study II, a multinational prospective population-based study, 8486 adults were surveyed twice, 9 years apart, in the 1990s. Questionnaire surveys showed that rhinitis was more prevalent in women than in men and that risk for early childhood rhinitis decreases with exposure to siblings and day care and adolescent rhinitis decreases with farm upbringing.¹ Although based on questionnaires and subjected to recall bias, the large number of subjects and repeated survey provide a comprehensive evaluation of the natural history of rhinitis in Europe. In another study Crump et al² analyzed data from 630,090 subjects from a national Swedish birth cohort (1973-2009) and found that low gestational age at birth, regardless of fetal growth, was associated with decreased risk of allergic rhinitis in young adulthood. Risk factors identified in European studies can differ from those identified in US studies.¹⁷

Research examining the relationship between vitamin D levels and allergic conditions continue to yields conflicting results.

Abbreviations used

25(OH)D:	25-Hydroxyvitamin D3
Cp110:	Centrosomal protein 110
CRS:	Chronic rhinosinusitis
CRSwNP:	Chronic rhinosinusitis with nasal polyps
CRSSNP:	Chronic rhinosinusitis without nasal polyps
CysLT:	Cysteinyl leukotriene
DBPC:	Double-blind, placebo-controlled
NAPT:	Nasal allergen provocation test
NAPT-M:	Nasal allergen provocation tests for multiple aeroallergens in a single day
NP:	Nasal polyp
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy

Analysis of 6590 children and adults in the United States in the National Health and Nutrition Examination Survey 2005-2006 indicated that allergic sensitization to ragweed, oak, and peanut (based on serum allergen-specific IgE levels to 17 allergens) was more common in children and adolescents with serum 25-hydroxyvitamin D3 (25(OH)D) deficiency (serum 25(OH)D level, <15 ng/mL) compared with those with vitamin D sufficiency (serum 25(OH)D level, >30 ng/mL).¹⁸ However, the prevalence of rhinitis symptoms did not differ significantly based on 25(OH)D serum levels. In addition, among adults, vitamin D levels did not correlate with allergic sensitization or rhinitis symptoms.¹⁸ Analysis of cord blood 25(OH)D levels from 219 subjects from a Tucson birth cohort showed that children with both low (<20 ng/mL) and high (>40 ng/mL) 25(OH)D levels had higher total plasma IgE levels compared with those seen in the reference group (20-40 ng/mL). However, 25(OH)D levels did not correlate with the presence of physician-diagnosed allergic rhinitis or asthma.¹⁹ These conflicting results suggest that other biological and environmental factors might interact with vitamin D levels to generate allergic disease phenotypes.

Pathogenesis

Respiratory tract viral infection might alter the epithelial barrier. Rezaee et al³ found that polyinosinic:polycytidylic acid, a ligand of Toll-like receptor 3 analogous to double-stranded RNA produced by replicating respiratory viruses, disrupts the airway epithelial barrier *in vitro*. Polyinosinic:polycytidylic acid disorganized several protein interactions in the intercellular adhesion structures in bronchial epithelial cells.³ Impairment of the epithelial barrier could facilitate penetration of allergens into the submucosa, causing allergic inflammation.

Genetic studies point to new molecules in the pathogenesis of allergic rhinitis. A genome-wide association study of 4 large

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TABLE I. Key advances in rhinitis, sinusitis, and conjunctivitis in 2011

1. Low gestational age and early exposure to siblings, pets, and/or a farm environment protect against the development of allergic rhinitis.^{1,2}
2. Double-stranded RNA a mimic of respiratory viral infection can disrupt the airway epithelial barrier, which could facilitate allergen diffusion to the submucosa.³
3. Nasal provocation with several allergens in a single day can expedite diagnosis of local allergic rhinitis.⁴
4. New experimental therapies for allergic rhinitis include an mAb against IL-13 and petasol butenoate complex Ze 339, an inhibitor of eosinophil degranulation and leukotriene synthesis.^{5,6}
5. Oxymetazoline can be a safe short-term add-on therapy to fluticasone for patients with allergic rhinitis.⁷
6. Molecules newly recognized to participate in the pathogenesis of CRS include the ciliogenesis suppressor Cp110, p63 and p73, molecules in the COX pathway, CCL23, and antinuclear autoantibodies.^{8-11,16}
7. Mepolizumab, a humanized anti-IL-5 mAb, might be beneficial for patients with recalcitrant CRSwNP.¹²
8. Oral methylprednisolone as an adjunct to antibiotic treatment in children with CRS improved symptoms and was well tolerated.¹³
9. CysLTs stimulate, and resolvins inhibit mucus secretion of conjunctival goblet cells.¹⁴
10. Preseasonal start of daily treatment with topical olopatadine improves control of symptoms of seasonal allergic conjunctivitis compared with starting treatment after the onset of symptoms.¹⁵

European adult cohorts (3933 patients with allergic rhinitis and 8965 control subjects) showed that a single nucleotide polymorphism on chromosome 11q13.5 near the gene *LRRC32* (leucine-rich repeat containing 32, which is active in regulatory T cells) was associated with allergic rhinitis to grass.²⁰ This locus is also associated with asthma.^{21,22} The genome-wide association study also confirmed a correlation between allergy and a single nucleotide polymorphism on chromosome 5q22.1 near the genes *TMEM232* (transmembrane protein 232), *SLC25A46* (solute carrier family 25, member 46), and thymic stromal lymphoprotein (*TSLP*). Candidate gene analysis in this cohort also implicated Toll-like receptor 6 and nucleotide-binding oligomerization domain containing 1 (*NOD1*, previously known as *CARD4*) in allergic rhinitis. These results are further evidence that genetic differences in the innate and adaptive immune system can contribute to the development of allergic rhinitis.

Management

Rondon et al⁴ developed a simpler and faster method to diagnose local allergic rhinitis (ie, local nasal production of specific IgE and reaction to aeroallergen provocation, but non-reactive allergy skin test and absent serum specific IgEs). Instead of performing nasal allergen provocation tests (NAPT) for a single aeroallergen once a week,²³ the authors performed NAPT for multiple aeroallergens in a single day (NAPT-M).⁴ NAPT-M involved 4 sequential single-allergen NAPT administered 15 minutes apart. Patients were challenged first with the aeroallergen least likely to be relevant based on history and ended with the most likely relevant aeroallergen. The NAPT-M results had 100% concordance with the gold standard of single weekly NAPT, and no false-positive or false-negative responses were observed.⁴ The NAPT-M is a more practical and economic approach to implement in the outpatient setting.

An mAb against IL-13 was tested in the nasal allergen challenge model and compared with placebo and fluticasone

propionate nasal spray in patients with allergic rhinitis.⁵ In this 3-arm study medications were started 5 days before challenge with timothy grass (*Phleum pratense*) pollen. Intravenous anti-IL-13 (named QAX 576) markedly decreased IL-13 levels in nasal secretions but did not alter eosinophil influx compared with placebo. Fluticasone decreased IL-13 and IL-5 levels and eosinophil counts compared with placebo. Neither drug had a significant effect on nasal symptoms after challenge.⁵ This modest effect is not as encouraging as that of another anti-IL-13 mAb (lebrikizumab) in patients with asthma.²⁴ Further investigations with different dosing regimens and selections of subjects will be necessary to determine whether QAX576 is beneficial in patients with allergic rhinitis.

An inhibitor of eosinophil degranulation and leukotriene synthesis named petasol butenoate complex Ze 339 was efficacious in patients with allergic rhinitis.⁶ Ze 339 is derived from *Petasites hybridus* and is available in Switzerland and elsewhere for the treatment of allergic rhinitis.⁶ Corroborating previous studies,^{25,26} Dumitru et al⁶ showed that Ze 339 was more effective than desloratadine and placebo in a double-blind, randomized, crossover study of 18 patients with allergic rhinitis to grass pollen. Ze 339 improved nasal symptoms and nasal patency assessed by means of rhinomanometry and decreased nasal IL-8 and leukotriene B₄ levels compared with placebo and desloratadine. Larger trials are needed to confirm these results.

Nasal decongestant can be used as add-on therapy to nasal steroids. In a double-blind, placebo-controlled (DBPC), 4-arm, parallel-group randomized clinical trial involving 60 subjects with perennial allergic rhinitis, combined treatment with the intranasal corticosteroid fluticasone plus the decongestant oxymetazoline was more beneficial than single therapy with either alone.⁷ Combination therapy significantly improved nasal symptoms and nasal patency measured with acoustic rhinometry. Importantly, there was no rhinitis medicamentosa with decongestant alone or with combination therapy. This promising proof-of-concept study will hopefully lead to larger clinical trials.

Costa et al²⁷ compared patients with allergic rhinitis from primary care clinics in France with those enrolled in clinical trials. They observed that only 7.4% of patients in primary care would qualify for trials. The remainder would have been excluded because of several factors, most commonly negative allergy skin test results, mild disease, and other comorbidities. This result raises questions about the applicability of clinical trial results to the primary care setting. It is unknown whether this observation is also true in other countries.

SINUSITIS

Pathogenesis

Lai et al⁸ investigated the role of centrosomal protein 110 (Cp110) in patients with chronic rhinosinusitis (CRS), which is associated with poorly ciliated mucosa. Cp110 prevents the final step in ciliary maturation.²⁸ Cp110 levels were increased in the sinus mucosal tissue of both patients with chronic rhinosinusitis without nasal polyps (CRSsNP) and patients with chronic rhinosinusitis with nasal polyps (CRSwNP) compared with those seen in control subjects. Moreover, *in vitro* experiments demonstrated that proinflammatory cytokines increased Cp110 levels and inhibited ciliogenesis.⁸ Inhibiting Cp110 and improving mucociliary clearance might be a therapeutic target for CRS.

The epithelial cell genes *p63* and *p73* are members of the *p53* gene family, but unlike the tumor suppressor gene *p53*, overexpression of *p63* and *p73* is associated with cell proliferation.⁹ Expression of *p63* and *p73* was higher in nasal polyp (NP) epithelium than in inferior turbinate epithelium from healthy subjects. Levels of *p63* correlated with the degree of epithelial hyperplasia in NPs. In patients, oral glucocorticoid therapy improved epithelial structure and significantly decreased *p63* and *p73* expression in NPs.⁹ Another molecule with increased levels in NPs is CCL23, which is produced by eosinophils and chemoattracts monocytes, macrophages, and dendritic cells.¹⁰ In another study Roca-Ferrer et al¹⁶ observed that IL-1 β stimulation of fibroblasts cultured from nasal mucosa of healthy subjects induced higher secretion of prostaglandin E₂ and higher levels of COX-1, COX-2, and the prostaglandin E₂ receptor EP2 than fibroblasts cultured from NPs. Future drugs targeting these pathways might suppress NP growth and inflammation.

Autoimmunity might play a role in the pathogenesis of CRSwNP. Tan et al¹¹ identified increased intranasal levels of total IgG, IgA, and antinuclear autoantibodies (eg, IgG and IgA anti-dsDNA) in the NP tissue compared with levels seen in inferior turbinate and uncinate process tissues from healthy control subjects, patients with CRSwNP, and patients with CRSsNP. Increased anti-dsDNA antibody levels correlated with more severe CRSwNP that required repeated surgeries.¹¹ Together with previous evidence of increased B cells and B-cell activating factor of the TNF family levels²⁹ in NPs, these results suggest that proliferation of self-reactive B cells participate in the pathogenesis of nasal polyposis.

Management

Because sinonasal eosinophilia occurs in more than 80% of white patients³⁰ and because IL-5 is a crucial eosinophilopoietin,³¹ Gevaert et al¹² examined the effect of mepolizumab, a humanized anti-IL-5 mAb, in 30 Belgian patients with severe steroid-refractory CRSwNP in a single-center, randomized, placebo-controlled trial. The patients had either recurrent polyposis after sinus surgery or high-grade polyp disease, as assessed by means of endoscopy at any time. Mepolizumab administered intravenously in 2 monthly injections was well tolerated and significantly reduced NP size based on rhinoscopic evaluation.¹² Although larger and longer trials are needed, these initial results are encouraging.

In children with CRS, systemic corticosteroids are often used empirically. Ozturk et al¹³ conducted a randomized placebo-controlled trial of children (ages 6-17 years) with clinically and radiologically proved CRS. Patients received 30 days of oral amoxicillin/clavulanate, and only 22 received 15 days of oral methylprednisolone (starting at 1 mg/kg/d), whereas the remaining 23 subjects received placebo. Symptoms and sinus computed tomographic scores improved significantly in both groups, but adjunctive methylprednisolone resulted in greater improvements regardless of atopic status. There was a trend toward reduction of clinical relapses. The rate of adverse events was similar in both groups. This trial confirms that oral corticosteroid as an adjunct to antibiotic treatment is efficacious and safe in children with CRS.

Noteworthy reviews on CRS published in 2011 include a review on chronic cough and irritable larynx³² and CRS reviews in the October issue of the *Journal* on epidemiology and

management,³³ genetics and phenotyping,³⁴ and pathogenesis.³⁵ Other reviews published elsewhere include a very useful comparison of guidelines on CRS management³⁶ and Cochrane reviews showing no evidence of benefit for topical or systemic antifungal agents in patients with CRS,³⁷ confirming the benefit of nasal steroids in patients with CRSsNP,³⁸ and suggesting that systemic steroids can improve symptoms of patients with acute sinusitis in the primary care setting.³⁹

CONJUNCTIVITIS

Dartt et al¹⁴ reported that the cysteinyl leukotrienes (CysLTs) LTC₄, LTD₄, and LTE₄ increased mucus production from cultured conjunctival goblet cells. This effect was reversed by the CysLT1 receptor antagonist MK571 and by resolvins.¹⁴ Resolvins originate from omega-3 fatty acids through a pathway that also uses the same enzymes that synthesize leukotrienes, and they regulate resolution of inflammation.^{40,41} These results suggest that resolvins and CysLT1 receptor antagonists could benefit patients with allergic conjunctivitis.

Shimura et al¹⁵ showed in an unblinded trial that topical ocular olopatadine 0.1% 4 times a day starting 2 weeks before the cedar tree pollen season better controlled symptoms of allergic conjunctivitis than starting olopatadine after the onset of seasonal symptoms. The trial was not placebo controlled, but the 2 treatments were applied to different eyes for each patient, allowing patients simultaneous comparison of the treatments. This could be a practical alternative when as-needed treatment fails to control symptoms.

IMMUNOTHERAPY

The January 2011 issue of the *Journal* was a special theme edition on specific allergen immunotherapy. This issue included a historical perspective on immunotherapy over the past 100 years,⁴² a review detailing future forms of immunotherapy,⁴³ an update on our current understanding of the mechanisms involved in allergen-specific immunotherapy⁴⁴ and a perspectives article discussing international expert recommendations on immunotherapy, as well as data on the safety and efficacy of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT).⁴⁵ Two additional editorials explored the economic implications of SCIT in the United States⁴⁶ and SLIT in Europe.⁴⁷ Another editorial examined the characteristics of patients that lead to initiation of allergen immunotherapy and subsequent adherence.⁴⁸ Several reviews on immunotherapy in Europe were also published in the June issue and July supplement of the journal *Allergy*.

Like its predecessors, "Allergen immunotherapy: a practice parameter third update"⁴⁹ provides guidelines for the safe and effective use of allergen immunotherapy while reducing unnecessary variation in immunotherapy practice. New developments or modifications in this document are highlighted here. There are now adequate data indicating that SCIT is effective for atopic dermatitis when it is associated with aeroallergen sensitivity, especially for patients with dust mite sensitivity who have mild-to-moderate disease.⁵⁰⁻⁵² Venom immunotherapy significantly reduces the size and duration of large local reactions and can be considered for patients who have frequent and disabling large local reactions caused by occupational exposures.⁵³ For patients who have had moderate-to-severe anaphylaxis to venom, the parameters now recommend measuring baseline serum tryptase

because increased levels are associated with more frequent and severe reactions to venom immunotherapy and a greater relapse rate after discontinuation.⁵⁴ The parameters continue to recommend a 30-minute in-office wait period after each SCIT injection. However, it is recommended that a discussion should occur on initiation of immunotherapy regarding the possibility of delayed and biphasic reactions. An action plan for such an event should be put in place, with a decision to prescribe an epinephrine autoinjector being at the physician's discretion. A new statement on premedication with an antihistamine for conventional immunotherapy indicates that antihistamines might reduce the frequency of systemic reactions and help achieve a target maintenance dose.⁵⁵

Mechanism of action

Progress continues in elucidating the mechanism of action of immunotherapy. A 4-year study of grass pollen SCIT in which patients with moderate-to-severe grass pollen-induced allergic rhinitis were randomized to 4 years of SCIT or 2 years of SCIT followed by 2 years of placebo injections looked at the levels and bioactivity of IgG₄ in relation to the persistence of tolerance to allergen.⁵⁶ This study found that although IgG₄ levels decreased to near-pretreatment levels in the placebo group at 4 years, clinical improvement and inhibitory bioactivity of allergen-specific IgG₄ were maintained, likely accounting for long-term clinical tolerance. Another longitudinal study investigating the phenotype and function of regulatory T cells before and 1 and 6 months after wasp venom immunotherapy found that at 1 month, the proportion of CD4⁺CD25⁺ forkhead box protein 3-positive and CD4⁺ forkhead box protein 3-positive cells significantly decreased in the peripheral blood and increased in the axillary lymph nodes.⁵⁷ In addition, increased activation markers (CD45RO and HLA-DR) of regulatory T cells correlated with effective *in vitro* suppression of wasp venom-driven T-cell proliferation. A study investigating the role of dendritic cells in allergen immunotherapy compared 20 patients with venom allergy with 20 control subjects before and 52 hours and 12 months after initiation of SCIT.⁵⁸ Although plasmacytoid dendritic cell numbers in patients with venom allergy were similar to those seen in control subjects at baseline, they decreased markedly 52 hours after SCIT, returning to baseline levels at 12 months. These studies add new insights into the mechanism of tolerance induced by immunotherapy.

SCIT

Strategies to better define dosing and duration of therapy, as well as the safety and efficacy of SCIT, continue to be a focus of research. Houlston et al⁵⁹ retrospectively evaluated 85 children with honeybee venom allergy younger than 14 years who underwent honeybee venom SCIT. A 50-μg maintenance dose prevented systemic reactions in 86.4% of children for 93.8% of stings, which is similar to the results of previous studies using a 100-μg maintenance dose in adults and children.^{60,61} Tabar et al⁶² compared 3 versus 5 years of maintenance SCIT to *Dermaphagoides pteronyssinus* and found similar benefits in rhinitis and asthma symptoms and quality of life. However, the 5-year maintenance provided an additional 19% decrease in rhinitis symptoms.

A new 3-year DBPC trial on mold SCIT showed benefit in children. Children aged 5 to 18 years with rhinitis, asthma, or both

and only allergic to *Alternaria alternata* were randomized to standardized *A alternata* extract or placebo. Benefits were noticed on years 2 and 3 when combined symptom-plus-medication scores decreased by 38.7% and 63.5%, respectively, in the treatment group.⁶³

Rondon et al⁶⁴ studied SCIT in a pilot trial of 20 adult patients with local allergic rhinitis to grass pollen. Six months of grass SCIT improved nasal tolerance to grass challenge compared with rescue medications alone. Skin prick test responses to grass pollen were positive in 40% of treated patients, and serum IgG levels to *Lolium* and *Phleum* species grasses increased at 12 months. Moreover, the treatment group experienced a 45% reduction in symptoms and rescue medication scores the following spring compared with control subjects.

Pollen SCIT to induce tolerance to triggers of oral allergy syndrome continue to disappoint. In a DBPC study of 19 adults with birch pollen and hazelnut allergy, birch pollen SCIT did not change oral tolerance to hazelnut, skin test titration to hazelnut extract or serum IgG₄ levels to hazelnut.⁶⁵ However, SCIT successfully increased serum IgG₄ levels to birch antigen. This suggests that pollen immunotherapy will need to increase food-specific IgG₄ levels to be successful in patients with oral allergy syndrome.

Matricardi et al⁶⁶ reviewed meta-analyses on SCIT and pharmacotherapy for seasonal allergic rhinitis that included 5 or more DBPC trials. SCIT reduced symptoms similarly to mometasone and to a greater extent than montelukast and desloratadine.

SLIT

Although the use of SLIT has become common clinical practice in Europe and elsewhere as a safer and more convenient alternative to SCIT, its use is not yet approved by the US Food and Drug Administration. Two large DBPC studies on the safety and efficacy of timothy grass allergy immunotherapy tablets in North America were reported in 2011.^{67,68} In 345 children and adolescents with timothy grass allergy randomized to once daily grass tablet treatment containing 2800 bioequivalent units (15 μg of Phl p 5) versus placebo, grass tablets improved symptom scores and medication use by 18% to 50%, increased specific IgG₄ levels, and caused only mild oral adverse events.⁶⁷ The second study with a similar protocol and identical dose of daily grass tablet versus placebo in 439 adults showed 18% to 26% improvements in symptom and medication scores with grass tablet treatment. A follow-up of a European trial of grass allergen immunotherapy tablets (75,000 SQ *P pratense*, 800-BAU tablet [Grazax, ALK-Abelló]) in adults with allergic rhinitis showed lasting benefits up to 2 years after stopping a 3-year treatment.⁶⁹ A European 3-arm study compared 2-month versus 4-month pre-seasonal SLIT followed by seasonal treatment or placebo treatment for 3 consecutive seasons. SLIT tablets containing 300 IR from 5 grasses or placebo were taken by 633 patients with allergic rhinoconjunctivitis.⁷⁰ Both preseasonal treatments provided an approximately 35% reduction in symptoms compared with placebo. The authors suggested that pre-seasonal and co-seasonal treatment might be as efficacious as year-round treatment with SLIT.

A trial of SLIT for house dust mite allergy compared either high-dose (4200 allergen units, 70 μg of Der f 1 per day), or low-dose (60 allergen units, 1 μg of Der f 1 per day) maintenance therapy with placebo in 31 *Dermatophagoides farinae*-sensitive

adults.⁷¹ Adverse events were mild to moderate, occurring in half of the subjects in all 3 groups. No severe reaction occurred. High-dose SLIT increased both serum specific IgG₄ levels and bronchial threshold for bronchoconstriction to allergen challenge. Low-dose SLIT and placebo had none of these effects. A Korean study reported that SLIT with house dust mite extract reduced symptoms and medication use to a similar extent in both monosensitized (n = 70) and polysensitized (n = 64) patients with allergic rhinitis,⁷² indicating that single-allergen SLIT might also be efficacious in polysensitized patients.⁷³

A Cochrane systematic review and meta-analysis of SLIT for allergic conjunctivitis evaluating 42 trials including 3958 participants found that SLIT significantly reduces ocular symptoms and increases allergen tolerance in conjunctival challenges without reducing medication use.⁷⁴

Novel delivery systems and modified extracts

In a novel approach to immunotherapy, 51 dust mite-sensitized children with mild-to-moderate asthma were randomized into one of 4 arms: SCIT, SLIT, SCIT buildup plus SLIT maintenance, or pharmacotherapy.⁷⁵ Maintenance doses contained 42 to 62 µg of each *D. pteronyssinus* and *D. farinae* per dose. Buildup and maintenance treatment lasted a total of 18 months. In general, groups receiving SCIT fared better in reducing asthma exacerbations and inhaled corticosteroid doses, as well as inducing IgG₄. Larger trials will be needed to further explore the combination of rapid onset and potency of SCIT with the safety and convenience of SLIT.

The effect of immunotherapy to a single tree nut on multiple tree nut allergy was studied in a murine model.⁷⁶ Cashew immunotherapy effectively prevented allergic reactions to cashew nut challenges and also to the cross-reactive pistachio and attenuated allergic symptoms to walnut challenge.

Development of peptide immunotherapy continues. A clinical study showed a good safety profile and induction of favorable immune responses (eg, IL-10) using 7 cat allergen peptides from Fel d 1⁷⁷ in patients with cat allergy. Another group had peptides from Ole e 1 that do not bind to IgE and induced IgG in rabbits, which inhibited binding of specific olive tree IgE to Ole e 1 from allergic subjects.⁷⁸ Peptides do not activate IgE-mediated reactions but induce tolerance in T cells.

The Global Allergy and Asthma European Network investigators assessed the quality of reporting of allergen immunotherapy trials according to the Consolidated Standards of Reporting Trials Statement criteria. Of 46 SCIT and 48 SLIT DBPC randomized trials published between 1996 and 2009,⁷³ only 1 SCIT and 3 SLIT trials met the Consolidated Standards of Reporting Trials criteria, leading the authors to conclude that the quality of reporting needs to improve. A task force on immunotherapy from the European Academy of Allergy and Clinical Immunology also found that reports need to better detail dosing regimens so that proper dose-response relationships can be compared across studies and dose recommendations can be developed.

CONCLUSION

Publications in upper airway disease in 2011 bring new evidence for risk factors for allergic rhinitis, pathogenesis of rhinitis and sinusitis, and new diagnostic and therapeutic approaches for rhinitis, conjunctivitis, and CRS (listed in

TABLE II. Key advances in allergen immunotherapy in 2011

1. "Immunotherapy: a practice parameter third update" was published.⁴⁹
2. Inhibitory bioactivity of allergen-specific IgG₄ rather than its level might account for long-term clinical tolerance induced after grass pollen SCIT therapy.⁵⁶
3. Plasmacytoid dendritic cells might have a role in inducing regulatory T cells in wasp venom SCIT.⁵⁸
4. SCIT for children and adolescents with *Alternaria alternata* improved symptom and medications scores at 2 and 3 years but not at 1 year.⁶³
5. SLIT to grass pollen induced persistent reductions in symptom and medication scores and prolonged increased allergen-specific IgG₄ levels for at least 2 years after completing a 3-year treatment.⁶⁹
6. A Cochrane systematic review and meta-analysis showed that SLIT reduces ocular symptom scores, but does not decrease eye drop use.⁷⁴
7. A combination of SCIT buildup and SLIT maintenance therapy appears to be more effective than SLIT alone and more convenient than SCIT alone.⁷⁵

Table I). Likewise, our understanding continues to advance in the mechanisms of allergen immunotherapy and in the clinical efficacy and safety of SCIT and SLIT. In addition, new approaches for allergen immunotherapy show promising early results in bench research, animal models, and phase I and II clinical studies (listed in Table II).^{49,56,58,63,69,74,75}

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