

# Advances in upper airway diseases and allergen immunotherapy in 2007

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The purpose of this review is to highlight important articles on upper airway diseases and immunotherapy that appeared in 2007. Advances in rhinitis include the realization that allergic rhinitis might be caused by local nasal IgE sensitization to aeroallergens in the absence of systemic evidence of IgE sensitization. After inhalation, allergens might reach systemic circulation. Epidemiologic studies continue to show that allergic rhinitis impairs school performance and is a risk factor for future asthma. New pathways are being identified in chronic sinusitis, as well as in different types of allergic ocular diseases. New treatments for patients with allergic rhinitis include use of  $\beta$ -1,3-glucan, a mushroom product that can reduce allergic symptoms by inducing T<sub>H</sub>1 response, and olopatadine nasal spray. Studies on immunotherapy in 2007 suggest that sublingual immunotherapy induces similar immunologic alterations as those induced by subcutaneous immunotherapy, although to a lesser degree. Among allergists in the United States, there is a sizable variation in clinical practice, particularly related to concomitant administration of immunotherapy and  $\beta$ -blockers, to administration of angiotensin-converting enzyme inhibitors, and to patients with HIV or autoimmune diseases. The combination of omalizumab with allergen subcutaneous immunotherapy can enhance clinical efficacy. Recombinant technology can modify allergen structure to prevent binding to IgE (allergenicity) while enhancing immunogenicity (stimulation of T cells), which might improve the safety and efficacy of immunotherapy. (*J Allergy Clin Immunol* 2008;122:481-7.)

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

Key advances in upper airway diseases are listed in Table I.<sup>1-27</sup>

## RHINITIS

Allergic rhinitis can be a localized disease without systemic evidence of IgE sensitization, such as a positive allergen skin test response or increased serum specific IgE levels. Patients initially given diagnoses of “nonallergic” rhinitis for having nasal

### Abbreviations used

CRS:	Chronic rhinosinusitis
CRSwNP:	Chronic rhinosinusitis with nasal polyps
EGFR:	Epidermal growth factor receptor
GPC:	Giant papillary conjunctivitis
IR:	Index of reactivity
MMP:	Matrix metalloproteinase
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy
TIMP:	Tissue inhibitor of metalloproteinases
VKC:	Vernal keratoconjunctivitis

symptoms for longer than 2 years, negative skin test responses, and a lack of serum specific IgE to *Dermatophagoides pteronyssinus* had nasal markers of allergic disease.<sup>1</sup> Approximately 54% of them had positive early responses to nasal allergen challenges with Der p 1, confirming allergic rhinitis, and 30% also had late-phase responses. In addition, at baseline and before nasal challenge, patients with persistent nonallergic rhinitis had increased eosinophil numbers, eosinophil cationic protein levels, albumin levels, specific IgE levels to *D pteronyssinus*, total IgE levels, and T-cell counts (mainly CD3<sup>+</sup>CD4<sup>+</sup> cells) in their nasal lavage samples compared with samples from healthy control subjects. These abnormalities were similar to but milder than those found in typical subjects with allergic rhinitis. This study indicates that individuals with persistent nonallergic rhinitis based on allergy skin test results and serum specific IgE test results might have a localized form of allergic rhinitis. Biomarkers of allergic sensitization and inflammation in nasal lavage fluid and nasal challenge test results might help identify these patients.

The fate of aeroallergens in the respiratory mucosa is unknown, but they must penetrate the mucosa to induce allergic sensitization. Hens et al<sup>28</sup> tracked ovalbumin in the airways and sera of mice after nasal or tracheal challenges of 1 mg of ovalbumin in 10  $\mu$ L of saline. Ovalbumin was detected in serum at 15 and 60 minutes after either type of challenge, reaching maximum concentrations of 5.0 to 7.5  $\mu$ g/mL at 60 minutes. Up to 14% of ovalbumin was absorbed into the serum. Histology showed that 10 minutes after challenge, ovalbumin was present in the lumens of nasal cavities, bronchi, and alveoli, as well as inside bronchial submucosal blood vessels. The authors speculated that allergens can traverse epithelium through transcytosis. Before generalizing these findings to human subjects, we should keep in mind that a mouse weighs 20 g and that they were challenged with the equivalent of 50 mg/kg protein or some 700 g (1.5 lb) of pollen for a 70-kg adult!

Epidemiologic studies have brought new insight into atopic diseases. The initial Allergic Rhinitis and Its Impact in Asthma document classified allergic rhinitis into 2 severity categories, namely mild and moderate/severe. Disease is mild unless there is impairment in any of these 4 quality-of-life areas based on the

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**TABLE I.** Key advances in upper airway diseases in 2007

1. Patients with absent systemic signs of allergic sensitization (negative skin allergy test result and absent specific serum IgE) can still have allergic rhinitis. These patients have nasal markers of IgE sensitization to aeroallergens.<sup>1</sup>
2. Evaluation of the number of areas of quality of life affected by allergic rhinitis might help distinguish moderate from severe disease.<sup>2</sup>
3. Additional epidemiologic studies confirm that frequent infections are associated with less atopy, that symptomatic allergic rhinitis impairs school performance, and that allergic rhinitis in childhood increases the risk of future onset of asthma.<sup>3-6</sup>
4. Clinical trials suggest that  $\beta$ -1,3-glucan derived from an edible mushroom can modestly attenuate allergic rhinoconjunctivitis.<sup>7</sup> In addition, fluticasone furoate<sup>8</sup> and nasal olopatadine<sup>9</sup> are efficacious as treatments for allergic rhinoconjunctivitis.
5. CRS is commonly present in patients with severe asthma.<sup>10</sup>
6. New pathways involved in the pathogenesis of different forms of CRS include nitric oxide, glycoprotein 340, lactoferrin, MMPs, Toll-like receptor 9, IL-22 receptor 1, and EGFR.<sup>11-18</sup>
7. Updated guidelines on CRS have been provided.<sup>19,20</sup>
8. Pathogenesis of VKC and GPC includes mediators and cells related to the T<sub>H</sub>2 type of inflammatory response.<sup>21-25</sup>
9. Topical ocular olopatadine 0.2% once daily<sup>26</sup> and nonsteroidal anti-inflammatory agents<sup>27</sup> are efficacious for the treatment of allergic conjunctivitis. Nonsteroidal anti-inflammatory eye drops relieve pruritus and conjunctival injection.

rhinitis-specific quality-of-life instrument<sup>29</sup>: sleep, daily activities, work/school attendance, and troublesome symptoms. To attempt to distinguish patients with “moderate” from “severe” rhinitis, Valero et al<sup>2</sup> evaluated 141 untreated patients from allergy and otorhinolaryngology clinics of 27 Spanish hospitals. Using the total symptom score scale and the Juniper Rhinitis Quality of Life Questionnaire, they assessed impairment in the aforementioned 4 areas and applied a series of regression models to reach the conclusion that the best discriminatory criterion to define “severe” allergic rhinitis is when disease affects all 4 areas and “moderate” when it affects 1 to 3 areas of quality of life. Although an interesting exercise, rarely are patients naive to treatment when they reach the specialist’s office. Future validation of this classification strategy in previously treated patients will be more relevant to allergists.

Infections were again associated with decreased atopy in a cross-sectional seroprevalence study of 1249 adults in Iceland, Sweden, and Estonia. Janson et al<sup>3</sup> measured serum IgE levels to 4 allergens and IgG levels against *Helicobacter pylori*, *Toxoplasma gondii*, hepatitis A virus, herpes simplex virus 1, *Chlamydia pneumoniae*, EBV, and cytomegalovirus. Serologic evidence of past infections with 3 or fewer of these microbes was associated with a 1.4- to 1.8-fold increase in the prevalence of allergic asthma or rhinitis. On the one hand, these results seem to support the hygiene hypothesis, which suggests that a clean environment and fewer infections increase onset of atopic diseases. On the other hand, these results can be explained by the possibility that atopic individuals are genetically predisposed toward strong T<sub>H</sub>2 responses<sup>30</sup> and weak T<sub>H</sub>1 responses, which impairs IgG production to microbes, whereas nonatopic individuals would be born with the inverse genetic predisposition.

Symptomatic allergic rhinitis impairs school performance based on a case-control study of 1834 students aged 15 to 17 years in Britain.<sup>4</sup> Cases were students who had a decrease in their grades between the practice winter examination and the final summer examination, whereas control students received similar or improving grades in the same period. Overall prevalence of symptomatic seasonal allergic rhinitis during the summer was 40%. Cases were 1.4 to 1.7 times more likely than control subjects to have had allergic rhinitis symptoms, to be taking any medication for allergic rhinitis, or to have taken sedating antihistamines during the summer examination period. This indicates that allergic rhinitis, medication side effects, or both can impair school performance in teenagers.

Allergic rhinitis was again found to be a risk factor for asthma. In a cohort study conducted in Tasmania, Australia, Burgess et al<sup>5</sup> surveyed more than 8500 subjects at 7 (1968), 13 (1974), and 44 years of age (2004). They found that the presence of allergic rhinitis at 7 years of age increased by 2- to 7-fold the risk of asthma later in adolescence to adulthood. In this same cohort,<sup>6</sup> subjects born to atopic mothers and exclusively breast-fed in the first 3 months of life had a small (approximately 20%) decrease in the risk of asthma prevalence by age 7 years but a 20% to 57% increased risk of having allergic rhinitis, asthma, or food allergy by the age of 44 years. A limitation of the study was that breast-feeding history was obtained at 7 years of age and subject to recall bias.

In the therapeutic arena a new immunomodulatory approach was tested in patients with allergic rhinitis. Yamada et al<sup>7</sup> explored the ability of microbes to induce T<sub>H</sub>1 immune responses by using  $\beta$ -1,3-glucan, a widely present substance in cell walls of fungi, to treat spring allergic rhinitis to cedar pollens in Japanese patients. The authors had previously shown *in vitro* and in animals that macrophages secrete IL-12 after taking up  $\beta$ -1,3-glucan and induce a strong T<sub>H</sub>1 response.  $\beta$ -1,3-Glucan was isolated from lentinan of the edible mushroom *Lentinus edodes* Berk (Sing) and made into shiitake extracts, an absorbable extract of superfine particles with a diameter of 0.08  $\mu$ m. Subjects received orally 15 mg in 100 mL once daily for 8 weeks, followed by 8 weeks of observation in a parallel-group, randomized, double-blind, placebo-controlled clinical trial of 30 subjects per group. Subjects graded improvement more often in the active group compared with the placebo group (treated with a nonabsorbable extract of large particles with a diameter of 288  $\mu$ m) based on nasal and ocular symptom scores recorded in diaries. In addition, serum total IgE and specific IgE levels to cedar pollens decreased by 10% to 20%. Although the improvement was very modest, this study corroborates animal studies showing that microbes and microbial products can induce T<sub>H</sub>1 responses and downregulate allergic responses.<sup>31,32</sup>

Clinical trials of new medications derived from the current armamentarium were reported. Fluticasone furoate nasal spray was effective for allergic rhinoconjunctivitis caused by ragweed pollen in subjects aged 12 years and older.<sup>8</sup> Fluticasone reduced nasal symptoms twice as much and ocular symptoms 40% more than placebo (40% vs 20% and 38% vs 27%, respectively,  $P < .005$ ). Onset of action was 8 hours from the first dose. These results were expected because the previous version of the molecule,

fluticasone propionate, is also efficacious for nasal and ocular symptoms,<sup>33</sup> as are most nasal corticosteroids.<sup>34</sup> In another trial, olopatadine, currently available as an eye drop for allergic conjunctivitis, was also efficacious for allergic rhinitis in a phase II dose-finding clinical trial of 320 Canadian adults allergic to ragweed. Subjects were challenged in an exposure chamber to 3000 to 4000 pollen grains/m<sup>3</sup> for 14.5 hours in a randomized, double-blind, single-dose, placebo-controlled study.<sup>9</sup> The onset of action of olopatadine was 30 minutes. Olopatadine 0.6% reduced nasal symptoms by 37% compared with 24% reduction in the placebo group at 4 hours of treatment. This treatment has recently become available in the United States as Patanase Nasal spray 0.6%. (Alcon Laboratories, Inc, Fort Worth, Tex).

## SINUSITIS AND NASAL POLYPS

An epidemiologic study showed that sinusitis is a feature of patients with severe asthma.<sup>10</sup> Among subjects with severe asthma, 54% have a history of sinusitis and 27% have had sinus surgery compared with rates of 37% and 11% in those with milder disease, respectively. This supports the concept of the "1-airway" disease, in which atopic subjects commonly have upper and lower airways involved. Another study compared 13 instruments that measure quality of life in patients with rhinitis or chronic rhinosinusitis (CRS).<sup>35</sup> The best instruments for rhinitis were the Rhinitis Quality of Life Questionnaire<sup>36</sup> and its standardized version,<sup>37</sup> whereas for sinusitis, the best instruments were the Rhinosinusitis Outcome Measurement<sup>38</sup> and the RhinoQOL for rhinosinusitis.<sup>39</sup> However, this comparison was based only on the main articles validating the tools instead of evaluating all available studies for each tool.

The pathogenesis of CRS is not completely understood, and several inflammatory mediators were described in different forms of CRS last year. Abnormalities in the nitric oxide metabolism were found in patients with CRS with nasal polyposis (CRSwNP). These include decreased concentrations of metabolites of nitric oxide (nitrite and nitrate) and increased inducible nitric oxide synthase levels in nasal lavage samples compared with samples from healthy subjects.<sup>11</sup> Another publication described a 20% increase in glycoprotein 340 levels in nasal polyps.<sup>12</sup> Glycoprotein 340 is an innate response molecule secreted by airway submucosal glands that agglutinates gram-positive and gram-negative bacteria, as well as influenza A viruses. Another innate defense molecule, lactoferrin, was decreased in surgical sinus mucosal samples of patients with CRS, particularly patients with CRSwNP (50% reduction), compared with control sphenoidal sinus mucosal samples from patients undergoing transsphenoidal pituitary surgeries.<sup>13</sup> Lactoferrin chelates iron to inhibit bacterial growth and also prevents formation of biofilms. Biofilms increase antibiotic resistance 10 to 1000 times and have recently been found in the middle-ear mucosa of children with chronic otitis media with effusion<sup>14</sup> and in the sinus mucosa of patients with CRS.<sup>15</sup> A limitation of these cross-sectional studies is that they only show association of innate immunity defects with CRS. Prospective studies will be necessary to establish causation.

Matrix metalloproteinases (MMPs) degrade matrix and are inhibited by tissue inhibitor of metalloproteinase (TIMP) 1. The ratio of MMP/TIMP-1 indicates the propensity for connective tissue degradation versus deposition. The MMP-8/TIMP-1 and MMP-9/TIMP-1 ratios were increased in surgical samples of sinus mucosal specimens from patients with CRSwNP without

eosinophilia.<sup>16</sup> Although these results suggest additional heterogeneity in this disease, the authors did not take into consideration previous treatments, a common problem in CRS studies. Ramanaathan et al<sup>17</sup> found that Toll-like receptor 9 was expressed 50% less in sinonasal epithelial cells from patients with CRS compared with those from control subjects, regardless of the presence of polyps. They also reported that IL-22 receptor 1 levels were decreased in the ethmoidal mucosa of patients with CRSwNP compared with levels seen in control subjects and patients with CRS without nasal polyps.<sup>18</sup> IL-22 is secreted by T<sub>H</sub>17 and T<sub>H</sub>1 cells, and its function is not well characterized. Ding et al<sup>40</sup> reported that epidermal growth factor receptor (EGFR) levels were 10 times higher in nasal mucosa of patients with CRS, regardless of the presence of polyps, than in samples from control subjects. EGFR was mainly expressed in goblet cells and basal cells, whereas its ligand, epidermal growth factor, was mostly expressed on the apical side of ciliated epithelial cells.<sup>19</sup> The EGFR pathway participates in epithelial repair and mucus production.

In the therapeutics arena 2 guidelines on CRS were updated in 2007: the European Position Paper<sup>19</sup> and the American Academy of Otolaryngology-Head and Neck Surgery's Clinical Practice Guideline.<sup>20</sup> In addition, a Cochrane review concluded that nasal saline irrigation is beneficial for patients with CRS, although it is very difficult to have a proper placebo group in such studies. It concluded that nasal saline irrigation can improve the 20-Item Sino-Nasal Outcome Test score by 45% at week 8 compared with a 20% improvement with nasal saline spray<sup>41</sup> in patients with chronic nasal symptoms.

## CONJUNCTIVITIS

In the field of allergic ocular diseases, several reviews were published in the October 2007 issue of *Current Opinion in Allergy and Clinical Immunology*,<sup>42,43</sup> and new findings in disease pathogenesis were reported. Tears of patients with vernal keratoconjunctivitis (VKC) have a 10-fold increase in stem cell factor<sup>21</sup> and an increased ratio of specific dust mite secretory IgA/total secretory IgA.<sup>22</sup> Tears of patients with VKC and giant papillary conjunctivitis (GPC) have a 5- to 10-fold increase in soluble IL-6 receptor levels.<sup>23</sup> Histologic examination of conjunctival biopsy specimens show increases in mast cell counts, CD4 lymphocyte counts, and eosinophil counts in patients with VKC<sup>24</sup> and GPC.<sup>25</sup> However, biopsy specimens from patients with VKC also have an increase in numbers of natural killer cells<sup>24</sup> and MMPs (MMP-1, MMP-3, MMP-9, and MMP-13),<sup>44</sup> and biopsy specimens from patients with GPC have an increase in numbers of mast cells (both tryptase and chymase positive) and CD8 lymphocytes and IL-4 and eotaxin levels.<sup>25</sup> Some of these findings indicate that VKC and GPC have features of T<sub>H</sub>2 inflammation.

Clinical trials in patients with allergic conjunctivitis have confirmed that once-daily olopatadine 0.2% eye drops are equally efficacious as the 0.1% strength given twice daily by using a model of conjunctival allergen challenge.<sup>26</sup> A meta-analysis showed that topical, ocular, nonsteroidal anti-inflammatory drugs can relieve pruritus and conjunctival injection.<sup>27</sup>

## IMMUNOTHERAPY

Specific allergen immunotherapy was the theme of the April 2007 issue of the *Journal* (Table 1). Its articles reviewed the current state of specific allergen immunotherapy, approaches to improve safety and convenience,<sup>45</sup> molecular mechanisms,<sup>46</sup> sublingual

immunotherapy (SLIT),<sup>47</sup> peptide immunotherapy,<sup>48</sup> and immunotherapy with recombinant allergens.<sup>49</sup> Also published in that issue was a significant update of the 2001 "Allergic Rhinitis and Its Impact on Asthma" document focusing on allergen immunotherapy.<sup>50</sup> This update reviewed in detail the experimental evidence on mechanisms, safety, and efficacy of subcutaneous immunotherapy (SCIT) and SLIT for allergic rhinitis, asthma, or both published between January 2001 and April 2006. The mechanism of action of SCIT includes blunting of allergen-driven T<sub>H</sub>2 responses, including reductions in IL-4, IL-13, IL-5, and IL-9 levels. The decrease in T<sub>H</sub>2 markers is accompanied by an immune deviation favoring T<sub>H</sub>1 responses to allergens. SCIT also promotes some level of immune tolerance by inducing IL-10- and TGF- $\beta$ -secreting T regulatory cells, which presumably suppress T<sub>H</sub>2 responses. IL-10 also promotes immunoglobulin isotype switching to IgG4, and TGF- $\beta$  mediates switching to IgA. IgG4 and IgA can downregulate allergic responses. Indeed, induction of allergen-specific IgG during SCIT mediates several beneficial biologic effects, including the ability of postimmunotherapy serum to inhibit binding of allergen-IgE complexes to B cells *in vitro*, to block IgE-facilitated allergen presentation and activation of allergen-specific T lymphocytes, and to prevent allergen/IgE-dependent activation of peripheral basophils. SLIT also induces some of these immunologic changes, although to a lesser degree than SCIT.

Another important event related to immunotherapy in 2007 was the Practice Parameter Second Update on Allergen Immunotherapy developed by the Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma, and Immunology; and the Joint Council of Allergy, Asthma, and Immunology.<sup>51</sup> Like the original,<sup>52</sup> this document establishes guidelines for the safe and effective use of allergen immunotherapy while reducing unnecessary variation in immunotherapy practices. The update provides specific recommendations for immunotherapy maintenance doses for some standardized allergens and suggests dose ranges for nonstandardized allergen extracts. New information on the effect of time, temperature, and dilution on standardized extract potency and an updated table on the cross-reactivity of allergen groups are provided to help in the selection of appropriate allergens for immunotherapy. The updated parameter continues to support the use of SCIT as safe and effective for allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity but not for food hypersensitivity, urticaria, or angioedema. Regarding the use of immunotherapy for atopic dermatitis and the efficacy of SLIT, limited data are available, and further studies are required.

## IMMUNOTHERAPY PRACTICE PATTERNS

The American Academy of Allergy, Asthma & Immunology Immunotherapy and Allergy Diagnostics committee reported the results of a survey of Academy members on immunotherapy practice patterns and concerns.<sup>53</sup> Despite the limited response rate (16%), it showed inconsistency in practice patterns with respect to the policy of administering immunotherapy to patients taking  $\beta$ -blockers and angiotensin-converting enzyme inhibitors, the role of prophylactic medications, and the safety of immunotherapy for patients with HIV and autoimmune disease. For example, 67% of respondents perform skin tests on patients taking  $\beta$ -blockers, 48% never start these patients on immunotherapy, 21% do so only for venom immunotherapy, 7% do not consider oral  $\beta$ -blockers as a contraindication for skin testing or

immunotherapy, and 21% did not see  $\beta$ -blocker eye drops as a contraindication for immunotherapy. Only 37% of respondents were concerned about the safety of immunotherapy in patients taking angiotensin-converting enzyme inhibitors. The wait period after immunotherapy varied from none (1%), 20 minutes (54%), and 30 minutes (45%) to greater than 30 minutes (1%). Eighty-one percent of survey participants indicated that they pretreated patients with antihistamines before immunotherapy injections to reduce adverse events, 15% did so routinely, and 66% only pretreated high-risk patients. When evaluating patients with HIV, 74% of responders perform skin tests on them, 40% of responders start them on immunotherapy as they would other patients, but 9% of responders start immunotherapy for insect venom therapy only. The committee concluded that further prospective and retrospective studies could help us understand this variability in practice.

## SLIT

Although SLIT is currently used in many European countries, questions about optimal dose, efficacy, and safety remain. In a multinational, randomized, double-blind, placebo-controlled study, 628 adults with grass pollen-induced rhinoconjunctivitis were assigned to either 100 index of reactivity (IR), 300 IR, or 500 IR of a standardized 5-grass pollen extract or placebo administered sublingually using a once-daily tablet form.<sup>54</sup> The 300 IR/mL dose was approximately equivalent to 25  $\mu$ g/mL of the group 5 major allergens. Treatment was started 4 months before the estimated pollen season and continued throughout the season. Both the 300- and 500-IR doses significantly reduced mean rhinoconjunctivitis total symptom scores compared with placebo (37% and 35% improvement, respectively). The 100-IR group was not significantly different from the placebo group. No serious side effects were reported, although the 500-IR tablet induced more adverse effects than the 300-IR dose. The authors concluded that the 300-IR 5-grass pollen tablet was the optimal dose for treatment.

Another double-blind, placebo-controlled study investigated the efficacy of grass pollen SLIT in children and adolescents in a primary care setting.<sup>55</sup> Children aged 6 to 18 years old ( $n = 204$ ) with hay fever and serum IgE levels to grass pollen of greater than 0.7 kU/L were assigned to receive twice weekly for 2 years aqueous grass pollen extract with a maintenance dose of 9500 biologic units (21  $\mu$ g equivalent Lol p 5) or placebo. Although this study found that SLIT with grass pollen was safe and compliance was generally good, there was no difference in the primary outcome of daily total symptom score during the second treatment year. The authors concluded that general practitioners should not administer SLIT to children or adolescents with grass pollen allergy.

In a study of birch pollen SLIT, researchers examined the effects on apple allergy or oral allergy syndrome to apple.<sup>56</sup> Nine of 20 SLIT-treated subjects experienced a decrease in nasal response to birch pollen extract, a decrease in skin test reactivity to birch, and an improvement of allergic symptoms during the birch pollen season. However, no subject showed a reduced sensitivity to oral challenge with apple or reported improvement in oral allergy symptoms with eating. SLIT significantly increased levels of Bet v 1 (from birch pollen)-specific IgE and IgG4 and decreased PBMC responses to Bet v 1 but failed to induce similar humoral and cellular responses to Mal d 1 (from apple). This contrasts with a previous report of SCIT with birch pollen reducing

**TABLE II.** Key advances in immunotherapy in 2007

1. The update on allergen immunotherapy of the 2001 "Allergic Rhinitis and Its Impact on Asthma" document was published.<sup>50</sup>
2. The American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma, and Immunology; and the Joint Council of Allergy, Asthma, and Immunology's Practice Parameter Second Update on Allergen Immunotherapy was published.<sup>51</sup>
3. Optimal dosing for SLIT with a 5-grass pollen extract for patients with seasonal allergic rhinitis was determined.<sup>54</sup>
4. SLIT for children and adolescents with grass allergy was not successful when administered by general practitioners in a large double-blind, placebo-controlled trial.<sup>55</sup>
5. SLIT with birch pollen might not alleviate symptoms of oral allergy syndrome to apple based on its ability to alter specific serum levels of IgE and IgG4 and *in vitro* T-cell proliferation to Bet v 1 (birch allergen) and Mal d 1 (apple allergen).<sup>56</sup>
6. SLIT to dust mite improved symptoms of atopic dermatitis in children.<sup>59</sup>
7. A recombinant hybrid molecule of 4 major allergens from timothy grass was safe and effective in the diagnosis of grass allergen sensitization, as determined by means skin of prick testing.<sup>61</sup>
8. Chimeric proteins of T- and B-cell epitopes of the Bet v 1 family used for allergen immunotherapy demonstrated low allergenicity while maintaining immunogenicity.<sup>63</sup>

oral allergy syndrome to apple,<sup>57</sup> indicating that SLIT might not be as efficacious as SCIT.

A mechanistic study of T-cell responses to allergen showed that SLIT induces T regulatory cells. After 4 weeks of SLIT with birch pollen, PBMCs studies showed increased CD4<sup>+</sup>CD25<sup>+</sup> T cells, increased mRNA expression of FoxP3 and IL-10, and reduced transcription of IL-4 and IFN- $\gamma$  compared with that seen in samples before SLIT.<sup>58</sup> Proliferation of PBMCs to Bet v 1, Mal d 1, and tetanus toxoid was also markedly reduced, an effect that was reversed with anti-IL-10 antibodies or by depleting CD25<sup>+</sup> cells. However, after 52 weeks, only the proliferation response to Bet v 1 remained suppressed. This shows that SLIT is comparable with SCIT in that it induces regulatory T-cell suppression through IL-10 during the early phase of therapy and specific non-reactivity and immune deviation of allergen-specific T cells during the later phase of SLIT. However, unlike SCIT, SLIT was unable to induce production of TGF- $\beta$ , which suggests a reduced ability to generate allergen-specific T regulatory cells.

SLIT might help patients with atopic dermatitis. In a double-blind, placebo-controlled study of 56 mite-sensitized children aged 5 to 16 years with atopic dermatitis, SLIT for 18 months<sup>59</sup> significantly improved SCORAD scores and reduced medication use beginning at 9 months of SLIT therapy. Stratification revealed that improvement was limited to those with mild-to-moderate disease, whereas those with severe disease had only a marginal benefit, and 2 patients withdrew because of aggravation of disease. These results are similar to those observed with SCIT.

## SCIT

Strategies to improve the safety and efficacy of SCIT continue to be the focus of several studies. The use of a combination of SCIT with anti-IgE (omalizumab) decreased systemic side effects and enhanced efficacy compared with SCIT alone in a 4-arm, double-blind, placebo-controlled study of ragweed immunotherapy.<sup>60</sup> The authors observed that SCIT alone induced allergen-specific IgG4 that partially blocked binding of allergen-IgE complexes to cells, but this binding was completely blocked with the addition of omalizumab, which might explain the enhanced efficacy.

## MODIFIED EXTRACTS

The development of effective recombinant allergens for skin testing and SCIT allows for defined molecules with known molecular, immunologic, and biologic characteristics that can

be produced with consistent quality and in unlimited amounts. A recombinant hybrid molecule consisting of 4 major allergens from timothy grass (Phl p 1, 2, 5, and 6) was expressed in *Escherichia coli* and evaluated for diagnostic use in skin tests in 32 subjects allergic to a mixture of natural grass extract and 9 control subjects.<sup>61</sup> Four concentrations of the hybrid molecule of timothy grass allergens (4, 12, 36, and 108  $\mu\text{g}/\text{mL}$ ), a mixture of natural grass pollen, and histamine were skin tested, and serum was collected to measure specific IgE antibody levels to the hybrid molecule, grass pollen extract, and a panel of recombinant Phl p 1, 2, 3, 6, and 7. Results of skin testing with the hybrid molecules were positive in all subjects with grass allergy and had less wheal variability than tests using natural grass pollen extract. There were no false-positive skin test results, and there was excellent correlation between IgE levels to the hybrid molecule and IgE levels to natural grass pollen extract measured with either ELISA ( $r = 0.98$ ,  $P < .0001$ ) or ImmunoCAP ( $r = 0.98$ ,  $P < .0001$ ) techniques.

Recombinant allergens can be modified for immunotherapy. Through deletion or site-directed mutagenesis, IgE epitopes can be removed from recombinant allergens without affecting the ability of the molecules to interact with T cells. The result is a reduction in allergenicity without reducing immunogenicity. In a study of genetically engineered hybrid proteins from *Parietaria judaica* pollen, hypoallergenic molecules were obtained by deleting B-cell epitopes.<sup>62</sup> Hybrid structures were compared with their natural components and found to have significantly reduced IgE binding *in vitro* and reduced skin prick test reactivity. However, the hybrid proteins were able to induce T-cell proliferation responses comparable with those elicited by the natural allergens. These modified recombinant allergens might improve the safety of immunotherapy. Another novel immunotherapy approach was to randomly combine 14 genes of the Bet v 1 family by means of DNA shuffling. The shuffled molecules were screened for proteins with a lower capacity to induce IgE-mediated responses and a higher capacity to induce T-cell responses compared with the native Bet v 1 allergens using *in vitro* and *in vivo* assays.<sup>63</sup> Two chimeric proteins consisting of randomly recombined T-cell and B-cell epitopes of the Bet v 1 family demonstrated that it is possible to engineer proteins with low allergenicity and high immunogenicity.<sup>63</sup> These allergens might possibly improve the safety of immunotherapy in the future, although development of allergen peptide immunotherapy, which follows a similar principle, has been hampered by marked late-phase adverse reactions (T cell mediated) without forewarning immediate reactions (IgE mediated).

**CONCLUSION**

The main publications in allergic upper airway diseases in the last year corroborate previous evidence that patients with allergic rhinitis can have a negative skin test response and might have impaired school performance. New innate immunity mediators and connective tissue markers have been implicated in the pathogenesis of CRS and T<sub>H</sub>2 mediators in the pathogenesis of VKC and GPC. Nasal olopatadine has recently become available for the treatment of allergic rhinitis (Table I). In allergen immunotherapy advances in 2007 include an update of the practice parameters, successful clinical trials of SLIT with multiple grass pollens, SLIT for atopic dermatitis, SLIT inducing T regulatory cells, and use of recombinant allergens both for skin testing and for decreasing IgE-mediated stimulation by allergens while maintaining the ability to modulate lymphocyte responses (Table II).<sup>50,51,54-56,59,61,63</sup>

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