

# Advances in upper airway diseases and allergen immunotherapy

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The purpose of this review is to highlight important articles on upper airway disease and immunotherapy that appeared in the *Journal of Allergy and Clinical Immunology* and elsewhere during 2005. In recent studies of tissue from patients with chronic hypertrophic eosinophilic sinusitis, increased leukotriene C<sub>4</sub> synthase and 5-lipoxygenase activity and increased levels of cysteinyl leukotriene production were demonstrated that correlated with disease severity but not with whether the patient was aspirin sensitive. However, the cysteinyl leukotriene 1 receptor was increased in leukocytes in the sinus tissue only in those patients with aspirin sensitivity. Major basic protein, released by eosinophils into the mucus in the paranasal sinus lumen, was found to reach concentrations capable of damaging the sinus epithelium, predisposing to bacterial infections. Testing the hypothesis that chronic hypertrophic eosinophilic sinusitis represents a reaction to common fungi, a double-blind trial of intranasal instillation of amphotericin B was conducted. There were marginal but significant differences in favor of amphotericin B treatment for sinus mucosal thickening on the basis of computed tomography and the evidence of eosinophilic inflammation in the sinus mucus. The effectiveness of topical nasal corticosteroids for treatment of nasal polyps was confirmed in 2 large studies. Improvement in sleep quality and daytime drowsiness in patients with allergic rhinitis treated with nasal corticosteroids was reported to correlate with reduction in nasal obstruction. The statistical analysis behind studies that reported a decrease in asthma exacerbations with nasal corticosteroids or oral antihistamines has been questioned. It appears that the results of at least one of these studies are indeed too good to be true.

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Although caution is still indicated in administering immunotherapy to patients receiving  $\beta$ -adrenergic blocking agents, the prohibition might not be absolute. A study in patients with Hymenoptera sensitivity given venom immunotherapy revealed no increase in serious adverse reactions to venom injections and no greater incidence of reactions to insect stings in those taking  $\beta$ -blocking agents. Sublingual immunotherapy for 8 to 12 weeks in patients with hazelnut sensitivity significantly increased their tolerance to hazelnut in double-blind, placebo-controlled challenges while inducing increased IgG<sub>4</sub> and IL-10 levels, indicating induction of regulatory T cells. There were a number of articles in the *Journal of Allergy and Clinical Immunology* in 2005 that addressed the entity of chronic hypertrophic eosinophilic sinusitis. In addition, an update of the "Practice parameters on sinusitis" was published. The major focus in allergen immunotherapy continues to be sublingual administration. (*J Allergy Clin Immunol* 2006;117:1047-53.)

**Key words:** Sinusitis, rhinosinusitis, rhinitis, skin testing, allergen immunotherapy, sublingual immunotherapy, food immunotherapy

This article continues a series of annual reviews of articles published in the *Journal of Allergy and Clinical Immunology* that deal with upper airway diseases and allergen immunotherapy.<sup>1,2</sup> Relevant articles published in other journals are also reviewed.

## THE UPPER AIRWAY

Key advances in upper respiratory diseases are listed in [Table I](#).

### Sinusitis

An update of the "Practice parameters on the diagnosis and management of sinusitis" appeared in the December 2005 issue of the *Journal of Allergy and Clinical Immunology*,<sup>3</sup> accompanied by an editorial debate on whether *sinusitis* or *rhinosinusitis* was the most appropriate terminology. The update of the sinusitis parameters reflects new information and a changing understanding of the nature of chronic sinusitis that has evolved since the original practice parameters printed in 1998. The document includes an executive summary, a management algorithm, a list of summary statements, and a comprehensive discussion of each of these points. Although the parameters continue

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

1. Tissue from patients with rhinosinusitis demonstrated increased LTC<sub>4</sub> synthase and 5-lipoxygenase activity and increased levels of cysteinyl leukotriene production, which correlated with disease severity but not with whether the patient was aspirin sensitive. However, the CysLT<sub>1</sub> receptor was increased in tissue leukocytes only in those patients with aspirin sensitivity.
2. Major basic protein, released by eosinophils in the mucus in the paranasal sinus lumen, reaches concentrations capable of damaging the sinus epithelium, predisposing to bacterial infections.
3. Testing the hypothesis that chronic hypertrophic eosinophilic sinusitis represents a reaction to common fungi, a double-blind trial of intranasal instillation of amphotericin B was conducted. There were marginal but significant differences in favor of amphotericin B treatment for sinus mucosal thickening on the basis of computed tomographic scans and evidence of eosinophilic inflammation in the sinus mucus.
4. The effectiveness of topical nasal corticosteroids for treatment of nasal polyps was confirmed in 2 large studies.
5. Improvement in sleep quality and daytime drowsiness in patients with allergic rhinitis treated with nasal corticosteroids correlates with reduction in nasal obstruction.
6. The statistical analysis behind studies that reported a decrease in asthma exacerbations with nasal corticosteroids or oral antihistamines has been questioned. It appears that the results of at least one of these studies were indeed too good to be true.

*Abbreviations used*

cysLT:	Cysteinyl leukotriene
IOP:	Intraocular pressure
LNIT:	Local nasal immunotherapy
LTC <sub>4</sub> :	Leukotriene C <sub>4</sub>
LTD <sub>4</sub> :	Leukotriene D <sub>4</sub>
LTE <sub>4</sub> :	Leukotriene E <sub>4</sub>
NCS:	Nasal corticosteroid
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy

to focus on infectious involvement of the paranasal sinuses and its treatment, they now acknowledge the presence of a noninfectious form of chronic sinusitis sometimes termed *chronic hyperplastic eosinophilic sinusitis* and often associated with nasal polyps, asthma, and aspirin sensitivity.

Exception to the continued use of the term *sinusitis* as opposed to *rhinosinusitis* was based on the fact that sinusitis in the absence of rhinitis was very uncommon and that the term *rhinosinusitis* is widely used and should be adopted universally to avoid confusion.<sup>4</sup> The opposing arguments in favor of the continued use of *sinusitis* instead of *rhinosinusitis* were summarized in an article entitled, "Maybe rhinitis, maybe sinusitis, maybe rhinitis and sinusitis, but certainly not rhinosinusitis!"<sup>5</sup> These include that there are no agreed-on diagnostic criteria for chronic sinusitis, the symptoms used to make the diagnosis are nonspecific, and many symptoms, such as rhinorrhea and stuffiness, arise from the nasal passages and not the sinus cavities, whereas so-called sinus headaches are more often migraine in origin. However, the biggest problem with the adoption of the term *rhinosinusitis* is that rhinitis and sinusitis are different diseases developing in different organs, and they require different treatments. Failure to accurately diagnose sinusitis can lead to unnecessary use of antibiotics and surgery.<sup>5</sup>

Some of the issues raised in the editorial opposing the use of the term *rhinosinusitis* are evident in an article comparing treatment of acute rhinosinusitis with either

mometasone furoate nasal spray (once or twice daily), amoxicillin, or placebo.<sup>6</sup> The 981 subjects, approximately one quarter of whom had perennial rhinitis, were required to have signs and symptoms of acute rhinosinusitis for at least 7 days but no signs of fulminant bacterial rhinosinusitis. Treatment with mometasone was continued for 15 days, and amoxicillin was continued for 10 days. Mometasone nasal spray administered twice daily was significantly superior to placebo and amoxicillin in reduction of the major symptom score, but the effectiveness was much greater for rhinorrhea ( $P \leq .001$ ) and nasal congestion ( $P \leq .001$ ) than for sinus headache ( $P \leq .01$ ) or facial pain-pressure ( $P \leq .05$ ), whereas mometasone nasal spray once daily showed superiority over placebo only for rhinorrhea and nasal congestion. Amoxicillin was marginally superior to placebo for rhinorrhea, nasal congestion, and cough. Although the study clearly showed superiority for mometasone over amoxicillin in treatment of this illness, it does leave a question as to whether the effect was primarily on rhinitis or rhinosinusitis.

Tissue eicosanoid production was compared with that seen in healthy subjects in 3 groups of patients with chronic rhinosinusitis, those without nasal polyps and those with nasal polyps with and without aspirin sensitivity.<sup>7</sup> Leukotriene C<sub>4</sub> (LTC<sub>4</sub>) synthase and 5-lipoxygenase mRNA and LTC<sub>4</sub>, leukotriene D<sub>4</sub> (LTD<sub>4</sub>), and leukotriene E<sub>4</sub> (LTE<sub>4</sub>) concentrations increased with disease severity among all patient groups. It was concluded that changes of tissue eicosanoid metabolism occur in chronic rhinosinusitis, even in the absence of clinical aspirin sensitivity, and these changes appeared to be related to the severity of eosinophilic inflammation. In a related study, the presence of the 2 cysteinyl leukotriene (cysLT) receptors, CysLT<sub>1</sub> and CysLT<sub>2</sub>, was studied in nasal biopsy specimens from 32 subjects with chronic rhinosinusitis and nasal polyps with and without aspirin sensitivity and in 9 healthy control subjects.<sup>8</sup> The percentage of mucosal leukocytes expressing the CysLT<sub>1</sub> receptor was increased only in aspirin-sensitive patients, whereas the percentage of leukocytes expressing the CysLT<sub>2</sub> receptor did not differ among the 3 groups. CysLT<sub>2</sub> receptor expression predominated on epithelial and glandular cells but here

too did not differ among the 3 groups. This latter finding has potentially important therapeutic implications.<sup>8</sup>

The role of the eosinophil and its major basic protein was further examined in patients with chronic rhinosinusitis.<sup>9</sup> Tissue from 22 consecutive patients undergoing endoscopic sinus surgery revealed the presence of eosinophils. The attached mucus revealed clusters of eosinophils with free major basic protein in concentrations that far exceeded those needed to damage epithelium from the luminal side. It was believed that this damage could then predispose patients with chronic rhinosinusitis to secondary bacterial infections.<sup>9</sup>

The basis for the eosinophilic inflammation in chronic rhinosinusitis is unknown. Although antibiotics might have a role in the short-term treatment of acute bacterial exacerbations in these patients, there are no reports that they affect long-term prognosis or prevalence of the disease.<sup>10</sup> It has been proposed that one stimulus for the eosinophilic inflammation is a unique immunologic response to ubiquitous fungi that are found in the eosinophilic mucin in the sinuses in 80% to 100% of patients undergoing surgery for chronic rhinosinusitis.<sup>10</sup> Two uncontrolled trials of intranasal administration of antifungal agents had reported improvement, and therefore a 6-month, randomized, double-blind, placebo-controlled trial of intranasal amphotericin B was undertaken in patients with chronic rhinosinusitis. In the 24 subjects completing the study, those receiving amphotericin B achieved a relative reduction in the percentage of mucosal thickening on computed tomographic scans compared with those receiving placebo ( $P = .03$ ). There was significantly greater reduction in intranasal mucus levels of eosinophil-derived neurotoxin and a trend toward lower levels of IL-5 in the amphotericin B-treated subjects ( $P = .046$  and  $P = .082$ , respectively). All the findings suggested decreased levels of eosinophilic inflammation in the actively treated subjects. An accompanying editorial cautions, however, that although significant differences were seen, they were small, and their overall clinical significance was not clear.<sup>11</sup> In view of the small number of subjects involved in the study, this should be, as the authors entitled it, a pilot study. The role of topical amphotericin treatment for chronic rhinosinusitis will be established only when large-scale, multicenter, placebo-controlled, double-blind studies have been performed.<sup>11</sup>

### Nasal polyps

Nasal polyps are a frequent complication of chronic hypertrophic eosinophilic sinusitis. They can be treated with surgical removal or systemic steroids, although there is a high rate of recurrence. Intranasal corticosteroid sprays have been reported to decrease polyp volume and improve symptom scores and peak nasal inspiratory flows. Nasal corticosteroid (NCS) drops might more effectively deliver medication to the middle meatus, from which the nasal polyps arise, than corticosteroid sprays.<sup>12</sup> A double-blind, placebo-controlled study was undertaken in 54 patients scheduled for endoscopic sinus surgery to assess whether treatment with fluticasone nasal drops could reduce the need for surgery. The fluticasone drops were

instilled into the nose once daily, with the subject lying on his or her back with his or her head hanging over the edge of the bed at a vertical angle. When reassessed after 12 weeks, 13 of 27 patients treated with fluticasone and 6 of 27 treated with placebo no longer required endoscopic surgery ( $P < .05$ ). There also were greater reductions in symptoms of obstruction, rhinorrhea, postnasal drip, and loss of smell in the fluticasone group.

The effectiveness of NCS sprays for treatment of nasal polyps was confirmed in a 4-month, double-blind comparison of placebo and mometasone nasal spray administered once or twice daily in 354 subjects.<sup>13</sup> Mometasone, particularly when administered twice daily, was markedly more effective than placebo ( $P < .001$ ) in reducing polyp size, congestion-obstruction, rhinorrhea, and postnasal drip and in improving the loss of smell. The authors suggest that in view of its effectiveness, mometasone nasal spray might reduce or delay the need for surgery.

### Rhinitis treatment

Levocetirizine, the active enantiomer of cetirizine, is approved for use in allergic rhinitis and urticaria in Europe and is undergoing study in the United States. In adults it has been shown to have a duration of action exceeding 24 hours. Because the rate of metabolism might differ with age, a study was performed in children 6 to 11 years of age using suppression of the wheal-and-flare skin test to histamine to gauge duration of action after a single 5-mg dose.<sup>12</sup> The mean maximum inhibition of the wheal ( $97\% \pm 1\%$ ) occurred from 2 to 10 hours, and the maximum inhibition of the flare ( $93\% \pm 1\%$ ) occurred from 2 to 24 hours. Levocetirizine provided significant antihistamine activity from 1 to 28 hours, and hence once daily dosing is appropriate in children.<sup>14</sup>

Allergic rhinitis is associated with impaired sleep quality and symptoms of daytime sleepiness.<sup>15</sup> It is not clear whether this effect on sleep is due to the associated nasal obstruction or release of inflammatory mediators. The results of 3 studies of nasal steroids in subjects with nasal obstruction and daytime somnolence, fatigue, or both were combined for analysis to test the hypothesis that reduction in nasal obstruction would correlate with improvement in sleep quality and daytime drowsiness. Each of the 3 studies showed improved sleep and daytime somnolence-fatigue in those receiving NCSs. With the pooled data, there was a significant ( $P < .01$ ) correlation between the reduction in nasal congestion and improvement of sleep and daytime somnolence.

A possible adverse effect of intranasal corticosteroids was reported from an eye institute.<sup>16</sup> In a retrospective study, 12 subjects using NCSs were identified who had had intraocular pressure (IOP) measured before introduction of NCSs. IOP was determined while they were still using nasal steroids and twice after discontinuation. The mean IOP was 15.4 mm Hg for the presteroid examination, 18.0 mm Hg for the examination during steroid use, and 14.5 mm Hg and 14.8 mm Hg for examinations after steroid discontinuation. Both the increase in IOP

with nasal steroids and the decrease after discontinuation were significant ( $P = .007$  and  $P < .001$ , respectively).

Two new potential therapies for seasonal allergic rhinitis were reported. Syk kinase is a transducer of signaling through the FcεRI receptor on mast cells.<sup>17</sup> A compound, R112, designed to inhibit Syk kinase was tested in a park study in subjects with allergic rhinitis who were sensitive to grass. After 2 hours of observation, qualifying subjects were randomized to nasal sprays of R112 or vehicle at 10 AM and 2 PM, with observation until 6 PM. R112 reduced the total nasal symptom score by 7 from a baseline of 18 compared with a reduction of 5.4 for placebo ( $P = .0005$ ), with an onset of action by 45 minutes. There were no significant adverse effects.

A quite different approach was the use of rhinophototherapy for treatment of seasonal allergic rhinitis.<sup>18</sup> The active therapy consisted of a mix of 5% UV-B, 25% UV-A, and 70% visible light, and the placebo consisted of visible light alone. Treatment was administered 3 times weekly for 3 weeks during the ragweed season. Active treatment was significantly more effective than placebo ( $P = .004$ ) and was accompanied by significant reductions not seen in control subjects in eosinophil counts, eosinophil cationic protein levels, and IL-5 levels in nasal lavage fluid. Further support for the activity of the phototherapy was the *in vitro* demonstration of a dose-dependent induction of apoptosis in lymphocytes and eosinophils and inhibition of mediator release from rat basophil leukemia cells.

Several retrospective analyses have suggested that nasal treatment with corticosteroids and, to a lesser extent, with antihistamines had a beneficial effect on asthma in the form of reduction in exacerbations. The statistical method used to reach this conclusion in one of these studies was reexamined.<sup>19</sup> It was demonstrated that the approach used in that study produced results that were both predictable and incorrect. In the approach used each subject who received an NCS was considered exposed for the entire time analyzed, even though they might not have received the prescription until some time had passed. If an exacerbation had occurred during the interval before the NCS prescription, the subject would not have received an NCS and would have been assigned to the non-NCS group. This introduced a predictable bias in favor of NCS use.

Although they are too brief to examine exacerbations, 2 studies published this year add a note of caution concerning the beneficial effect of nasal therapy on asthma. Treatment with nasal fluticasone, inhaled fluticasone, their combination, or placebo was compared in 262 subjects with pollen-induced rhinitis and asthma.<sup>20</sup> Nasal fluticasone significantly improved nasal symptoms compared with inhaled fluticasone or placebo; however, only inhaled fluticasone improved pulmonary function, methacholine sensitivity, or sputum eosinophilia. In the second study nasal fluticasone, oral montelukast, and placebo were compared during seasonal allergic rhinitis in patients whose asthma was incompletely controlled with a fluticasone-salmeterol combination (100/50).<sup>21</sup> Over 2 weeks of treatment, fluticasone reduced nasal symptoms about 17% more than placebo, whereas montelukast improved nasal

symptoms 6% more than placebo. Neither active drug was more effective than placebo in reducing asthma symptoms or asthma rescue medication requirements.

Factors associated with the occurrence of allergic rhinitis were examined in several articles. A cross-sectional study examined the relationship between dietary soy products and allergic rhinitis in 1002 pregnant Japanese women.<sup>22</sup> A high intake of soy and soy-derived isoflavones was associated with a reduced prevalence of allergic rhinitis. Japanese investigators also reported that genetic variations in a haplotype block spanning the SDA1 domain containing 1 and CXC chemokine genes on 4q21 might contribute to the development of seasonal allergic rhinitis in the Japanese population.<sup>23</sup> An examination of nasal biopsy tissue from subjects with allergic rhinitis (most with sensitivity to perennial allergens) revealed a significantly increased frequency of IgE and IgA V<sub>H</sub>5 transcripts.<sup>24</sup> The results provided evidence for the activity of a superantigen in the nasal mucosa in patients with allergic rhinitis. The identity of this superantigen was not determined, but a *Staphylococcus* species source was suggested as a possibility.<sup>23</sup>

### Ocular allergy

The January 2005 issue of the Journal contained a review entitled "Allergic conjunctivitis: update on pathophysiology and prospects for future treatment."<sup>25</sup> The article pointed out that 98% of ocular allergy is represented by seasonal and perennial allergic conjunctivitis. The ocular inflammation is usually mast cell driven and therefore is ideally treated with drugs that are a combination antihistamine–mast cell stabilizer. For the more severe ocular allergies, vernal and atopic keratoconjunctivitis, treatment is less satisfactory, but new approaches are under development on the basis of recent progress in understanding these diseases.

## SKIN TESTING AND IMMUNOTHERAPY

Key advances in skin testing and allergen immunotherapy are listed in [Table II](#).

### Skin testing

The Immunotherapy Committee of the American Academy of Allergy, Asthma and Immunology sponsored a study comparing 8 different skin prick–puncture devices (4 single-head devices and 4 multihead devices).<sup>26</sup> As in previous assessments of skin prick test devices, considerable variation in the size of reactions to histamine among devices was observed. Reactions of larger than 3 mm to saline were uncommon, but wheal responses of less than 3 mm to 10 mg/mL histamine were disturbingly common (1% to 4% for the single-head devices and 3% to 22% for the multihead devices). This article reemphasizes the need to assess the performance of a technician and device with blinded histamine and saline tests before accepting the results of skin testing in allergy diagnosis.

**TABLE II.** Key advances in skin testing and allergen immunotherapy

1. The reactions to histamine and saline were assessed with 8 skin prick test devices. Wheal reactions of less than 3 mm with histamine were disturbingly common, especially with multihead devices. This emphasizes the need to assess the performance of both technician and device before accepting the results of skin testing in the allergic patient.
2. Initiation of immunotherapy to house dust mites with a cluster regimen achieved symptom improvement more rapidly than with a conventional build-up, without an increase in adverse reactions.
3. Although caution is still indicated in administering immunotherapy to patients taking  $\beta$ -adrenergic blocking agents, the prohibition might not be absolute. A study in patients with Hymenoptera sensitivity who were administered venom immunotherapy revealed no increase in serious adverse reactions and no greater incidence of reactions to insect stings in those receiving  $\beta$ -blocking agents.
4. In a large study in children conducted in Italy, persistence with a 3-year course of injection immunotherapy (89.1%) was significantly better than with SLIT (78.5%).
5. SLIT for 8 to 12 weeks in patients with hazelnut sensitivity significantly increased their tolerance to hazelnut by double-blind placebo-controlled challenge while inducing increased IgG<sub>4</sub> and IL-10 levels.
6. In a double-blind, placebo-controlled study subjects with grass allergy were treated with a mixture of 5 recombinant allergens of timothy grass. Those receiving active treatment had decreased symptoms, increased quality of life, increased IgG<sub>4</sub> levels, and decreased IgE levels.

### Injection immunotherapy

Initiating allergen immunotherapy with a cluster approach is attractive because it can achieve maintenance injections and likely clinical response more rapidly than the conventional weekly build-up schedule. A biologically standardized depot extract of *Dermatophagoides pteronyssinus* was administered on either a 6-week cluster or 12-week conventional schedule in a double-blind, placebo-controlled study.<sup>27</sup> There was no difference in the rate of systemic reactions; however, the cluster regimen achieved decreased rhinitis and asthma symptoms 6 weeks earlier than the conventional schedule. Thus in this study use of a cluster regimen achieved more rapid clinical and immunologic improvements, with no increase in systemic reactions.<sup>27</sup>

In Northern Italy, where short, but not giant, ragweed has invaded, it was observed that patients treated with immunotherapy with giant ragweed often failed to obtain clinical benefit.<sup>28</sup> Skin prick testing revealed that patients generally reacted more to short than giant ragweed extract, and 15% reacted only to short ragweed. Immunoblots with and without preabsorption revealed significant differences between the 2 ragweed extracts. It was recommended that immunotherapy should be performed with ragweed species present in that specific geographic area.

Administration of allergen immunotherapy to patients receiving  $\beta$ -adrenergic blockers has been considered contraindicated because the  $\beta$ -blocker is capable of aggravating anaphylactic reactions and also of interfering with treatment of the reaction. However, Hymenoptera venom immunotherapy is potentially life saving in sensitized patients. Therefore the risk of venom immunotherapy in patients receiving  $\beta$ -blockers was assessed.<sup>29</sup> Of 1389 patients in whom venom immunotherapy was recommended, 44 were receiving  $\beta$ -blockers. In 31 patients the drug could be replaced with one of another class. In 9 patients it was discontinued during build-up only, and in 4 patients it was continued throughout the build-up period. In 12 additional patients  $\beta$ -blockers were initiated during venom immunotherapy. In these 25 patients there was no increase in the incidence of allergic reactions to

the injections or to re-stings, and no severe reactions occurred in the patients undergoing  $\beta$ -blockade. The authors conclude that immunotherapy can be given to patients undergoing  $\beta$ -blockade who have severe cardiovascular disease and heavy exposure to the insect to which they are sensitized.

### Sublingual immunotherapy

Seventy-nine adults with rhinitis and asthma who were monosensitized to birch were observed through one season and then randomly assigned to either continue on drug therapy or to combine drug therapy with sublingual immunotherapy (SLIT) to birch.<sup>30</sup> Treatment was continued for 3 years, with a cumulative dose about 12 times greater than the subcutaneous dose. The subjects were followed through 4 birch pollen seasons. Significant improvements in symptoms and methacholine sensitivity were seen beginning in the first pollen season with treatment, and significant improvements in medication use, pulmonary function, and nasal eosinophil counts began in the second season of treatment. All improvements relative to the observational group became greater with each year of observation.

Twenty-three subjects with a history of hazelnut allergy, positive skin prick test responses to hazelnut, and a positive double-blind oral hazelnut challenge result were randomly assigned to receive sublingual immunotherapy (SLIT) with either hazelnut extract or placebo.<sup>31</sup> Build-up was achieved over 4 days in a hospital outpatient setting, followed by 8 to 12 weeks of maintenance dosing at home. Systemic reactions were observed in only 0.2% of doses administered. The mean dose of hazelnut tolerated in subsequent double-blind oral challenges increased from 2.29 g to 11.56 g ( $P = .02$ ) in the active group versus 3.49 g to 4.14 g in the placebo group (not significant). Laboratory assessment showed an increase in IgG<sub>4</sub> and IL-10 levels only in the active group.

A survey from Italy assessed persistence of immunotherapy by 2774 children prescribed a 3-year treatment program either in a hospital or private practice setting.<sup>32</sup> The percentage of children prematurely discontinuing treatment was 10.9% for injections (subcutaneous immunotherapy [SCIT]), 21.5% for sublingual treatment

(SLIT), and 73.2% for local nasal immunotherapy (LNIT). Most discontinued after the first year except in the case of patients receiving LNIT, where more discontinued in the first 12 months because of nasal side effects. Of those discontinuing SCIT, 39.6% discontinued because of cost, 12.0% because it was ineffective, and 8.7% because it was unpleasant. The corresponding percentages for those discontinuing SLIT were 36.4% because of expense, 24.9% because it was ineffective, and 5.8% because it was unpleasant. The authors concluded that SCIT is to be considered to date the most suitable form of immunotherapy in children and adolescents. SLIT, however, is well accepted by more than three quarters of the patients.

### New approaches

Recombinant DNA technology offers the possibility of pure and reproducible products for allergy diagnosis and treatment. A double-blind, placebo-controlled test of this approach was conducted with a mixture of 5 recombinant grass pollen allergens in the treatment of patients with grass pollen-induced rhinoconjunctivitis with or without asthma.<sup>33</sup> Subjects receiving the recombinant allergens had significant improvement in symptoms, medication use, and quality of life compared with those receiving placebo, accompanied by promotion of IgG<sub>4</sub> and reduction in the IgE response consistent with the induction of IL-10-producing regulatory T cells. A double-blind, placebo-controlled injection immunotherapy study was also conducted with genetically modified derivatives of the major birch pollen allergen Bet v 1 (Bet v 1 trimer and Bet v 1 fragments), both with reduced allergenicity.<sup>34</sup> In a subset of the patients, studies were performed on serum and nasal secretions obtained before and up to 1 year after vaccination was started. Vaccination with the genetically modified Bet v 1 derivative induced Bet v 1-specific IgG<sub>1</sub>, IgG<sub>2</sub>, and IgG<sub>4</sub>, antibodies and low levels of IgA. The levels of IgG<sub>4</sub> in the nasal secretions were significantly ( $P < .05$ ) associated with reduced nasal sensitivity to natural Bet v 1, as objectively determined by using controlled nasal challenge.

Additional reports of recombinant DNA engineering have appeared in the Journal during the last year. A single hybrid molecule was constructed that contained 4 major allergens of timothy grass.<sup>35</sup> The hybrid could be used to diagnose allergy in 98% of subjects with grass pollen allergy. When used for immunization of mice and rabbits, it induced stronger and earlier IgG antibody responses than equimolar mixtures of the component allergens. The antibodies induced by vaccination blocked the immediate allergic reaction in the rat basophil degranulation assay. A fusion protein containing 2 major bee venom allergens, phospholipase A<sub>2</sub> and hyaluronidase, was constructed.<sup>36</sup> The fusion protein induced T-cell proliferation, whereas IgE reactivity was abolished and basophil degranulation and type 1 skin test reactivity were profoundly reduced. Pretreatment of mice with the fusion protein significantly suppressed the development of specific IgE and other antibody isotypes after immunization with the native allergens. In a mouse model of polysensitization

to timothy and birch, the ability to block sensitization by means of intranasal administration of a mixture of rBet v 1, rPhl p 1, and rPhl p 5 or allergen-immunodominant peptides applied either as a mixture or as a synthetic hybrid peptide was compared.<sup>37</sup> Application of complete allergen molecules did not prevent polysensitization to the same allergens. In contrast, pretreatment with a mixture of the immunodominant peptides or the hybrid peptide led to significantly reduced allergen-specific IgE responses, IL-4 production, and suppressed airway inflammation. The study thus demonstrated it is possible to suppress allergic immune responses simultaneously to several clinically important allergens.

### CONCLUSIONS

Articles published this year highlighted advances in the understanding of chronic hypertrophic eosinophilic sinusitis. Studies assessed the immunologic basis, the differences in those sensitive to aspirin, and the response to conventional and unconventional therapies. The updated practice parameter on sinusitis was published in the Journal. Articles addressed the devices used for skin prick testing, assessed the tolerance of and time to clinical improvement with cluster compared with conventional build-up of immunotherapy, and evaluated the safety of venom immunotherapy in patients receiving  $\beta$ -adrenergic blocking agents, compliance with immunotherapy through different routes of administration, and the safety and effectiveness of SLIT in patients sensitive to hazelnuts.

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