
Clinical efficacy of microencapsulated timothy grass pollen extract in grass-allergic individuals

Elizabeth C. TePas, MD; Elisabeth G. Hoyte, MSN; Jennifer J. McIntire, PhD; and Dale T. Umetsu, MD, PhD

Background: Conventional allergen immunotherapy is clinically effective in reducing the symptoms of allergic rhinitis and asthma. It differs from other pharmacotherapies in that it can induce long-term clinical remission of these diseases. However, it requires years of treatment and is associated with serious allergic reactions.

Objective: To evaluate the safety, clinical efficacy, and immunologic mechanisms of immunotherapy with an oral, microencapsulated form of timothy grass allergen.

Methods: In this double-blind, placebo-controlled study, 24 patients aged 19 to 55 years with grass pollen allergy were randomized to receive either microencapsulated timothy grass pollen extract or placebo once a day for 10 weeks. The dose of study drug was doubled weekly. Safety was evaluated through weekly visits, daily symptom diaries, and routine laboratory tests. Efficacy was evaluated by comparing medication use and symptoms scores during peak grass pollen season before and after treatment. Allergen-specific T-cell responses, cytokine production, and IgG, IgE, and skin reactivity were measured to evaluate immunologic mechanisms.

Results: Eleven of 12 patients in the active treatment group had a decrease in the combined medication and symptom score, but only 4 of 10 patients in the placebo group had a decrease in scores. The proliferative response to timothy grass was reduced by at least 30% in 9 of the 12 grass-treated patients, but only 3 of 11 placebo patients had a proliferative response reduction. Timothy grass-induced interleukin-5 messenger RNA was reduced in the active group, but not in the placebo group. There were no significant changes in either group in IgG, IgE, and skin reactivity.

Conclusions: Oral immunotherapy with microencapsulated allergen induces a form of immunologic tolerance to the allergen and is a safe, efficient, and effective method of allergen immunotherapy.

Ann Allergy Asthma Immunol. 2004;92:25–31.

INTRODUCTION

The prevalence of asthma and allergic rhinitis has increased significantly during the past 2 decades, and this trend is likely to continue in the decades to come.^{1–3} Current pharmacotherapy for these allergic diseases focuses primarily on the relief and prevention of symptoms rather than on altering the underlying disease processes. In contrast, long-term clinical remission of these disorders can be achieved with the administration of conventional allergen immunotherapy, which is performed by the subcutaneous administration of increasing amounts of allergen.⁴ With traditional subcutaneous immunotherapy, T_H2-biased allergic immune responses are replaced with protective, allergen-specific immunity.^{5,6} In children, allergen immunotherapy may prevent the progressions from monosensitization to polysensitization⁷ and from allergic rhinitis to asthma.⁸ However, because conventional allergen immunotherapy is time-consuming, painful, and associated with serious allergic reactions, it is not as widely used as other pharmacotherapies, such as antihistamines and nasal steroids.

The purpose of this study was to evaluate the safety, clinical efficacy, and immunologic mechanisms of a novel method of immunotherapy, developed by Allergenes Inc, South San Francisco, CA, in which allergen is administered orally, microencapsulated in enteric-coated beads that bypass the stomach and deliver the antigen to the small intestine in a highly immunogenic form.^{9–11} Oral exposure to antigen is known to induce antigen-specific suppression of cellular and/or humoral immune responses and even inhibit the development of airway hyperreactivity in mice in a process called oral tolerance.^{12,13} Oral administration of allergen has been used to desensitize patients with allergy to antibiotics and other medications.^{14,15} Sublingual administration of allergen reduced symptoms in patients with allergic rhinitis, but high doses of allergen and long periods of treatment were required to achieve clinical benefits.^{16,17} By using a microencapsulated form of timothy grass allergen, which is not degraded in the stomach, we were able to use much lower doses of allergen (similar to subcutaneous immunotherapy). This was administered in a double-blind, placebo-controlled fashion in patients with grass pollen allergy.

METHODS

Participants and Study Design

Twenty-four patients, aged 19 to 55 years, were enrolled from July to October 2000. Entry criteria included a minimum

Division of Immunology and Allergy, Department of Pediatrics, Stanford University, Stanford, California.

This study was supported by the Glaxo Wellcome Allergy Fellowship Award, the AAAAI/GlaxoSmithKline Respiratory Diseases Research Award, and funding and technical assistance from Allergenes Inc.

Received for publication June 4, 2003.

Accepted for publication in revised form August 27, 2003.

2-year history of seasonal allergic rhinitis attributed to grass pollen, a positive skin prick test result to standardized timothy grass pollen extract, and a 3-fold dilution number for the sum of erythema of 50 mm (D_{50}) for intradermal timothy grass extract of between greater than or equal to 9 and less than or equal to 18 as determined by the Center for Biologics Evaluation and Research (US Food and Drug Administration) D_{50} intradermal skin test method. Patients were excluded if they had moderate-to-severe persistent asthma or a history of allergen immunotherapy with grass pollen extracts in the prior year. The study was performed with the approval of the Stanford Investigation Review Board and was performed under the auspices of the Food and Drug Administration. All study patients gave written, informed consent.

The study was performed as a phase 1/2, double-blind, placebo-controlled trial with an ascending dose and parallel design. Subjects were randomized 1:1 to receive capsules containing microencapsulated timothy grass pollen extract or placebo capsules containing either sucrose and starch or microbeads (Allergenic Inc) once a day for 10 weeks. All patients began dosing at least 1 month after the peak grass pollen season (range, 1–4 months). The dose of study drug was doubled weekly, ranging from 12.5 bioequivalent allergy units (BAU) at the start to 6,400 BAU at completion (week 1, 12.5 BAU in 1 capsule; week 2, 25 BAU in 2 capsules; week 3, 50 BAU in 1 capsule; week 4, 100 BAU in 2 capsules; week 5, 200 BAU in 1 capsule; week 6, 400 BAU in 2 capsules; week 7, 800 BAU in 1 capsule; week 8, 1,600 BAU in 1 capsule; week 9, 3,200 BAU in 2 capsules; and week 10, 6,400 BAU in 4 capsules). Patients were required to fast for at least 2 hours before and 1 hour after taking the study drug. They were observed for reactions for 2 hours in the General Clinical Research Center at Stanford University Hospital after receiving the first dosage at each of the 10 dose levels.

Allergen Preparation

Standardized, lyophilized timothy grass pollen was prepared by Greer Laboratories (Lenoir, NC). The microencapsulation process has been described in detail in previous studies.¹⁰ In brief, the nonpareil microspheres were first coated with allergen and then an outer core of water-soluble enteric coating, which provided the pH-dependent release properties to the microbead. Acid resistance of the microbeads was confirmed, as was release of intact timothy grass pollen allergen at a pH greater than 6 (by radioallergosorbent test inhibition, enzyme-linked immunosorbent assay inhibition, and isoelectric focusing patterns; data not shown). The 200-BAU capsules contained 0.438 g of standardized timothy grass pollen extract.

Clinical Assessments

Safety was evaluated by recording daily allergic and gastrointestinal symptoms during the 10-week study period in patient diaries. Patients were given 10 mg of loratadine (Claritin, Schering Corporation, Kenilworth, NJ) and 0.3 mg of epinephrine (Epi-Pen, Dey, Napa, CA) as rescue medications. Symptoms reported at each weekly visit were also recorded.

Peak expiratory flow rate measurements were taken 3 times a day: just before dosing, 2 hours after dosing, and at bedtime. Routine laboratory tests, including complete blood cell count, urinalysis, serum chemical analyses, and a pregnancy test (for women of child-bearing age), were performed at baseline (screening) and week 11 (end dosing).

Clinical efficacy was measured by monthly symptom and medication scores. Symptoms included sneezing; other nasal symptoms (eg, congestion, rhinorrhea, and nasal itching); itchy, watery, or red eyes; palatal pruritus; and wheezing or chest tightness. Each symptom was scored on a 4-point scale (0, none; 1, mild; 2, moderate; and 3, severe). The maximum symptom score per month was 15. Each allergy or asthma medication was scored 1 point for each day of use (assuming a standard dosage), with a maximum total score of 30 per month for each medication. Patients were allowed to use any prescription or over-the-counter allergy and asthma medications during the grass pollen season. Monthly symptom and medication use data were gathered by recall for the pretreatment season, because patients were not enrolled in the study until after the completion of the peak grass pollen season in 2000. Since the pretreatment data were based on recall, we believed that a more valid comparison could be made if the post-treatment data were obtained in the same manner. Therefore, post-treatment peak grass pollen season symptom and medication use data were also gathered by recall several months after the peak season. Peak grass pollen seasons were determined by analyzing pollen counts obtained via a Burkard sampler for the months of April, May, and June in 2000 and 2001 (counts courtesy of Theodore Chu, MD, Los Altos, CA). Sampling was performed for 24 hours on a daily-to-weekly basis at a single site. In the San Francisco Bay Area, there is significant variability in both the daily grass pollen counts during the peak season and the pollen counts between cities on the same day due to the numerous microclimates. Comparing monthly medication and symptom scores would diminish the impact of this variability.

Skin prick testing was performed with timothy, Bermuda, and rye grass pollens and dust mite mix extracts in glycerin (Greer Laboratories). The prick tests were performed on the flexor aspect of the forearm with bifurcated needles (Allergy Labs of Ohio, Columbus, OH). Glycerin saline was used as a negative control and histamine (1.8 and 0.1 mg/mL) as a positive control. The prick test response was evaluated at 15 minutes by measuring and summing the longest and orthogonal diameters of erythema (ΣE) and wheal (ΣW). The D_{50} intradermal skin test to timothy grass was performed using the method favored by the Center for Biologics Evaluation and Research to evaluate the relative potency and compositional differences of allergenic extracts. Serial 3-fold dilutions were made from undiluted allergen extract, with the first dilution from concentrate designated as 1, the second as 2, and so on; 0.05 mL of diluted extract was injected intradermally into the forearm. After 15 minutes, the ΣE and ΣW were measured. Four serial 3-fold dilutions with graded erythema responses, which bracket an ΣE of 50 mm and an end

point ΣE of 0 or $\Sigma E \sim \Sigma W$, were plotted to generate the dose response line (y-axis = ΣE , x-axis = serial 3-fold dilution). The point where the slope of the dose response line intersects with the ΣE of 50 mm was found and the corresponding D_{50} value determined. Both skin tests were performed at baseline and end-dosing visits.

Immunologic Assays

Timothy grass pollen specific IgG (total IgG, IgG1, and IgG4) and timothy grass pollen specific IgE were measured at baseline and end-dosing visits by the Pharmacia CAP System Specific Fluorezyme Immunoassay (Pharmacia Diagnostics, Uppsala, Sweden) at IBT Reference Laboratory (Lenexa, KS). IgG and IgE specific for timothy grass pollen were also measured at weeks 5 and 15 (4-week follow-up).

To evaluate T-cell immune response to timothy grass, Bermuda grass, and dust mite allergens, lymphocyte proliferation assays were performed at baseline and week 15. Blood was collected in heparinized syringes and leukocytes isolated by flotation over Ficoll-Hypaque gradients. Cells were washed 3 times with phosphate-buffered saline and then resuspended in complete Dulbecco modified Eagle medium (1×10^6 cells/mL). Cells (2×10^5 cells/well) were plated in a 96-well culture plate and stimulated with timothy, Bermuda, or dust mite (Der f) antigens (31 and 125 $\mu\text{g/mL}$ for timothy, 125 and 500 $\mu\text{g/mL}$ for Bermuda, and 0.5 $\mu\text{g/mL}$ for dust mite) in triplicate. The same lyophilized timothy grass allergen that was used in the microencapsulated pills was also used for the proliferation assays. Bermuda and timothy grass allergens have low allergenic cross-reactivity. Bermuda grass and dust mite were chosen as controls to evaluate the specificity of the therapy. Tetanus toxoid (1 $\mu\text{g/mL}$) was used as a positive control antigen, and unstimulated cells were used as the negative control for the assay. On day 5 cells were pulsed with 1 $\mu\text{Ci/well}$ of [^3H]-thymidine. After an 18-hour incubation, the cells were harvested and incorporated radioactivity was determined. Because the study was performed over the course of several months and the absolute amount of [^3H]-thymidine incorporated depended on

variables such as the absolute number of CD4^+ cells cultured and length of stimulation and pulsing with [^3H]-thymidine, the proliferative responses to timothy grass, Bermuda grass, and dust mite were normalized to that for tetanus toxoid.

Cytokine production was also evaluated at baseline and week 15. Peripheral blood mononuclear cells (PBMCs) were collected and processed as described herein. Cells were plated in a 24-well plate (2×10^6 cells/well) and stimulated for 6 days with timothy, Bermuda, and dust mite antigens at the same concentrations, with unstimulated cells serving as the negative control. Cells were restimulated with phytohemagglutinin and phorbol myristate acetate on day 7 to maximize cytokine production,^{5,18} harvested 6 hours later, and messenger RNA (mRNA) purified. Levels of cytokine mRNA were evaluated with the Riboquant Multi-Probe Ribonuclease Protection Assay System (PharMingen, San Diego, CA), which included probes for interleukin (IL)-2, IL-4, IL-5, IL-9, IL-10, IL-13, IL-15, interferon- γ , and the housekeeping genes *GAPDH* and *L32*.

Statistical Analysis

Patient demography, sex, and race were analyzed by the χ^2 test, and the *t* test was used for age, wheal diameter, and D_{50} . These tests were performed to verify that randomization was effective. The active and placebo groups were compared before treatment and were not found to differ significantly ($P = .50$, 2-sided *t* test). Therefore, the Wilcoxon signed-rank test was used to analyze medication and symptom scores after treatment in both the active and placebo groups. The Fisher exact test was used to analyze lymphocyte proliferative responses, and the 2-tailed *z*-test was used to evaluate the cytokine data.

RESULTS

Baseline Characteristics and Participants

Twenty-four grass allergic patients were enrolled in this double-blind, placebo-controlled trial of encapsulated timothy grass allergen. The 2 treatment groups did not differ with

Table 1. Patient Demographics

Characteristic	Active group	Placebo group	P value*
Sex, M/F	5/7	4/8	.67
Age, median (range), years	31 (19–55)	30 (20–45)	.76
Race			
White	9	6	.42
Black	0	2	
Asian	2	3	
Other	1	1	
Wheal diameter, median (range)†	18 (9–35)	23 (10–42)	.15
D_{50} , median (range)‡	13 (12–17)	15 (11–17)	.90

* There were no statistically significant differences between the 2 treatment groups with respect to any of the demographic or baseline characteristics (sex, age, race, wheal diameter, and D_{50}). The χ^2 test was used for sex and race, and the *t* test for age, wheal diameter, and D_{50} .

† Wheal Σ (sum of longest diameter and orthogonal diameter from midpoint).

‡ The 3-fold dilution number for sum of erythema of 50 mm using the ID_{50}EAL (intradermal dilution for 50-mm sum of erythema determines bioequivalent allergy units) method.

respect to age, sex, and race (Table 1). There were no patients who had undergone allergen immunotherapy in the previous 5 years (19 patients had never undergone allergen immunotherapy, 3 had undergone immunotherapy >10 years ago, and 2 had undergone immunotherapy >5 years ago). Immediate skin reactivity (wheal diameter for prick skin testing and D_{50} for intradermal testing) was similar in both groups. There was no difference between the 2 groups with regard to pretreatment medication use and symptom scores. Approximately 60% of the patients were women. Approximately 40% of the patients were of nonwhite racial origin. Because there were no significant differences in outcomes measured between placebo patients taking sucrose and starch capsules vs those taking microbeads, these 2 groups were combined for all data analysis.

Pollen Counts

Twenty-four-hour grass pollen counts were obtained on a daily-to-weekly basis for the months of April, May, and June in 2000 and 2001. Although the peak season appeared to start a bit earlier in 2001 (late April), overall the highest counts were observed in May of both 2000 and 2001 (Fig 1).

Clinical Symptoms

Clinical symptoms were evaluated during the peak grass pollen season before and after treatment with oral timothy grass (May 2000 and May 2001). Figure 2 shows that after the 10-week treatment with encapsulated timothy grass allergen, 11 of 12 treated patients had a decrease in the combined medication and symptom score in the subsequent grass pollen season. The mean medication and symptom score during the 2000 season was 26, whereas the mean score during the 2001 season was 15. This difference was statistically significant ($P < .01$). In contrast, only 4 of 10 patients in the placebo group had a decrease in their symptoms and medication scores. The mean score pretreatment was 21, with a post-treatment mean score of 30 (most of the increase in the post-treatment score was due to increased medication use). This difference was not statistically significant ($P > .10$). There was no statistically significant difference between the active and placebo groups at baseline ($P = .50$). One placebo patient dropped out at week 8 and was lost to long-term follow-up; this patient was excluded from analysis because no post-treatment data were available. Another placebo pa-

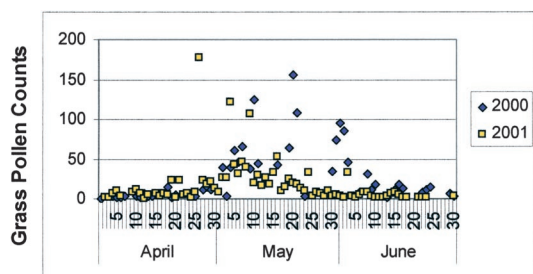


Figure 1. In both 2000 and 2001, peak grass pollen counts were observed in May. The 24-hour samples were obtained using a Burkard sampler. All samples were obtained at the same site by Theodore Chu, MD, in Los Altos, CA.

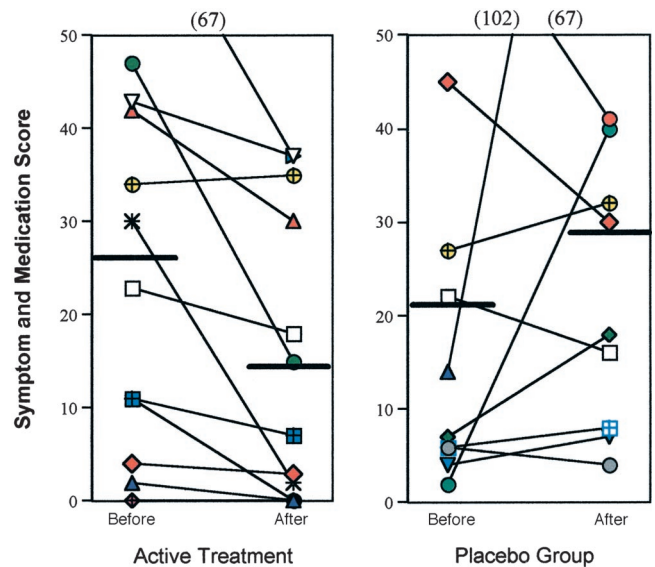


Figure 2. Oral allergen immunotherapy reduces combined symptom and medication scores. Each line represents a single patient and connects symptom and medication scores before and after treatment with oral allergen. The bold horizontal bars represent the mean scores ($P < .01$).

tient completed the study but was lost to long-term follow-up; therefore, this patient was included in the proliferation analysis (pretreatment and post-treatment data available) but not the symptom and medication score analysis (post-treatment data not available).

Induction of T-cell Tolerance

To evaluate the effects of oral immunotherapy with timothy grass pollen on T-cell function, in vitro lymphocyte proliferation in response to timothy grass antigen was measured before and after treatment. Figure 3 shows that after 10 weeks of oral treatment the proliferative response to timothy grass was reduced by at least 30% in 9 of the 12 grass-treated patients (8 of these 9 patients also had a decreased medication and symptom score; data not shown). In contrast, only 3 of 11 placebo patients had a reduction in their proliferative response (only 1 of these patients had a decreased medication and symptom score; data not shown). This was a statistically significant difference ($P = .04$). The reduction in T-cell proliferation was antigen specific, since there were no significant changes in lymphocyte proliferative responses to Bermuda grass or dust mite allergens in either group (data not shown).

Additional Immunologic Parameters

We examined whether oral allergen immunotherapy altered the cytokines produced by allergen-specific T cells by examining timothy grass antigen-simulated PBMCs for cytokine mRNA using RNase protection assays. Timothy grass-induced IL-5 mRNA was reduced in the active group, but this finding was not statistically significant ($P = .06$; data not shown). There was no reduction in IL-5 production in the

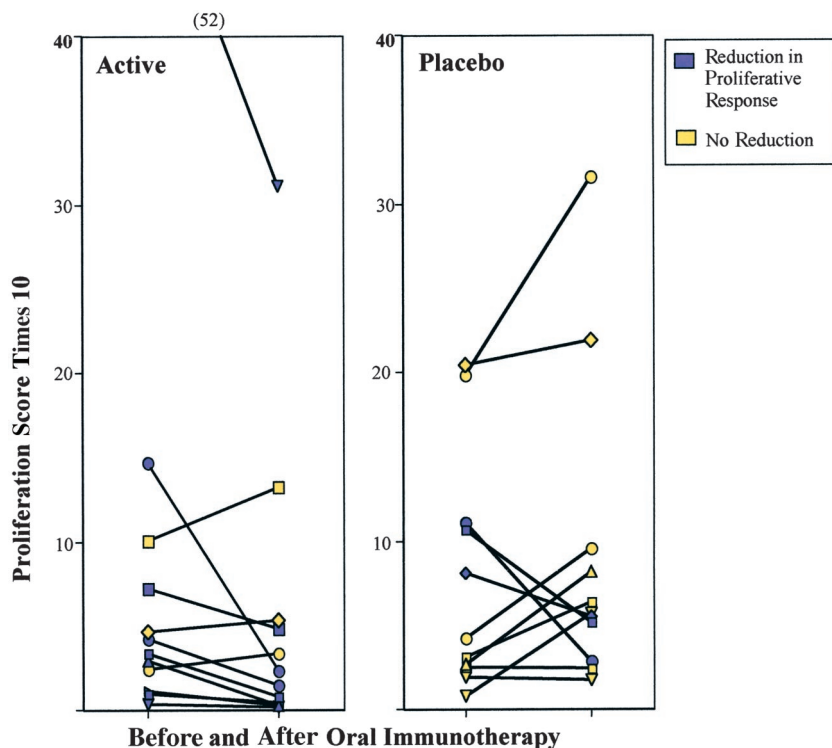


Figure 3. Oral immunotherapy reduces allergen-specific T-cell proliferation in patients with established allergic disease. Peripheral blood mononuclear cells were stimulated with antigen (timothy grass and tetanus) for 5 days and then pulsed for 18 hours with [^{3} H]-thymidine. Counts for timothy grass were normalized to tetanus proliferation because the measurements were taken at different times. A responder was defined as any patient whose normalized value decreased by at least 30% from before to after treatment. Nine of 12 active patients had decreased proliferation after treatment (all had a decrease of at least 30%); the other 3 active patients had increased proliferation. In contrast, only 3 of 11 placebo patients had reduced proliferation after treatment; the proliferative response was essentially unchanged (<5% change) or increased in the remaining 8 placebo patients. There was a statistically significant difference in lymphocyte proliferative responses between active and placebo groups before and after treatment ($P = .04$, Fisher exact test).

placebo group. In addition, no significant changes were seen in the production of IL-2, IL-4, IL-9, IL-10, IL-13, IL-15, or interferon- γ mRNA levels in either group.

We also examined serum levels of timothy grass specific IgG and IgE before and after treatment. There were no significant changes in these levels throughout the study in each individual, in the placebo and active groups, and between the placebo and active groups (data not shown). In addition, there were also no significant changes in immediate skin reactivity as measured by skin prick test (wheal diameter) and intradermal testing (D_{50} ; data not shown).

Safety of Oral Immunotherapy

Oral, encapsulated timothy grass allergen was well tolerated. There were no significant adverse events associated with the study drug and no significant early or late systemic allergic reactions. The most common adverse events reported were allergic and gastrointestinal symptoms, as well as viral infections, such as upper respiratory tract infections and gastroenteritis. However, there were no significant differences in these events between active and placebo groups and no differences between the 2 placebo groups (sucrose and starch or microbeads), suggesting that the adverse reactions were not due to the novel microencapsulated formulation. Only 1 patient (placebo group) withdrew from the study due to fatigue and personal stressors.

DISCUSSION

In this double-blind, placebo-controlled study, we examined the safety and clinical efficacy of oral immunotherapy with

microencapsulated timothy grass pollen. In addition, we studied some potential mechanisms by which oral tolerance induced clinical improvement in grass-allergic patients. We found that a 10-week course of oral allergen immunotherapy with microencapsulated timothy grass pollen was safe, well tolerated, and not associated with anaphylaxis or significant gastrointestinal adverse effects. Furthermore, it effectively reduced allergic symptoms and medication use in patients with grass allergy. In addition, it induced T-cell hyporesponsiveness in an antigen-specific manner, suggesting that oral administration of microencapsulated allergen provides an effective method for immunotherapy by inducing a form of oral tolerance.

Tolerance is a feature of the immune system that has been studied extensively in the context of discrimination between self and nonself and in the protection against autoimmunity. Tolerance is also important in the discrimination between pathogenic microorganisms and innocuous antigens encountered in the lung and gastrointestinal tract. The mucosa of the gastrointestinal and respiratory tracts is exposed to a large number of food and environmental antigens to which the immune system remains tolerant under normal circumstances. In the absence of inflammatory signals, administration of allergen into the intestine induces allergen-specific T-cell tolerance, which in murine models protects against the development of T_H2 sensitization and allergen-induced airway hyperreactivity.¹³ We believe that in our studies oral exposure to microencapsulated timothy grass allergen induced a form of immunologic tolerance, which reduced

symptoms of allergic rhinitis. The specific mechanisms by which tolerance and the reduction of allergy symptom occurred are not clear, particularly since we were unable to detect statistically significant changes in the production of T_H2 cytokines after treatment with microencapsulated timothy grass allergen. Reduced T-cell proliferative responses have also been shown in patients treated with sublingual immunotherapy¹⁹ and conventional, subcutaneous immunotherapy.^{20–22} However, previous studies examining cytokine production (using PBMC cultures) in patients treated with immunotherapy have yielded conflicting results.^{5,20–23} It is possible that the clinical benefits of oral allergen immunotherapy do not occur by conversion of T_H2 into T_H1 cytokine production but rather involve deletion of allergen-specific T cells or development of T-cell anergy or regulatory or suppressor cells secreting inhibitory cytokines, such as transforming growth factor β (TGF- β).^{12,24–26} Such mechanisms may be more desirable than converting a T_H2 predominant profile to a T_H1 predominant profile, since pure T_H1 responses may have deleterious rather than protective effects in the respiratory tract.²⁷ Alternatively, changes in T-cell cytokine production or in IgE and IgG levels may require longer periods to become apparent.

Induction of oral tolerance has been previously studied as a means to treat autoimmune and chronic T_H1 -mediated inflammatory diseases in mouse models.^{28,29} In these models, immunotherapy with low doses of oral antigen induced active suppressor or regulatory CD4⁺ T cells that secreted IL-10 (Tr1 cells)^{24,30} and TGF- β (T_H3 cells),³¹ whereas high doses of oral antigen induced T-cell anergy or deletion. Although oral administration of antigen prevented disease in such murine models, translation of oral tolerance into a therapy for human disease has been difficult³²; clinical trials of oral immunotherapy for the treatment of autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, and type 1 diabetes mellitus, to date have been unsuccessful.^{33–36}

On the other hand, our study was clinically effective in treating patients with an established allergic disease. The success of our study may reflect the fact that the antigens in allergic disease are more clearly defined than they are in autoimmune disease and that delivery of antigen into the intestine by oral administration with microencapsulated beads is efficient. In contrast, subcutaneous administration of allergen,⁴ although clinically effective, requires several years of allergen injections and is associated with significant potential adverse effects. Although sublingual allergen immunotherapy has been shown to be effective in numerous studies,^{17,37,38} high allergen doses are required and gastrointestinal adverse effects are more prominent than with microencapsulated oral immunotherapy. These differences strongly suggest that microencapsulation of allergen, which reduces degradation of the allergen in the stomach, thus enhancing delivery of allergen into the intestine, provides an effective, rapid, and tolerable method for oral allergen immunotherapy.

For future studies, it would be preferable to measure daily medication use and symptom scores prospectively (rather

than by recall) for both the pretreatment and post-treatment peak grass pollen seasons. In addition, newer and more sensitive methods for detecting cytokine levels, such as real-time reverse-transcriptase polymerase chain reaction or Elispot, could be used. Evaluation of levels of regulatory cytokines, such as IL-10 and TGF- β , may prove more revealing than the examination of T_H1 and T_H2 cytokines. Immunologic assessments during and after the post-treatment peak grass pollen season would be useful in determining whether any of the changes observed after therapy persisted and whether they were altered by allergen exposure. The optimal dose of encapsulated timothy grass allergen, as well as timing and duration of therapy, also remains to be determined.

CONCLUSION

In this double-blind, placebo-controlled trial, we showed that a 10-week course of oral, microencapsulated timothy grass allergen was safe and clinically effective. Furthermore, in patients with grass pollen-induced allergic rhinitis, this treatment decreased allergy symptoms and medication use during the peak grass pollen season 4 to 8 months after completion of therapy. In addition, treatment with oral, microencapsulated timothy grass allergen significantly reduced the in vitro T-cell proliferative response to timothy grass, indicating that this therapy induced the development of a form of T-cell tolerance. These results demonstrate that oral immunotherapy with microencapsulated allergen is a promising, new, and effective treatment for allergic diseases.

ACKNOWLEDGMENT

We thank Alice Tinker for her invaluable assistance with the statistical analysis.

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- Requests for reprints should be addressed to:
Elizabeth C. TePas, MD
Massachusetts General Hospital
Pediatric Allergy/Pulmonary
15 Parkman St
ACC 712
Boston, MA 02114
E-mail: etepas@partners.org