

The Safety and Efficacy of ALLERVAX CAT in Cat Allergic Patients¹

Peter Maguire,* Christopher Nicodemus,† Donna Robinson,† Don Aaronson, and Dale T. Umetsu*

*Department of Pediatrics, Stanford University, Stanford, California 94305,
and †ImmuLogic Pharmaceutical Corporation, Waltham, Massachusetts

Conventional immunotherapy for cat allergy is effective in reducing cat allergy symptoms in many patients, but this type of immunotherapy can cause severe reactions, including anaphylaxis, and often requires years of injections for successful desensitization. To improve the efficacy of immunotherapy for cat allergic patients, synthetic cat allergen peptides (ALLERVAX CAT) were generated, based on analysis of the immunodominant T cell epitopes of cat allergen. These peptides lack the tertiary structure of native *Fel d1* and possess a significantly reduced capacity to bind to *Fel d1*-specific IgE. Using these peptides, we performed a multicenter, randomized, double-blind, placebo-controlled study of 133 cat allergic patients chronically exposed to cats or who had failed previous conventional cat immunotherapy. We evaluated the safety of ALLERVAX CAT treatment and determined whether ALLERVAX CAT treatment improved tolerance to cat allergen, as measured by symptom analysis and pulmonary function testing. Three of the ALLERVAX CAT-treated patients required systemic epinephrine for adverse reactions, but the frequency of all adverse reactions in both groups was not statistically different from that of the placebo group. The majority of adverse events were "late" events, most commonly associated with respiratory symptoms, and these events declined with successive injections. ALLERVAX CAT given at a dose of 750 µg/dose improved pulmonary function in patients with reduced baseline FEV₁, and global evaluation of the subjects' ability to tolerate cats improved significantly in the actively treated groups relative to placebo. Thus, although therapy with ALLERVAX CAT is associated with some adverse events in patients with severe cat sensitivity, such therapy is an effective approach for the management of cat allergy, since it improves tolerance to cats and improves pulmonary function in cat allergic patients with reduced FEV₁. © 1999 Academic Press

Key Words: ALLERVAX; cat; asthma; allergy; immunotherapy.

INTRODUCTION

Exposure to cat allergen is a frequent cause of both rhinitis and asthma. Recent studies showed that approximately 30% of asthmatics have an allergic sensitivity to cats (1, 2). Treatment focusing on avoidance of cats is difficult and often inadequate for many cat allergic patients because of the prevalence of cat dander in many buildings and homes and because episodic exposure may occur through contact with friends and relatives who own cats (3). In many other instances, exposure to cats is unexpected or inadvertent. Pharmacological therapy, including antihistamines and anti-inflammatory agents, may alleviate symptoms of rhinitis and asthma in many cat allergic patients, but these medications are not always effective, and long-term compliance with pharmacological treatment in cat allergic patients is problematic. Conventional immunotherapy administered to cat allergic patients can be effective in reducing allergic symptoms caused by cat allergen (*Fel d1*)² exposure (4, 5); however, many patients require years of immunotherapy to obtain significant clinical improvement. Additionally, in some patients on cat allergen immunotherapy, adverse effects caused by IgE-mediated allergic reactions during standard immunotherapy, including anaphylaxis, significantly hamper the administration of full doses of allergen, limit its efficacy, or require cessation of treatment (6). Finally, most studies that demonstrate the effectiveness of immunotherapy focus on those patients who are able to complete a course of immunotherapy and neglect those who cannot tolerate or fail to achieve full maintenance therapy.

To reduce the adverse effects of conventional allergen immunotherapy and to increase its effectiveness, synthetic cat allergen peptides were generated for use as immunotherapy for cat allergic patients, based on a detailed analysis of the immunodominant T cell epitopes of the major cat allergens. Two peptides of 27 amino acids containing regions enriched in T cell epitopes from the *Felis domesticus* cat allergen *Fel d1* chain I were produced (ALLERVAX CAT) (2, 7). Be-

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² Abbreviations used: *Felis domesticus*, *Fel d*.

cause such peptides lack the tertiary structure of the native *Fel d1* and have significantly reduced binding to *Fel d1*-specific IgE, the two cat peptides have a significantly reduced IgE/mast cell reactivity compared to native *Fel d1*, allowing administration of much larger allergen doses, much more rapidly than is possible with conventional allergen (2). Recent studies have shown that administration of these peptides in humans decreased respiratory symptoms in cat allergic patients and reduced bronchial reactivity following cat room challenge (8, 9), presumably by decreasing allergen-specific IL-4 production in antigen-specific T cells (10, 11). Improvements, however, in symptoms following cat room challenge after ALLERVAX CAT immunotherapy do not necessarily indicate that such patients will have reduced symptoms during cat exposure in a natural setting, where cat exposure is much more chronic. Furthermore, the safety and effectiveness of ALLERVAX CAT in patients with either chronic cat exposure or previous conventional cat immunotherapy have not been assessed. The goals, therefore, of the study described herein were to determine whether administration of ALLERVAX CAT was safe in such patients, as determined by symptom diary monitoring and physician assessment, and to determine whether patients treated with ALLERVAX CAT were improved in terms of a global evaluation, as determined by symptom analysis and pulmonary function monitoring during cat exposure in the natural setting. The study was performed as a multicenter, randomized, double-blind, placebo-controlled, parallel-design fashion in patients with significant cat allergy.

MATERIALS AND METHODS

Subjects. One hundred thirty-three cat-allergic patients, ranging in age from 13 to 64 years, were enrolled in this study at five centers. A total of 94 of the 133 enrolled patients (70.7%) were female; 95% were Caucasian. The study was approved by human subjects committees at each of the five involved centers (Stanford University, Stanford, CA, center principal investigator, Dale T. Umetsu, M.D., Ph.D.; Aaronson Asthma & Allergy Associates, Inc, Des Plaines, IL, center principal investigator, Donald W. Aaronson, M.D.; Dallas Clinical Research, Inc., Dallas, TX, center principal investigator, Jeffrey M. Adelglass, M.D.; Atlanta Allergy & Immunology Research Foundation, Atlanta, GA, center principal investigator, Robert B. Berkowitz, M.D.; and Intermountain Clinical Research, Salt Lake City, UT, center principal investigator, Edwin Bronsky, M.D.), and informed consent was obtained from each study subject prior to enrollment. All patients had a history of significant allergic symptoms on exposure to cats and a positive skin prick test to *Fel d1*. Subjects were excluded from the study if they (1) had unstable asthma, defined as being symptomatic

within 48 h before the screening visit, (2) had an FEV₁ less than 70% of predicted at the screening visit, (3) had symptoms, signs, or laboratory values suggestive of renal, hepatic, cardiovascular, pulmonary, or psychiatric diseases, (4) were women of childbearing potential unless using effective continuous birth control, (5) had a history of alcohol or drug abuse, (6) had used an experimental drug within 30 days of the screening visit, or (7) had previously participated in an ALLERVAX CAT clinical trial. Twenty-seven patients were randomized to receive placebo (20% of patients) and 53 to receive 75 μ g of ALLERVAX CAT consisting of equal amounts of peptides IPC-1 and IPC-2 (see below) (40% of patients), while 53 patients received 750 μ g of ALLERVAX CAT (40% of patients). All 133 patients received at least one dose of study medication and were included in the safety analysis, and 96 patients completed the study.

Cat dander extracts and peptides. A lyophilized and standardized cat extract (ALK, Laboratories, Horsholm, Denmark), reconstituted in isotonic saline, was used for skin testing. ALLERVAX CAT *Fel d1* peptides were provided as sterile, injectable, freeze-dried powder, containing 75 or 750 μ g of each peptide, IPC-1 and IPC-2, in a buffered excipient. The peptides were reconstituted with H₂O and were administered subcutaneously in the lateral aspect of the upper arm of each patient. Placebo vials containing excipient alone were of identical appearance. Vials were prelabeled by patient number.

Skin testing. Subjects were skin tested with cat hair extract (ALK Laboratories) at a concentration of 3.3 FDA U/ml of *Fel d1* at three time points: the initial visit, visit 6, and visit 11, or skin tested with study medication in a blinded fashion before each treatment. A positive skin test was defined as the presence of erythema greater than wheal, and sum of longest and orthogonal diameter of the wheal at least 6 mm greater than the diluent control. If a skin prick test to study medication was positive, then the subject did not receive a dose at that visit. Subjects were monitored for 2 h after the initial injection and for a minimum of 1 h after the subsequent injections. Before the first dose, each subject was given 10 mg loratadine, but for subsequent ALLERVAX CAT doses, loratadine was administered only if needed. The individual investigators managed clinically significant allergic symptoms according to acceptable standards of care.

Study design. The study was conducted in a double-blind, placebo-controlled, parallel fashion at five centers. After eligibility was established and skin testing completed, the patients were randomized into one of the three study groups. Each subject received subcutaneous injections of ALLERVAX CAT or placebo, admin-

istered twice weekly for 2 weeks at the initial treatment phase and twice weekly for 2 weeks at retreatment 4 months later (a total of eight injections) (Fig. 1). Peak flow was measured prior to administration of the injection and prior to departing the clinic. At each visit the patient's general ability to tolerate cats was assessed, skin testing was performed, and the symptom diary collected. A follow-up visit 3 weeks after each treatment phase occurred to assess skin prick testing to ALLERVAX CAT and for pulmonary function testing.

Laboratory testing. Complete blood cell counts, liver function tests, and RAST tests (Pharmacia CAP System, Pharmacia Diagnostics AB, Uppsala, Sweden) were performed at SmithKline Beecham Clinical Laboratories (Van Nuys, CA). There were no abnormalities in clinical laboratory evaluation judged to be an adverse effect of treatment.

Efficacy and symptom evaluation. A primary efficacy variable for safety was assessment of daily peak flow. Additional variables assessed for safety and efficacy were pulmonary function studies, immediate responses to skin tests with cat extract, symptom diary, and global evaluation to cat exposure. Pulmonary function tests were done at the initial visit, at the 3-week posttreatment visits, and prior to the patient receiving the fifth injection. Global evaluation was performed by having patients assess their ability to tolerate exposure to cats over the preceding month. The assessment was made on a five-point scale: excellent, very good, good, fair, poor, or not applicable (if no cat exposure occurred). This assessment of cat exposure tolerance was evaluated at the beginning and end of each of the two treatment phases for all groups (visits 2, 6, 7, and 11).

Statistical methods. Differences between treatment groups with respect to any nominal categorical variables were assessed using the Cochran–Mantel–Haenszel test. Treatment group comparisons on continuous variables were performed using analysis of variance and analysis of covariance with or without rank transformation. Logistic regression, χ^2 analysis, and generalized estimating equations methods were used to assess differences between treatment groups with respect to adverse event profiles. Van Elteren's test was used to assess treatment group differences in global evaluation with respect to the change in evaluation from pretreatment with an adjustment for study center at each visit (12).

RESULTS

The three treatment groups (placebo, 75 μ g/dose ALLERVAX CAT, and 750 μ g/dose ALLERVAX CAT)

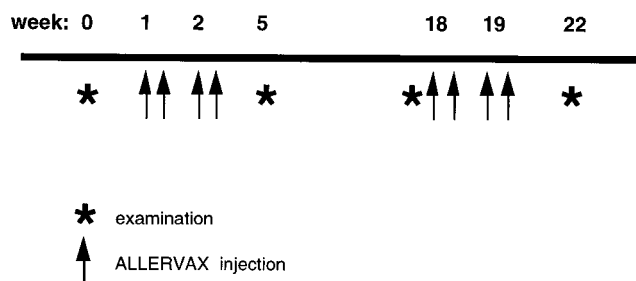


FIG. 1. Study timeline.

did not differ with respect to mean age, percentage of cat ownership, history of asthma, and mean baseline FEV1 (Table 1), and all patients had symptoms of allergic rhinitis on exposure to cats. Over 86% of the patients enrolled had chronic exposure to cats, including 66% who were cat owners. A history of asthma was reported in 44% of the patients, although 70% reported a history of allergic symptoms that were chest-related including wheezing, chest tightness, cough, and shortness of breath. Approximately one-third of the patients in each of the three treatment groups had received prior immunotherapy to cats. All study participants were skin prick test positive to standardized cat hair extract, and 99% were negative on skin prick testing to ALLERVAX CAT at baseline.

Ninety-six of the 133 enrolled subjects received all eight subcutaneous injections of ALLERVAX CAT or placebo. Of the 37 patients who did not receive all eight injections, 6 patients (22.2%) were in the placebo group, 16 (30.2%) were in the 75- μ g ALLERVAX CAT group, and 15 (28.3%) were in the 750- μ g group. Fourteen of the 37 subjects missed one or more doses but completed the study, but 23 of the 37 subjects withdrew prematurely from the study because of adverse events.

Adverse Events

A total of 108 patients experienced at least one adverse event during the study, but these occurred in all groups, including the placebo patients. Adverse events occurred 20% more frequently in the active groups versus the placebo group, and there was no difference in adverse event occurrence rates between the 75- μ g ALLERVAX CAT dose group and the 750- μ g ALLERVAX CAT dose group. Adverse events occurred in 66.7% of the placebo patients, 86.8% of the patients receiving the 75- μ g dose (compared to control, $P = 0.03$, χ^2 analysis) (Table 2). Fourteen patients missed at least one injection due to adverse events, including 7.4% of the placebo group (2 of 27 subjects), 7.5% of the subjects in the 75- μ g ALLERVAX group (4 of 53 subjects), and 15.1% of subjects in 750- μ g ALLERVAX

TABLE 1

Demographic Characteristics of Study Subjects

Characteristic	Placebo	ALLERVAX CAT	
		75 μ g	750 μ g
No. of patients	27	53	53
Gender			
Female	18	42	34
Male	9	11	19
Race			
Caucasian	27	52	50
Black	0	1	3
Age			
Mean ($\pm$ SD)	35.6 $\pm$ 14	32.1 $\pm$ 11	34.2 $\pm$ 12
Cat owners	66.7%	69.8%	64.2%
History of asthma	40.7%	39.6%	49.1%
Baseline FEV1			
($\pm$ SD, L/s)	2.6 $\pm$ 0.6	2.6 $\pm$ 0.4	2.8 $\pm$ 0.5
Dropouts	3 (11%)	12 (23%)*	8 (15%)**

Note. Percentages are based on the total number of patients in each treatment group.

* Compared to control, $P = 0.21$.

** Compared to control, $P = 0.62$.

group (8 of 52 subjects). Of the 23 patients who withdrew from the study prematurely (Table 1), 9 discontinued treatment due to adverse events related to injections, including 4 in the 75- μ g ALLERVAX CAT group and 5 in the 750- μ g ALLERVAX CAT group. Five of these 9 patients who discontinued treatment did so after receiving only one dose.

Adverse events were most commonly reported in the respiratory system organ class with 77 patients reporting at least one event in this body system. Events categorized as respiratory included symptoms of chest tightness, dyspnea, coughing, throat irritation, wheezing, and asthma aggravation. Patients in the 75- μ g ALLERVAX CAT group had the most respiratory events with 67.9% of patients reporting events compared with 56.6% in the 750- μ g and 40.7% in the placebo group. Patients with a history of asthma were more likely to report adverse events than patients without such a history. However, this trend was observed across all treatment groups. In fact, this was particularly apparent in the placebo group, in which 100% of the patients with a history of asthma reported adverse events during the study compared to only 44% of patients without a history of asthma. However, it is important to note that no decrements in peak flow were documented in association with any study medication injection in any treatment group.

Forty-one patients reported at least one event in the body as a whole system organ class. Adverse event rates in this system organ class were similar among the three treatment groups (placebo, 25.8%; 75 μ g, 34.0%; 750 μ g, 30.2%). Headache was the most com-

mon reported adverse event (11.1% of placebo patients, 22.6% of the 75- μ g ALLERVAX group, and 17.0% of the 750- μ g ALLERVAX group (Table 2). The most common dermatologic reaction experienced was pruritis. Limited dermatological reactions occurred primarily 30 min after injection of study medication. Taken as a whole, the majority of adverse events were judged by the investigators to be of mild or moderate severity. Twenty patients, including 2 (7.4%) of the 27 patients in the placebo group, 9 (17.0%) of the 53 patients in the 75- μ g ALLERVAX CAT group (not significant compared to control, $P = 0.24$, χ^2 analysis), and 9 (17.0%) of 53 patients in the 750- μ g group (not significant compared to control, $P = 0.24$, χ^2 analysis) experienced events that were judged to be severe (Table 2). However, these events did not always require treatment, and the frequency of antihistamine use for reactions did not differ between any of the groups (Table 3).

Early Onset Symptoms

Twelve patients (2 in the placebo group, 5 in the 75- μ g group, and 5 in the 750- μ g group) experienced an allergic or adverse reaction within 30 min of an injection (Table 2). Nine of these 12 patients who experienced adverse events within 30 min had only mild to moderate symptoms as judged by the investigators.

TABLE 2

Adverse Events to ALLERVAX CAT by Body System

System organ class	Placebo (%)	ALLERVAX CAT (%)	
		75 μ g	750 μ g
Total number of patients	27	53	53
Any allergic adverse event	18 (66.7)	46 (86.8)*	44 (83.0)**
Respiratory tract	11 (40)	36 (67.9)*	30 (56.6)***
Neurologic	4 (14.8)	15 (28.3)***	12 (22.6)**
Dermatologic	1 (3.7)	6 (11.3)***	8 (15.1)**
Any "severe" event	2 (7.4)	9 (17.0)***	9 (17.0)***
Early onset symptoms	2 (7.4)	5 (9.4)***	5 (9.4)***
Late onset symptoms	5 (19)	19 (36)**	19 (36)**
Injection 1	0 (0)	12 (22.6)*	10 (19.2)*
Injection 3	1 (4.2)	7 (15.0)***	8 (16.7)**
Injection 8	0 (0)	1 (2.4)***	3 (7.1)***

Note. Safety data were collected throughout the study and adverse event inquiries were conducted at each study visit. During the 1- to 2-h observation period following each injection of study medication, adverse events were captured spontaneously. At the end of the observation period, prior to departure from the clinic, patients were asked a nondirected question to capture adverse events not spontaneously reported. Daily diary cards were provided to the patient at each study visit to record information each day between visits. Information entered by patients on diary cards was reviewed as part of the adverse event inquiry.

* Significantly different from control, $P < 0.05$, χ^2 analysis.

** Not significantly different from control, $P \geq 0.1$, χ^2 analysis.

*** Not significantly different from control, $P < 0.2$, χ^2 analysis.

TABLE 3
Loratadine Usage during the Study

Time point	Placebo (%)	ALLERVAX CAT (%)	
		75 μ g	750 μ g
Injection 1	27/27 (100.0)	53/53 (100.0)	52/52 (100.0)
Injection 2	0/25 (0.0)	0/48 (0.0)	0/48 (0.0)
Injection 3	1/24 (4.2)	1/47 (2.1)	0/48 (0.0)
Injection 4	1/24 (4.2)	1/46 (2.2)	1/47 (2.1)
Injection 5	1/25 (4.0)	4/45 (8.9)	1/47 (2.1) ^a
Injection 6	2/24 (8.3)	3/42 (7.1)	1/44 (2.3)
Injection 7	1/24 (4.2)	4/41 (9.8)	1/42 (2.4)
Injection 8	1/23 (4.4)	3/40 (7.5)	1/40 (2.5)
Total for Injections 2–8	2/26 (7.7)	4/49 (8.2)	3/50 (6.0) ^a

Note. All patients were required by study protocol to receive loratadine after the first injection.

^a Includes loratadine use for one patient who received the first injection at Visit 8.

These symptoms were primarily of the *respiratory* system organ class as well. Symptom reactions included nasal congestion, wheezing, coughing, dyspnea, and nasal irritation. Only 1 of these 12 patients in the 750- μ g group had a local reaction at the injection site as well. Three of the 12 patients who experienced reactions within 30 min required treatment with systemic epinephrine.

Use of Systemic Epinephrine

The three patients who were treated with systemic epinephrine included one patient in the 75- μ g group (one for dyspnea and pruritus) and two in the 750- μ g group (for pruritus; and for dyspnea, flushing, throat constriction, coughing, and chest tightness). One of the patients who required epinephrine (750- μ g group) was chronically exposed to cats, had failed a previous course of standard cat immunotherapy, and had a cat allergy RAST score of Class 5 (RAST results are graded 0 to 6). The reaction occurred 20 min after Injection 7. At Visit 11 the patient had detectable IgE to both IPC-1 and IPC-2 peptides (2.82 and 0.51 units, respectively) (determined by immunoassay), suggesting that the reaction was IgE mediated. The second patient who required treatment with epinephrine (750- μ g group) had a history of chronic cat exposure and was moderately allergic to cat (RAST to cat was Class 4). A late reaction occurred 3.5 h after the first injection, even though baseline levels of IgE against IPC-1 and IPC-2 were negative, suggesting that the reaction was *not* IgE mediated. The patient in the 75- μ g group who required epinephrine had asthma, was severely allergic to cats (RAST to cat was Class 6) (13), had previ-

ously failed standard cat immunotherapy, and was chronically exposed to cats. The reaction in this subject was also late, occurring 2 h after receiving the first injection. Follow-up IgE levels to IPC-1 and IPC-2 were below measurable limits, suggesting that this reaction was also *not* IgE mediated.

Late Onset Symptoms

Late onset symptoms, those allergy-related events reported after 30 min but within 24 h of dosing, occurred about twice as frequently in the active groups versus the placebo group (36% in active groups compared to 19% in the placebo group). There was no difference in the frequency of late onset symptoms between the 75- μ g and 750- μ g dose groups. The most common late onset symptoms were chest tightness, dyspnea, coughing, and nasal congestion and were mild to moderate in severity, requiring no intervention other than patient self-management. The majority of these events were reported during the initial treatment phase and, in particular, occurred following the first study medication injection. During subsequent treatment injections, the number of patients reporting any late onset symptoms was lower compared to that of the first treatment injection, and the number of late phase allergic or adverse events declined for all groups with successive treatment injections. After Injection 1, 0/27 of the placebo group, 12/53 (22.6%) of the 75- μ g group, and 10/52 (19.2%) of the 750- μ g group experienced late onset symptoms (Table 2). The second highest incidence of late onset symptoms occurred after Injection 3: 1/24 (4.2%) in the placebo group, 7/47 (14.9%) in the 75- μ g group, and 8/48 (16.7%) in the 750- μ g group. By the eighth injection, 0/23 of the placebo group, 1/41 (2.4%) of the 75- μ g group, and 3/42 (7.1%) of the 750- μ g group experienced late onset symptoms. Although subjects with severe reactions were removed from the study, these results suggested that during the initial phase of the investigation, late reactions were more prominent than immediate reactions, but that tolerance to the injections developed over the course of the study (Table 2).

IgE to *Fel d1* and Late Onset Symptoms

In order to determine whether a patient's screening value of IgE to *Fel d1* could predict the occurrence of late onset symptoms, a correlation analysis was performed. Levels of IgE to *Fel d1* were defined as either low: 0–5.66 U/ml; medium: >5.66 to 59 U/ml; or high: >59 U/ml. Patients who had medium to high levels of IgE to *Fel d1* were more likely to report a late onset symptom during the study than patients with low levels. This was true in all treatment groups including the

placebo group in which all three patients who reported late onset symptoms had high levels of IgE to *Fel d1* at baseline. Patients in the active treatment groups were more likely to experience a late onset symptom than patients in the placebo group; there was no difference between the 75- μ g and 750- μ g dose groups. Of the three patients who reported late onset symptoms in the placebo group, all had high levels of IgE to *Fel d1*. Of the 53 patients in the 75- μ g dose group, 19 patients reported late onset symptoms. Of these 19 patients, 2 had low levels, 7 patients had medium levels, and 10 patients had high levels of IgE to *Fel d1*. Of the 52 patients in the 750- μ g dose group, 19 patients (3 in the low, 11 in the medium, and 5 in the high level category of IgE to *Fel d1*) reported late onset symptoms. However, there was no statistically significant interaction between the level of IgE to *Fel d1* at screening and treatment ($P = 0.4675$) on the occurrence of late onset symptoms.

Skin Sensitivity to ALLERVAX CAT

All cat allergic patients treated with ALLERVAX CAT had IgE against whole cat antigen, but most had no detectable antibodies to the peptide components of ALLERVAX CAT. There was no correlation between the presence of antibody and occurrence of late onset adverse events. Overall, skin testing to ALLERVAX CAT, performed in a blinded fashion prior to each injection and before and after treatment, did not demonstrate significant reactivity. Only 1 subject was positive on the first test, and only 9 (0.95%) of the 943 intended injections with the study medication were withheld during the study because of positive study medication skin testing. In the active treatment groups, 13 subjects developed detectable peptide-specific IgE, including 10 subjects in the 750- μ g dose group (21.7%) and 3 subjects in the 75- μ g dose group (7.0%), while none in the placebo group developed anti-peptide IgE (Table 4). Of the 13 patients with detectable IgE to the peptides only 1 had an adverse event within 30 min of dosing (750 μ g of ALLERVAX), which manifested as generalized pruritis, treated with epinephrine (discussed above). However, this event suggests that those patients with detectable anti-peptide IgE have an increased risk of developing systemic reactions, particularly after receiving many ALLERVAX injections.

Skin Test Sensitivity to Standardized Cat Hair Extract

Skin sensitivity to standardized cat hair extract as measured by wheal diameter reaction did not change significantly for any of the groups through the course of

TABLE 4
Patients with Detectable IgE Levels to Either Peptide, IPC-1 or IPC-2

Time point/visit	Placebo (%)	ALLERVAX CAT (%)	
		75 μ g	750 μ g
Screening (Visit 1)	1/27 (3.7)	0/53 (0.0)*	0/52 (0.0)*
Post initial treatment (Visit 6)	1/25 (4.0)	0/47 (0.0)*	2/50 (4.0)**
Preretreatment (Visit 7)	1/25 (4.0)	0/44 (0.0)*	1/47 (2.1)**
Postretreatment (Visit 11)	1/24 (4.2)	3/43 (7.0)**	10/46 (21.7)*

Note. Percentages are based on *N*, the number of patients with antibody data collected at each time point.

* Not significantly different from control, $P \geq 0.1$, χ^2 analysis.

** Not significantly different from control, $P > 0.2$, χ^2 analysis.

this study. Posttreatment evaluation (Visit 11) of mean wheal diameter reaction to standardized cat hair extract demonstrated moderately small declines in mean baseline and final wheal diameter in all three groups: placebo group (14.0 and 10.6 mm), 75- μ g ALLERVAX CAT group (13.4 and 10.8 mm), and 750- μ g ALLERVAX CAT group (13.9 and 10.9 mm).

Pulmonary Function Testing and Peak Flow Measurements

Treatment with ALLERVAX CAT improved pulmonary function in subjects with diminished FEV1 at baseline by week 6 of the study. The mean baseline FEV1 for the entire study population was $>87\%$ of that predicted. However, since improvement in pulmonary function would only be expected in patients with impaired pulmonary function at baseline, patients with FEV1 at least 15% less than predicted at screening were analyzed separately. A total of 48 patients were included in the analysis, including 15 patients in the placebo group, 17 in the 75- μ g ALLERVAX CAT group, and 17 in the 750- μ g group. After the initial treatment phase (Visit 6, 3 weeks posttreatment), there was a significant increase in FEV1 in the high peptide dose group compared to the placebo group (Fig. 2). The mean changes were -0.01 L in the placebo group, 0.04 L in the 75- μ g group, and 0.28 L in the 750- μ g group ($P = 0.01$); the corresponding values for percentage of predicted FEV1 were -0.08% , $+1.34\%$, and $+6.27\%$, respectively ($P = 0.0318$). At Visit 11 (21 weeks postretreatment) the mean increases in actual and percentage of predicted FEV1 were greater in both the active treatment groups when compared to the placebo group; however, the differences were not statistically significant. The resulting analysis of peak flow measurements was consistent with the FEV1 data, but was not

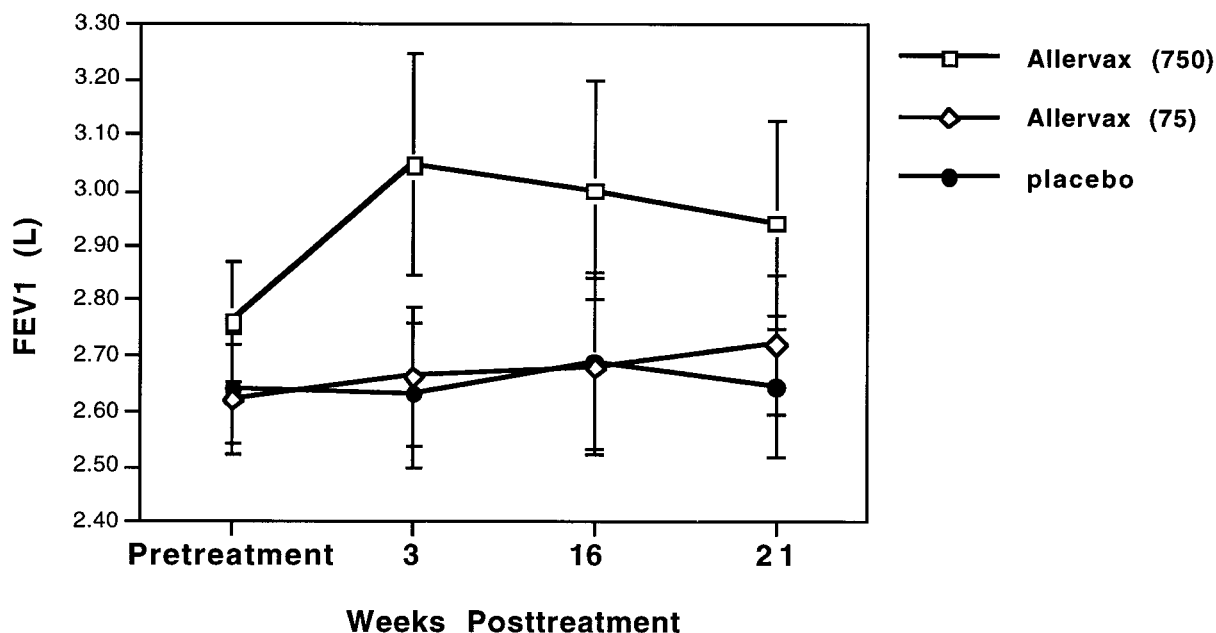


FIG. 2. ALLERVAX CAT improves pulmonary function in subjects with diminished FEV1 at baseline. *P* value for 750- μ g group compared to placebo group at 3 weeks posttreatment = 0.01. *P* = 0.07 at 16 weeks compared to placebo and 0.08 at 21 weeks compared to placebo.

statistically significant. By the final injection, the mean peak flow had decreased in the placebo group and increased slightly in both active treatment groups.

Global Evaluation to Cat Exposure

Overall, the ability to tolerate exposure to cats improved in the active treatment groups. Before treatment, approximately 30% of the patients in all three groups assessed their tolerance to cat as good to excellent (Table 5). After completion of the first four study medication injections (initial treatment phase–Visit 6), 46% of the patients in the placebo group, 58% of the patients in the 75- μ g group, and 72% of the patients in the 750- μ g group rated their tolerance to cat as good to excellent (*P* = 0.050, comparing treatment groups versus placebo group). Similar results were observed after completion of all study medication injections (Visit 11) as 57, 71, and 81% of patients in the placebo, 75- μ g, and 750- μ g groups, respectively, rating the tolerance to cat exposure as good to excellent (*P* = 0.042, comparing treatment groups [53 subjects in each treatment group] versus placebo group [27 patients in placebo group]).

DISCUSSION

We studied ALLERVAX CAT in a multicenter, randomized, double-blind, placebo-controlled, parallel-design study in 133 cat-allergic patients with either chronic cat exposure or previous conventional cat im-

muno-therapy. The peptides were administered twice weekly for 2 weeks at dose levels of 75 and 750 μ g and readministered 4 months later. We demonstrated that treatment with high-dose (750 μ g) ALLERVAX CAT peptides was clinically effective in improving pulmonary function in patients with reduced FEV1 at baseline compared to placebo therapy during part of the study (*P* = 0.01). Moreover, global evaluation of patients' ability to tolerate cats improved significantly in the actively treated high-dose group relative to placebo.

Although severe, immediate allergic reactions were rare with ALLERVAX CAT, our study is consistent with previous studies, which have shown that mild respiratory symptoms are common with peptide immunotherapy (8). The antigen peptides in ALLERVAX CAT have 27 amino acids residues and bind poorly or not at all to cat-specific IgE antibody on the surface of mast cells, thus limiting immediate reactions. Adverse events occurred in the ALLERVAX-treated group with a frequency of about 80%, compared to a frequency of 67% in the placebo-treated group, but with few exceptions, these adverse events were mild and easily controlled, primarily with antihistamines.

Roughly 20% of the ALLERVAX CAT-treated patients experienced late onset symptoms after injection 1. These late reactions (symptoms occurring 35 min to 6 h after injection) are most likely T cell mediated, due to the activation by the peptides of a large population of cat-specific T cells, which produce factors that cause

TABLE 5
Subject Global Evaluation

Time point/visit	Placebo	ALLERVAX		P value
		75 µg	750 µg	
Pre initial treatment (Visit 2)				
N	24	50	47	
Mean ± SD	4.0 ± 0.88	3.8 ± 1.07	3.8 ± 1.02	0.715
Median	4.0	4.0	4.0	
Post initial treatment (Visit 6)				
N	22	45	46	
Mean ± SD	3.5 ± 1.19	3.3 ± 1.14	2.8 ± 1.23	0.050
Median	4.0	3.0	3.0	
Preretreatment (Visit 7)				
N	25	42	43	
Mean ± SD	3.4 ± 1.35	3.0 ± 1.10	2.8 ± 1.29	0.141
Median	4.0	3.0	3.0	
Postretreatment (Visit 11)				
N	23	41	42	
Mean ± SD	3.2 ± 1.19	2.7 ± 1.21	2.5 ± 1.13	0.042
Median	3.0	2.0	2.0	

Note. The score range for patient global evaluation is 1, excellent; 2, very good; 3, good; 4, fair; 5, poor. *P* value assesses the significance of the difference between the treatment groups versus placebo and was determined using van Elteren's test adjusting for study center (12).

respiratory symptoms. The late reaction rate, however, compares favorably with the rate of late reactions occurring with conventional immunotherapy (38% in one study, which evaluated the safety of conventional immunotherapy) (14–18). Moreover, the incidence of late onset symptoms declined through the study with repeated administration of ALLERVAX CAT, suggesting that clinical tolerance to the injections developed over the course of the study. This possibility requires further consideration and study, since the most efficacious regimen for administering ALLERVAX to induce optimal tolerance is not yet clear. For example, it is possible that a rapid escalating immunization schedule rather than a fixed dose schedule could considerably reduce the frequency of these late reactions.

A few of the reactions caused by ALLERVAX CAT may have been IgE and mast cell mediated, since 13 of 89 patients receiving ALLERVAX CAT developed IgE against the peptide during the course of the study (Table 4). One of the 13 patients with anti-peptide IgE had a severe reaction. This still compares favorably with the incidence of systemic reactions caused by standard immunotherapy, which is reported to be in the range from 3 to 15% and as high as 36% in rush immunotherapy (14–18). None of the subjects in this study had IgE against the peptides at the outset of the study, and the 1 patient who developed a severe immediate reaction did so on the seventh injection, after a 4-week hiatus (between injections 4 and 5, as per the protocol). As discussed earlier, it is possible that an escalating immunization schedule, rather than a fixed dose schedule, could considerably reduce the frequency

of these systemic reactions by inducing more effective T cell and B cell tolerance, anergy, or immune deviation (19–22). The specific pharmacology of allergen peptides, however, and the mechanisms resulting in symptoms, are still poorly understood and will require further experience and study.

The results of this study demonstrate that administration of T-cell-reactive peptide components of *Fel d1* is a potentially effective therapy for patients with severe cat allergy, in patients who are chronically exposed to cats, and in those who previously received cat immunotherapy. Previous studies have shown that ALLERVAX CAT reduces symptoms when treated patients are challenged with cat allergen in an experimental cat room settings (8), but there have been no previous clinical reports examining patients who have natural exposure to cat allergen in an outpatient setting. Our study therefore extends the results of previous ALLERVAX CAT studies, but is the first to show that high-dose ALLERVAX CAT therapy improved the capacity of patients with severe cat allergy to tolerate cat exposure in clinically important situations.

Previous studies have shown that *conventional* immunotherapy, although clinically effective for allergic rhinitis, is less effective as a treatment modality for asthma (23), and therefore it is interesting to note that FEV1 improved in those cat allergic patients with reduced initial FEV1 who were treated with high-dose ALLERVAX CAT. In patients with allergic rhinitis, conventional immunotherapy is known to reduce allergy symptoms, reduce the need for rescue medications, and reduce allergic inflammation and late phase

reactions (24, 25). In contrast, recent studies with conventional immunotherapy suggest that immunotherapy is only marginally effective for asthma (26), although meta-analysis of multiple previous studies indicates that conventional immunotherapy may be efficacious for asthma (27). Our results may reflect the fact that ALLERVAX CAT is designed to avoid mast cell degranulation and immediate reactions, thereby avoiding aggravation of respiratory symptoms, whereas conventional allergen immunotherapy may cause allergic reactions that exacerbate pulmonary disease.

Although the ALLERVAX CAT-treated patients in this study had improved tolerance to cat exposure as measured by global evaluation symptom analysis, the degree of improvement may have actually been limited by this study's patient recruitment criteria. In general, our patient cohort included patients with a high level of cat sensitivity as determined by history and by RAST scoring and skin testing (13). Additionally, about 30% of all treatment groups had previously failed at least one course of standard cat immunotherapy (failure defined as minimal or no improvement with therapy or development of severe reactions to the injections). More than 40% of patients had asthma and nearly all had repetitive cat exposure. Because of these patient characteristics, their propensity for immunologic change regarding allergy to *Fel d1* may have been limited (28). A potentially less immunologically "resistant" patient population may have had more dramatic improvement as measured by pulmonary function testing and symptom analysis. Furthermore, the severity of allergic disease in this population and their chronic exposure to cat dander may also explain the high rate of adverse reactions in this study (66.7% of placebo patients with asthma had an adverse event, and 20% of placebo patients developed late reactions).

The results of this study taken together suggest that ALLERVAX CAT peptide immunotherapy is an effective approach for the management of cat allergen-induced allergic rhinitis and asthma. Although ALLERVAX CAT peptide immunotherapy was associated with adverse side effects in some patients, pharmacotherapies for allergic rhinitis and asthma are also associated with potential side effects. Currently available anti-inflammatory therapies include inhaled corticosteroids, which may increase the risk for the development of cataracts, glaucoma, and short-term growth arrest (29–32) or leukotriene antagonists, such as zafirlukast, which may increase the risk for Churg–Strauss disease (33). Moreover, unlike these medications, peptide immunotherapy has the additional benefit of potentially modifying the clinical course of the asthma and rhinitis. Immunotherapy functions as a vaccine to specifically induce a protective immune response (10, 34), and this occurs without immunosup-

pressive side effects associated with other forms of immune modification therapies. The beneficial effects of peptide immunotherapy, however, in contrast to that of conventional immunotherapy, appear to occur with much fewer doses over a much shorter period of time.

Although the occurrence of late onset reactions during peptide therapy has raised some concerns about the safety of this therapeutic alternative, peptide therapy appears to be a safe and effective form of therapy. However, further studies are required to optimize the dose and schedule, to optimize the use of concomitant medications (antihistamines or leukotriene receptor antagonists) in order to minimize acute and late peptide effects and augment tolerogenic effects, to determine whether incorporation of additional cat antigen immunodominant peptides into the preparation could improve clinical effectiveness, and to determine the permanence of any beneficial effects. Additionally, clinical and immunological evaluation of such peptide-treated patients after a longer period of time posttreatment may be of value. Furthermore, since the incidence of side effects associated with ALLERVAX CAT appears to decrease with subsequent injections and the intermediate dose of ALLERVAX CAT (75 μ g) seems to induce less anti-peptide IgE compared with the 750- μ g dose, the most successful schedule of peptide therapy may incorporate an escalating dose over a 6-month or longer period of time. This schedule of peptide therapy would still allow a substantial reduction in the number of injections required to induce immunologic and clinical improvement compared with conventional allergen immunotherapy.

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