Immunotherapy with Fel d 1 peptides decreases IL-4 release by peripheral blood T cells of patients allergic to cats

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Background: Cells producing a Tn2-cytokine profile play an important role in the onset and maintenance of atopic diseases, and therefore specific immunotherapy is aimed to induce a switch to cells producing a Tn1 or Tn0-cytokine profile. Recently, a novel form of immunotherapy making use of synthetic peptides from the major cat allergen Fel d 1 has been developed, but its mechanisms of action are unknown.

Objectives: We examined the effects of immunotherapy with Fel d 1 peptides on the response to bronchial provocation tests (PD_{20}FEV_1) with a standardized Fel d 1 cat extract on Fel d 1-specific serum IgE and IgG levels and in vitro IL-4 and IFN-γ production.

Methods: Patients allergic to cats received 6 weekly injections of 7.5 μg (low dose), 75 μg (medium dose), or 750 μg (high dose) of Fel d 1 peptides (25 patients) or a placebo (6 patients).

Results: Six weeks after ending immunotherapy, posttreatment PD_{20}FEV_1 was not significantly different between the treated and placebo groups. However, in the medium- and high-dose groups there was a significant improvement between baseline and posttreatment days. IL-4 release was significantly reduced in the high dose-treated group (P < .005, Wilcoxon W test), whereas it was unchanged in the low or medium dose- and in the placebo-treated groups. In all groups, IFN-γ, IgE, and IgG levels remained unchanged.

Conclusion: There was no correlation between the improvement of PD_{20}FEV_1 and the decrease in IL-4 production. These data suggest that peptide immunotherapy may act by shifting the Fel d 1-induced response of PBMCs in vitro from the Tn2* to the Tn0-like phenotype. (J Allergy Clin Immunol 1998;102:571-8.)

Key words: Tn2/Tn0 allergy, T-cell cytokines, allergens, peptides, T-cell epitopes

The regulation of IgE synthesis is controlled by several factors, among which cytokines play a central role. As in the mouse, 3 subsets of CD4+ T helper/inducer cells have been identified in humans on the basis of their cytokine production profiles. Tn1 cells release predominantly IFN-γ and IL-2, whereas Tn2 cells secrete predominantly IL-4 and IL-5, but low amounts of IL-2 and IFN-γ. A third group, called Tn0 cells, secrete the cytokines of both subsets on activation.1,2 The Tn2 cytokine IL-4 plays a critical role in allergy by inducing IgE synthesis, whereas IFN-γ has inhibitory effects.3-7 Although in humans a strict dichotomy between T-cell subsets is not as clear as in the murine system,8 an imbalance of Tn1 and Tn2 cells has been proposed to be involved in IgE-mediated allergic diseases and asthma as a result of the regulation of IgE synthesis and cellular recruitment at the sites of inflammation.9-11

Allergen-specific immunotherapy, widely used in the treatment of allergic rhinitis and asthma, is effective by using standardized allergenic extracts.12 The cloning and characterization of the structure of major allergens has made it possible to generate allergen-derived synthetic peptides. Two peptides of 27 amino acids that contain some, but not all, of the T-cell epitopes from the Felis domesticus cat allergen Fel d 1 chain I have been synthesized (ALLERVAX CAT).13 In mice subcutaneous tolerization with the peptides prevented the T-cell response to nasal challenge with cat allergen by decreasing the T-cell proliferation to the entire recombinant Fel d 1 chain I.14 In humans immunotherapy with Fel d 1 peptides resulted in a decrease of clinical symptoms of patients allergic to cats and bronchial reactivity after nasal challenge with Fel d 1 in a cat room.15 Several studies reporting the modulation of IL-4 and/or IFN-γ release by allergen-specific T cells have suggested a correlation between successful immunotherapy and the induction of a phenotypic switch from a Tn2 to a Tn0 or a Tn1 cytokine phenotype.17-19 However, the mechanisms of action of immunotherapy with peptides such as those derived from Fel d 1 are still unknown.

Here we describe the results from a double-blind, placebo-controlled study carried out in 31 patients allergic to cats making use of Fel d 1 peptides to evaluate the clinical (bronchial challenge with a standardized cat extract) and immunologic (IL-4 and IFN-γ release by

Abbreviations used
A23187: Calcium ionophore A23187
BPT: Bronchial provocation test
PMA: Phorbol myristate acetate

From the INSERM U. 454 and the Clinique des Maladies Respiratoires, Hôpital Arnaud de Villeneuve, Montpellier, and 'ImmuLogic, Waltham. Supported by Hoechst Marion Roussel, Kansas City, Mo.

Received for publication May 27, 1997; revised May 26, 1998; accepted for publication June 4, 1998.
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0091-6749/98 $5.00 + 0 1/1/92394
TABLE I. Treatment schedule with Fel d 1 peptides

<table>
<thead>
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<th>3</th>
<th>4</th>
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<tr>
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<tr>
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<td>7.5</td>
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<td>75</td>
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<tr>
<td>Medium dose</td>
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<td>0</td>
<td>75</td>
<td>75</td>
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<td>75</td>
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<tr>
<td>Medium dose</td>
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<td>750</td>
<td>750</td>
</tr>
<tr>
<td>High dose</td>
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<td>0</td>
<td>750</td>
<td>750</td>
<td>750</td>
<td>750</td>
</tr>
<tr>
<td>High dose</td>
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<td>750</td>
<td>750</td>
<td>750</td>
<td>750</td>
<td>750</td>
<td>750</td>
</tr>
</tbody>
</table>

*The patients were clustered in 4 groups according to the treatment they received: placebo or low, medium, or high doses of Fel d 1 peptides.

Values are amount of ALLERVAX CAT received (μg/mL).

PBMCs, as well as serum Fel d 1–specific IgE and IgG) effects of the treatment.

METHODS

Patients

Nineteen men and 12 women, ranging in age from 20 to 37 years (mean ± SD: 27.7 ± 5.1 years), were recruited in the Allergy Department of the Montpellier Hospital on the basis of a clinical history of allergy to cats and enrolled in the present double-blind, placebo-controlled study of cytokine release by PBMC in vitro. All patients were first seen with (1) a positive skin prick test response performed as previously described to the Aquagen extract, (2) a positive bronchial challenge to the same extract, and (3) the presence of cat dander-specific serum IgE. All patients had respiratory symptoms during cat exposure. Moreover, they had positive methacholine and cat allergen challenge results. Many patients were also sensitive to other allergens. Patients, matched for asthma severity, had mild asthma, the definition of asthma being based on recent symptoms during cat exposure. Moreover, they had positive methacholine and cat allergen challenge results. Many patients were also sensitive to other allergens. Patients, matched for asthma severity, had mild asthma, the definition of asthma being based on recent symptoms during cat exposure.

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Specific immunotherapy

This study was part of a large European multicentric, double-blind, placebo-controlled study on clinical efficacy of Fel d 1 peptides that included 140 patients receiving multiple doses of placebo or 7.5, 75, or 750 μg of ALLERVAX CAT. Patients were placed in 3 groups depending on the cumulative dose of ALLERVAX CAT received: 6 patients received placebo, 8 patients received 15 to 45 μg and were placed in the "low dose" group, 6 patients received 150 to 450 μg and were placed in the "medium dose" group, and 11 patients received 1500 to 4500 μg and were placed in the "high dose" group. Fel d 1 peptides or placebo were administered by subcutaneous injection once a week for 6 weeks. Assignment of subjects to study medication was at random. Patients who received the treatment for less than 6 weeks were given placebo on the other weeks. The protocol of immunotherapy is given in Table I.

Fel d 1 peptides (ImmLogic Pharmaceutical, Waltham, Mass) were provided as sterile, injectable, freeze-dried powder. Each vial contained 7.5, 75, or 750 μg of the 2 T-cell epitope-containing peptides IPC-1 and IPC-2 in sodium phosphate and mannitol excipient. For injection, the peptides were reconstituted with water and diluted in isotonic saline the day of the administration. Placebo vials were of identical appearance and contained the same excipients.

All subjects underwent the exact same investigations, including BPTs to cat extract and immunologic tests carried out before immunotherapy and 6 weeks after the last injection of study medication. More specifically, methacholine challenge was carried out 2 weeks before the first allergen challenge. Bronchial challenges were carried out 2 weeks before immunotherapy and 6 weeks after immunotherapy, which consisted of 6 weekly injections of peptide or placebo for every patient. Skin tests were done just before allergen provocation, 2 weeks before immunotherapy, and 6 weeks after immunotherapy. Blood was drawn at 8 AM the day of the bronchial challenge.

BPTs

BPTs were performed by using the Aquagen extract that was freshly reconstituted at each test day. Dilutions from 10 to 106 SPU/mL were used. Pulmonary function tests were carried out with the same equipment (Pneumoscreen; E. Jaeger Laboratories, Würzburg, Germany). Administration of all drugs that might interfere with performance of BPTs, in particular β2-agonists, was interrupted for at least 12 hours. The baseline FEV1 was always over 70% of predicted value. Diluent or allergen extracts were delivered by using an automatic, inhalation-synchronized dosimeter jet nebulizer (Spira Elektro 2; Respiratory Care Center, Hameenlinna, Finland). The reproducibility of the generation of the aerosols was controlled by a constant aerosolization pressure of 2 bar. The dosimeter recorded the number of inhalations taken by each patient. The bronchial response to aerosol challenge was assessed by measuring serial FEV1. Inhalations were continued until PD20FEV1 was obtained or until the maximal concentration had been administered.

Allergen-specific IgE and IgG

Fel d 1–specific serum IgE and IgG levels were measured with an ELISA as previously described.

Cytokine release by PBMCs stimulated by cat extract

Twenty milliliters of peripheral venous blood from each patient was drawn into a tube containing heparin, and PBMCs were isolat-
FIG 1. Effect of Fel d 1 peptides on cat allergen PD20FEV1. Patients were divided into 4 groups according to the treatment they received as indicated in Methods section. Bronchial challenge of patients was performed as described in Methods section before (baseline) and after the specific immunotherapy with Fel d 1 peptides (6 weeks). Statistical analysis is according to the Wilcoxon signed-rank test.
Increased release of IL-4 and IFN-γ before immunotherapy protocol had been initiated and 6 weeks after its end. PBMCs from 17 of the 31 patients allergic to cats spontaneously released IL-4 when cultured in vitro for 24 hours, whereas those of the 14 other patients did not produce detectable levels of IL-4 (mean ± SD for the entire group: 263.7 ± 522.3 pg/mL). PBMCs from 11 other patients, the IFN-γ levels were under the limit of detection of either placebo or 7.5 μg (low dose), 75 μg (medium dose), or 750 μg (high dose of Fel d 1 peptides as described in the Methods section).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>6 weeks</th>
<th>Baseline</th>
<th>6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>263.7 ± 622.3</td>
<td>175.9 ± 395.0</td>
<td>11.6 ± 4.3</td>
<td>11.2 ± 3.0</td>
</tr>
<tr>
<td>Low dose</td>
<td>218.4 ± 441.7</td>
<td>288.0 ± 598.8</td>
<td>18.1 ± 15.3</td>
<td>25.9 ± 31.6</td>
</tr>
<tr>
<td>Medium dose</td>
<td>40.2 ± 56.4</td>
<td>31.3 ± 47.4</td>
<td>13.6 ± 7.1</td>
<td>12.4 ± 7.5</td>
</tr>
<tr>
<td>High dose</td>
<td>186.1 ± 398.5</td>
<td>131.5 ± 238.5</td>
<td>13.7 ± 9.1</td>
<td>13.9 ± 7.4</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

*Serum cat allergen-specific IgE and IgG were titrated as described in Methods section.
†Patients received weekly injections of either placebo or 7.5 μg (low dose), 75 μg (medium dose), or 750 μg (high dose of Fel d 1 peptides as described in the Methods section.
§IgE and IgG titers before immunotherapy.
¶IgE and IgG titers after the end of immunotherapy.

**RESULTS**

**Clinical efficacy of peptide immunotherapy**

PD_{20}FEV_{1} varied widely between the different groups of patients. As shown in Fig 1, 6 weeks after ending immunotherapy, posttreatment PD_{20}FEV_{1} was not significantly different between the treated and placebo groups. However, in the medium and high groups there was a significant improvement between baseline and posttreatment days. The effects of administration of low doses of peptide on the PD_{20}FEV_{1} were less pronounced, whereas 3 of 8 patients in these group had a decrease in PD_{20}FEV_{1}. Bronchial challenge in patients treated with placebo was similar before and after treatment (Fig 1).

**Immunotherapy does not modify serum allergen-specific IgE and IgG titers**

Concentration of cat allergen-specific IgE and IgG in the serum of the patients 6 weeks after the end of immunotherapy were compared with the serum levels obtained before its initiation (Table II). There were no significant changes in IgE and IgG levels after administration of either placebo or Fel d 1 peptides whatever the dose of peptide received and the number of injections, indicating that immunotherapy with various doses of Fel d 1 peptides had no effect on the serum levels of Fel d 1-specific IgE and IgG antibodies.

**In vitro activation of PBMCs by allergen extract induces cytokine production**

The cytokine release by PBMCs was tested before the immunotherapy protocol had been initiated and 6 weeks after its end. PBMCs from 17 of the 31 patients allergic to cats spontaneously released IL-4 when cultured in vitro for 24 hours, whereas those of the 14 other patients did not produce detectable levels of IL-4 (mean ± SD for the entire group: 77 ± 55 pg/mL). PBMCs from 20 patients produced IFN-γ spontaneously, whereas for the 11 other patients, the IFN-γ levels were under the limit of sensitivity of the assay (mean ± SD for the entire group: 230 ± 430 pg/mL).

As shown in Fig 2, stimulation of the PBMCs for 24 hours with the cat allergen extract resulted in an increased release of IL-4 and IFN-γ before immunotherapy, and this effect was found to be statistically dose dependent for the production of IL-4 only (P < .0001, Kruskall-Wallis test). The maximal stimulatory dose was different for the 2 cytokines because the maximal production of IFN-γ was observed at a concentration of allergen that was about 25-fold greater than that for IL-4. Depending on the patients, optimal allergen concentration for induction of IL-4 secretion ranged from 0.0024 to 0.3 μg/mL and peaked generally at 0.06 μg/mL (mean ± SD of net maximal allergen-induced IL-4 production: 89 ± 80 pg/mL; P < .0001, Mann-Whitney U test). At the highest allergen concentrations, there was a strong decrease in IL-4 production. After immunotherapy, the dose-response curve was lowered by comparison with that before immunotherapy, and IL-4 production was found not to be statistically dose dependent, although the doses causing the maximal IL-4 response were of the same order as those obtained before treatment (from 0.0024 to 0.3 μg/mL). The optimal allergen concentration for inducing IFN-γ secretion ranged from 0.06 to 4.5 μg/mL depending on the patients and peaked generally at 1.5 μg/mL (mean ± SD of net maximal IFN-γ production: 75 ± 144 pg/mL; P < .04, Wilcoxon W test). Doses of allergen greater than 1.5 μg/mL induced a decrease of IFN-γ production.

Stimulation of the PBMCs with the combination of PMA and A23187, which served as the positive control, induced the production of IL-4 (mean ± SD of net induced IL-4 production: 494 ± 1317 pg/mL; P < .0001, Wilcoxon W test) in all but 1 patient. PMA/A23187-induced stimulation almost always resulted in a greater release of IL-4 as compared with Fel d 1-specific stimulation (P < .02, Wilcoxon W test). In all but 1 patient, IFN-γ was also significantly higher on PMA + A23187 activation as compared with spontaneous levels (mean ± SD of net IFN-γ production: 4400 ± 8170 pg/mL; P < .0001, Wilcoxon W test). This nonspecific stimulation almost always resulted in a greater release of IFN-γ than cat allergen (P < .0001, Wilcoxon W test).

**Cat allergen-induced IL-4 and IFN-γ release is not due to basophil activation**

To determine whether the IL-4 detected in the culture supernatants was produced by basophils or T cells, the
cytokine release by the PBMCs of 10 of the 31 donors allergic to cats was compared with that of histamine. First, we regularly found less than 0.1% of basophils in the PBMC preparations of all patients. As shown in Fig 3, PBMCs of all patients spontaneously released histamine, and histamine levels were not significantly increased after stimulation for 24 hours with Fel d 1 or PMA and A23187. However, the spontaneous IL-4 release by the PBMCs was increased significantly on Fel d 1- or PMA/A23187-induced activation (both $P < .008$, Wilcoxon W test). IFN-$\gamma$ release by the PBMCs was also significantly increased by the Fel d 1 activation ($P < .02$, Wilcoxon W test) and by the PMA + A23187 activation ($P < .006$, Wilcoxon W test). Finally, a 4-hour activation resulted in the secretion of similar levels of histamine (not shown), and histamine levels detected in the culture supernatants were stable because measurements were found constant until 72 hours in culture (not shown). These results suggest that the IL-4 release 24 hours after allergen stimulation is not due to the production of basophils.

**Cat allergen-induced IL-4, but not IFN-$\gamma$, release by activated PBMCs is suppressed**

The maximal in vitro release of IL-4 by PBMCs 6 weeks after the end of the treatment with Fel d 1 peptides was compared with that obtained before its initiation as determined in the allergen concentration range defined in Fig 2. The spontaneous in vitro release of IL-4 by PBMCs was not modified by Fel d 1 peptide injections or by placebo (not shown).

It was found that PBMCs from most patients treated with Fel d 1 peptides produced lower levels of IL-4 after in vitro stimulation with Fel d 1 as compared with IL-4 production by these cells before immunotherapy ($P < .0007$, Wilcoxon W test). However, as shown in Fig 4, only immunotherapy with the high doses of peptide resulted in a significant decrease in Fel d 1-induced IL-4 production ($P < .005$, Wilcoxon W test), whereas in the other groups the decrease in IL-4 production was statistically nonsignificant. There was no correlation between naïve IL-4 release and ADP$_{20}$FEV$_{1}$. Treatment with Fel d 1 peptides had no effect on the polyclonally induced production of IL-4 after stimulation with PMA and A23187 (results not shown), indicating that the intrinsic capacity of the cells to produce this cytokine was not affected. IL-4 production after stimulation with Fel d 1 peptides or with PMA and A23187 was unaltered in the placebo-treated patient group. Interestingly, Fel d 1 treatment at any of the doses administered did not significantly modulate the in vitro Fel d 1-induced production of IFN-$\gamma$ by PBMCs 6 weeks after the end of the treatment (not shown).

**DISCUSSION**

The results presented in this study show that immunotherapy with Fel d 1 peptides (ALLERVAX CAT) of individuals allergic to cats results in an increase of PD$_{20}$FEV$_{1}$ and is accompanied by a suppression of the
patients are protected during exposure to a living cat. A previous study carried out with cat room challenge showed that immunotherapy with medium and high doses of Fel d 1 peptides significantly increase PD20FEV1, confirming previous studies performed with less than 6 weeks were given placebo on the other weeks. Although the data analysis should have taken into consideration this classification, it would have yielded results that are not statistically significant because of the low number of patients studied. Therefore to have a sufficient number of patients, we combined patients into 4 groups (placebo and low-, medium-, and high-dose groups). Depending on the final clinical results of the whole study, it appears that the selection was correct. These results accord with previously published data, showing significant improvement irrespective of the injection protocol.

In vitro activation of the patients’ PBMCs by a cat allergen extract induced the release of IL-4 and, to a lesser extent, IFN-γ. Although the IL-4 production induced by Fel d 1 stimulation was low compared with the spontaneous release, it was detectable, and a strong statistical difference was found ($P < .001$). In addition, the effects of the cat allergen extract on IL-4 production were dose dependent, indicating the stimulation of T cells. The production of IL-4 is, however, not restricted to T cells. Previous studies showed that IL-2 is the key cytokine required for the development of Th2-type responses. The very low frequency of allergen-specific T cells in PBMCs and the fact that IL-4 is a key cytokine required for the development of Th2-type responses support the hypothesis that basophils may contribute to the initiation and maintenance of allergic reactions as one of the principal source of early IL-4 production. Our results suggest that, using our model and time course of mediator release, it is unlikely that the

![Graph](https://example.com/graph.png)

**FIG 4.** Effect of Fel d 1 peptides on cat allergen-induced IL-4 release. Patients were divided into 4 groups according to treatment they received as indicated in Methods section. PBMCs collected from patients before (baseline) and after specific immunotherapy with Fel d 1 peptides (6 weeks) were stimulated in vitro by various amounts of cat allergen extract as described in Methods section. IL-4 release in culture supernatant was determined by ELISA as described in Methods section. Only optimal IL-4 response is presented. Statistical analysis is according to Wilcoxon signed-rank test.
bee venom immunotherapy decreased IL-4 and IL-5 pro-
eosinophil activation at the sites of allergic inflammation.
induced T-cell and eosinophil recruitment, as well as
action might be the result of the inhibition of allergen-
immunotherapy and proposed that its mechanisms of
ing transcripts for IFN-\( \gamma \) after successful grass pollen
duction and increased IFN-\( \gamma \) production. Durham et
patterns in peripheral blood T ceils by decreasing IL-4
immunotherapy was reported to alter cytokine mRNA
most studies allergen-specific IgG antibodies were
increased during treatment with a native aeroallergen or
venom. However, except for the early effects of
immunotherapy, a significant decrease of specific serum IgE antibodies,
allergens are administered in increasing doses.
We found that cat allergen–specific IgE and IgG levels
in the serum were not affected by Fel d 1 peptide
immunotherapy. It is tempting to associate the
immunotherapy-induced decrease of IL-4 secretion by T
cells with a decrease in IgE concentrations. However,
such an effect is rarely observed in the short term for
immunotherapy with inhalant or venom allergens. Our
results are in accordance with those of Jutel et al\(^4\) who
showed that the decrease in IL-4 and IL-5 secretion after
bee venom immunotherapy was not accompanied by a
significant decrease of specific serum IgE antibodies,
whereas increased IgG concentrations became only sig-
nificant after 9 months. On the other hand, our result
suggest that peptides may induce an immune response
different than that induced by native allergens because in
most studies allergen-specific IgG antibodies were
increased during treatment with a native aeroallergen or
bee venom. However, except for the early effects of
venom immunotherapy, a significant correlation
between serum antibody levels and the clinical benefits
of immunotherapy has been rarely observed.\(^4\)

We thank Drs François Roussel and Jacques Banchereau for pro-
viding the mAbs anti-IFN-\( \gamma \), and Dr Alison Campbell for revising
the manuscript.

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