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Lack of de novo Sensitization to Tropomyosin in a Group of Mite-Allergic Patients Treated by House Dust Mite-Specific Immunotherapy

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Key Words

Immunotherapy · House dust mite · Shrimp · Food allergy

Abstract

Background: There is some evidence that specific immunotherapy may induce de novo sensitization to proteins contained in the allergen extract. This raises the possibility that the novel sensitization to cross-reacting allergens may cause food allergies. ***Objective:*** The aim of this study was to assess whether injection of mite-specific immunotherapy (SIT) may induce sensitization to shrimp tropomyosin. ***Methods:*** Seventy mite-allergic subjects who did not show any shrimp sensitization at baseline were followed up for at least 3 years. Thirty-one of them underwent a 3-year SIT course, 39 served as controls. At the follow-up visit, SPTs with both fresh shrimp and commercial extract were performed, and patients underwent an open oral challenge with shrimp. ***Results:*** Neither patient nor control had become sensitized to shrimp allergens at the end of the study period. Both patients and controls reported the regular intake of crustaceans and/or molluscs. ***Conclusion:*** Injection SIT with house dust mite extracts does not seem to induce de novo tropomyosin sensitization in mite-allergic patients.

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Introduction

Allergen-specific immunotherapy (SIT) is the only available treatment able to modify the natural history of allergic disease. Its efficacy for rhinoconjunctivitis and asthma caused by inhalant allergens has been demonstrated by a number of properly performed clinical studies and is now widely accepted [1–5]. Presently, both injection and sublingual SIT are carried out using commercial extracts of whole airborne allergens (pollens, house dust mites, animal dander or molds); this causes patients undergoing SIT to be exposed to proteins to whom they are sensitized and to proteins (either allergenic or not allergenic) to whom they are not sensitized. As a consequence, one potential side effect of SIT is the induction of de novo sensitization to allergenic proteins. This issue has received comparatively little attention in the past. Moverare et al. [6] recently observed the appearance of IgE specific for birch profilin, Bet v 2, and calcium-binding protein, Bet v 4, in 65% of birch pollen-allergic patients submitted to rush immunotherapy, and Ball et al. [7] detected an IgE and IgG4 response to Phl p 1 epitopes not recognized before SIT, and in one case, the de novo appearance of IgE against a new allergen in grass pollen-allergic subjects. The induction of IgE showing new specificities to allergenic components present in extracts used for SIT has been observed in some earlier studies as well

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[8–11]. The clinical significance of the onset of these new sensitivities is still unclear, but the possibility that SIT with airborne allergens may sensitize patients to cross-reacting proteins present in foods is particularly concerning. In this regard, tropomyosin represents a typical example. This protein belongs to the muscular apparatus of invertebrates and is present both in airborne allergens (e.g. house dust mite, cockroach) and foods (e.g. crustaceans and mollusks). Tropomyosin is a highly cross-reacting allergen [12–15], and due to its heat stability and pepsin resistance [16], it may induce severe allergic reactions in sensitized individuals. One previous study suggested that SIT with house dust mite may cause the appearance of new cross-reacting IgE antibodies to snail and shrimp and lead to a worsening of clinical symptoms after the ingestion of these foods [17]. Recently, the same authors suggested that mite SIT may represent a risk factor for severe snail-induced reactions [18]. The present prospective study aimed to detect whether mite SIT induces de novo sensitization to cross-reacting food allergens and should therefore be considered as a possible risk factor for food allergy.

Methods

Patients

Seventy adults (M/F 38/32, age 13–53 years, mean 30 years) seen at the allergy unit of Bollate Hospital from January 1999 to June 2001 were studied, fulfilling the following admission criteria:

(1) House dust mite allergy diagnosed on the basis of both clinical symptoms (perennial rhinoconjunctivitis with or without asthma) and positive SPT with commercial mite extract (50.000 SBU/ml; Allergopharma, Reinbeck, Germany); (2) negative SPT with both fresh shrimp and commercial shrimp extract (ALK-Abello 5% w/v), and (3) a history of clinical tolerance to crustaceans, mollusks and snails.

In view of respiratory symptom severity, 31 patients underwent a 3-year course of injection SIT (see below) that was completed in all cases by the end of June 2004. The remaining 39 subjects served as controls. During the study period, patients and controls were free to eat crustaceans as well as other invertebrates (shellfish, octopus, squid, snails) and were specifically recommended to communicate any intolerance to these foods as soon as they appeared.

At the end of the 3-year SIT course (patients) or in June 2004 (controls), study participants were thoroughly interviewed about their average intake of crustaceans and mollusks (including frequency, amounts ingested and type) and about any intolerance to these foods, and SPTs with both fresh shrimp and commercial shrimp extract were repeated. Moreover, patients underwent an open oral challenge with fresh shrimp: patients were asked to ingest 1 boiled shrimp and were kept under control at the allergy center for the following 2 h. The effect of SIT on respiratory allergy was assessed on the basis of drug consumption recording and of clinical scores recorded on a visual analogue scale.

Skin Tests

SPTs were carried out and read following established methods [19]; wheals showing a mean diameter >3 mm were considered positive.

Injection Immunotherapy

All patients underwent injection SIT with a commercial depot aluminium hydroxide-adsorbed house dust mite extract (Allergopharma). Weekly doses were given during the 'build-up' (induction) phase in order to reach the planned maintenance dose (1.0 ml of the final vial) that was achieved in all patients. Maintenance doses were given at 3- to 4-week intervals to all patients. All shots were given at this allergy unit.

Results

The 3-year SIT course proved clinically effective; all patients reported disappearance or a marked reduction of respiratory symptoms. These data were confirmed by visual analogue scale recordings that showed either a marked reduction or a zero setting of clinical scores in all cases. Moreover, 29 out of 31 patients had been able to discontinue all their treatments including nasal and inhaled corticosteroids and β-agonists. SIT was well tolerated by all patients and no adverse reactions to SIT were observed. At the follow-up visit, no patient (0/31) nor control (0/39) reported any episode of allergy following the ingestion of crustaceans and/or mollusks. Subjects from both groups reported the regular ingestion of shrimps, squid and/or shellfish (by average once every 2 weeks) whereas snails had been eaten only by 1 control subject on some occasions. No skin reactivity to fresh shrimp or commercial shrimp extract was observed at the control visit and all 31 (100%) patients tolerated the ingestion of shrimp on open oral challenges.

Discussion

Previous observations that SIT may induce de novo production of IgE specific for allergenic proteins [6–11] and one study reporting an increase in specific IgE to snail after mite SIT [17] raised the possibility that SIT extracts containing cross-reacting allergens may induce potentially severe food allergies. The present prospective study aimed to clarify this point in mite-allergic patients. Shrimp is by far the most frequent cause of allergic reactions among crustaceans and mollusks and was therefore chosen as a representative of tropomyosin-containing foods. SPTs with both fresh shrimp and commercial shrimp extract were used to assess shrimp hypersensitiv-

ity; as in a previous study the sensitivity of these skin tests proved good [20], one can be rather confident that no mite-allergic subjects were sensitized to tropomyosin or other shrimp proteins at the beginning of the study. The fact that both patients and controls remained negative on SPT after 3 or more years and that they could eat crustaceans and mollusks without any consequence seems to rule out a de novo shrimp sensitization during the study period. The possibility that the extract used for SIT did not contain tropomyosin was considered. However, Allergopharma immunotherapy preparations are made using purified mite bodies (Dr. O. Cromwell, personal communication); it is therefore reasonable to assume that such extracts contain relatively large amounts of allergenic material derived from the body parts, including tropomyosin (Der p/f 10), as clearly demonstrated by in vitro studies carried out at Allergopharma Laboratories, showing a clear band at 37 kDa on SDS-PAGE and immunoblots, showing cross-reactivity with shrimp and prawn extracts (Dr. O. Cromwell, personal communication). Therefore, it is possible to conclude that (at least in the patients in this study) the repeated administration of mite tropomyosin by SIT did not induce any appreciable sensitization to this cross-reacting protein. Recently, some authors claimed that mite SIT might even protect from snail sensitization [21], but this opinion has been tackled by other researchers suggesting that, on the contrary, mite SIT is a risk factor for severe reactions after snail ingestion [18]. Based on the findings of the present study, mite SIT does not seem a risk factor for sensitization to tropomyosin-containing foods; it is also unlikely that it exerts any protective activity in this sense. Genetic predisposition of the individual towards developing a Th2 response to specific allergens is one of the key determinants of allergenicity, and although some data point to the level of allergen exposition as a relevant factor in sensitization [22–24], it seems unlikely that the repeated administration of an allergen to a patient that is not prone to become allergic to that protein may eventually induce sensitization. So far, no patient with shrimp allergy seen at this allergy center has undergone mite SIT, as respiratory symptoms were extremely slight in all cases. Obviously, it cannot be excluded that in such patients mite SIT may exacerbate shrimp allergy, although this might be extremely difficult to demonstrate as these subjects are normally strongly recommended to exclude crustaceans and mollusks from their diets, irrespective of SIT. In conclusion, the present study suggests that the onset of food allergy to invertebrates as a consequence of mite SIT is unlikely in patients who do not show any baseline shrimp hypersensitivity.

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