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Sublingual immunotherapy for cow's milk protein allergy: a preliminary report

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Key words: cow's milk allergy; sublingual immunotherapy; tolerance.

After the age of 5, cow's milk allergy (CMA) has a low probability of spontaneous recovery (1). The aim of this study was to apply sublingual immunotherapy (SLIT), an efficient desensitization method (2), in patients with persistent immunoglobulin E (IgE)-mediated CMA.

Eight children (> 6 years) with IgE-mediated CMA were recruited and underwent two milk challenges (before and after SLIT), to determine the eliciting dose (ED). In case of symptoms difficult

Six months of milk sublingual immunotherapy induced tolerance in four of eight children with immunoglobulin E-mediated cow milk allergy.

to interpret, a double-blind placebo-controlled food challenge (DBPCFC) was undertaken. SLIT began the day after the challenge using cow milk (CM), for 6 months. Patients kept the milk in their mouth for 2 min (0.1 ml for the first 2 weeks, increasing by 0.1 ml every 15 days until 1 ml/day).

Cow milk-specific IgE (Phadia CAP System®, Saint Quentin en Yvelines, France) were measured before each challenge.

During the first challenge, the mean ED was 39 ml, range 4–106 ml. In six patients, this ED was reached following subjective symptoms elicited by lower milk doses and disappearing spontaneously. Recurrent subjective symptoms in patient 6 led to a positive DBPCFC. Patient 8 withdrew from the SLIT protocol after 5 months because of an oral syndrome attributed to the presence of milk in the mouth. Among the remaining seven patients, six completed the protocol, with a poor compliance in one, none experiencing any side-effects (Table 1).

During the second challenge, the mean ED increased, 143 ml, 44 to > 200 ml ($P < 0.01$, paired t -test). Three patients did not react with 200 ml of CM and normalized their diet. Patient 4 presented abdominal pain following ingestion of 150 ml and parents denied continuing the challenge, but CM was progressively reintroduced at home until a normal diet 3 months later. The ED increased in the two others who completed the SLIT protocol and remained unchanged in the patient with a poor compliance.

Casein-specific IgE decreased in five children and increased in one, albeit with no significant differences.

Cow milk oral desensitization, based on the intake of increasing doses of CM during 6 months, was successful in 70% of patients, with 50% exhibiting side-effects and 15% withdrawn because of uncontrolled side-effects (3, 4).

We tested a SLIT, already reported for hazelnut and kiwi allergy (5, 6), to desensitize IgE-mediated CMA in children older than 6, for whom the prognosis of persistent CMA has become highly predictable (1). All patients had an immediate severe reaction to CM during the first challenge, rendering any diag-

nosis difficulties unlikely, with a DBPCFC still required in one case. Subjective symptoms nonetheless occurred in 75% of patients, for low doses of CM, probably reflecting anxiety, in children having previously experienced severe allergic manifestations.

The ED increased in the six children who completed the SLIT and four, with the highest milk ED at the first challenge (> 30 ml), normalized their diet. The ED remained unchanged in the patient with a poor compliance. Patient 8 does not allow concluding. Recently, a younger child (4.5 years) completed the same SLIT, with an oral syndrome during the week preceding the second challenge, even though the ED increased from 37 to 177 ml (data not shown). Subjective symptoms before the second challenge might be a manifestation of anxiety.

Cow milk-specific IgE did not vary following SLIT, suggesting that tolerance relies on other mechanisms, able to counterbalance the triggering effect of IgE levels.

Briefly, SLIT, using a CM dose below the ED is safe, easy, and increased the milk ED after 6 months, suggesting a potential alternative to the elimination diet in patients with persisting IgE-mediated CMA. Confirmation with larger studies should aim at determining the optimal duration of the procedure, which might prove dependent on the ED at first challenge.

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Table 1. Results of cow's milk challenge, before and after the sublingual immunotherapy during 6 months

Patients no. (years)	First cow's milk challenge			Second cow's milk challenge		
	Subjective symptoms (dose of CM)	ED (ml)	Objective symptoms	ED (ml)	Symptoms	Evolution/remarks
1 (12)	4 (pruritus)	44	Angioedema, RC	–	None	Normal dairy diet
2 (6)	–	106	Angioedema, urticaria	–	None	Normal dairy milk
3 (8)	0.1 (tickly throat)	37	Digestive anaphylaxis*	–	None	Normal dairy milk
4 (6)	5 (erythema)	36	Digestive anaphylaxis*	150	Abdominal pain	Normal dairy milk 3 months later
5 (17)	0.5 (tickly throat)	8	Asthma, RC	93	Asthma	
6 (9)	0.1 (tickly throat), 4 (cough)	14	Asthma, urticaria	44	Urticaria	DBPCFC at first challenge
7 (6)	9 (cough)	68	Asthma	70	Asthma	Poor compliance
8 (9)	–	4	Digestive anaphylaxis*, urticaria	Not done		Withdrawn

ED, eliciting dose; RC, rhinoconjunctivitis; DBPCFC, double-blind placebo-controlled food challenge.

*Abdominal pain, vomiting and diarrhea.

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Occupational asthma from dried flowers of *Carthamus tinctorius* (safflower) and *Achillea millefolium* (yarrow)

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Key words: *Achillea millefolium*; *Carthamus tinctorius*; occupational asthma safflower; yarrow.

A 44-year-old woman, non-smoker, with a clinical history of spring seasonal rhinoconjunctivitis and asthma. She had no family history of atopy. For the last 6 years, she had been working temporarily as instructor of personnel making dried flower arrangements (centre-pieces and baskets). Since 5 months after

her first contact with dried flowers of safflower and yarrow she began to experience rhinitis, asthma and urticaria symptoms in the workplace when she handled these dried flowers.

The physical examination was normal. Basal spirometry and chest X-ray was normal. Methacholine inhalation test was positive with a PC₂₀ of 2.5 mg/ml. Total serum IgE was 7.94 kU/l. Skin prick test with common aeroallergens were positive to pollen from *Cupressus sempervirens*, *Olea europaea*, *Lolium perenne*, *Salsola kali*, *Artemisia vulgaris* and *Parietaria judaica* and to cat and dog epithelium.

Skin prick test with aqueous extracts from dried flowers were positive to safflower (8 × 5 mm) and yarrow (10 × 7 mm). Specific Inhalation Bronchial Challenge with aqueous extract of safflower (0.625 mg/ml) and yarrow (1.25 mg/ml) elicited an asthmatic response with a fall in FEV₁ of 27% and 31% respectively (Fig. 1). Specific IgE (EAST) with safflower and yarrow flowers was 1.4 and 0.9 kU/l respectively. Immunoblotting with safflower flowers revealed several IgE binding bands of 64, 61, 47, 45, 41, 21, 18.6, and between 14–15 kDa and with yarrow flowers bands of 51, 21 and 18 kDa.

Occupational respiratory symptoms caused by decorative flowers are seldom reported in the literature (1). Only two dried flowers (*Limonium tataricum* and *Gypsophila paniculata*) have been reported as a cause of allergic asthma (2, 3).

We report two dried flowers (*Achillea millefolium* and *Carthamus tinctorius*) as new causes of occupational asthma.