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Cow's milk epicutaneous immunotherapy in children: A pilot trial of safety, acceptability, and impact on allergic reactivity

To the Editor:

To date, the only therapeutic option in general practice for cow's milk allergy consists of avoiding cow's milk proteins in the diet. However, this is hard to implement in older children,¹ and it puts them at risk in case of accidental ingestion. The recent clinical trials investigating immunotherapy for milk allergy all favored the oral route, including oral^{2,3} and sublingual immunotherapy.⁴ Epicutaneous immunotherapy (EPIT), consisting of the repeated application of allergens to the intact skin, may be an alternative method for food allergy treatment. Recently, a new epicutaneous delivery system (EDS) has been developed and successfully tested in animals.⁵ This pilot study evaluates the safety and acceptability of EPIT in children.

This bicenter, double-blind, placebo-controlled study enrolled children (age 3 months to 15 years) with a history of systemic symptoms related to milk ingestion, serum cow's milk protein-specific immunoglobulin (sIg)-E levels >0.35 KU_A/L and/or a positive skin prick test to cow's milk protein (wheal > 3 mm), and willingness to participate. If the oral food challenge (OFC) was positive—that is, the cumulative tolerated dose (CTD) was below 10 mL—subjects were randomized (1:1) to receive blind therapy with active or placebo products. The study scheme and tests performed are described in Fig 1.

Treatment consisted of three 48-hour applications of the EDS per week (Viaskin; DBV Technologies SA, Paris, France) for 3 months. Active EDS contained 1 mg skimmed cow's milk powder. Placebo contained 1 mg glucose. EDS was applied to the interscapular area without specific preparation of the skin. The powder solubilizes by perspiration and disseminates in the thickness of the stratum corneum.⁶

The CTD was determined with OFCs carried out in the hospital. First, 0.1 mL of a commercially available milk formula was applied to the internal side of the inferior lip (labial test, no ingestion). This was followed by the ingestion, every 30 minutes, of increasing doses of the formula (0.1 mL to 20 mL).

Parents signed informed consent. The study was approved by the local ethics committee and registered with the French Health Agency.

Patients with at least 1 treatment dose were included in the intent-to-treat (ITT) analysis. The per protocol (PP) analysis included patients not lost to follow-up who completed the study without major protocol deviation.

Local reactions exceeding simple erythema, with or without local pruritus, and associating erythema, edema, and infiltration (grade I of the International Contact Dermatitis Research Group classification)⁷ were considered local adverse events (AEs). Respiratory, ear nose throat (ENT) and digestive manifestations, and generalized cutaneous disorders were considered general AEs.

Twenty-one patients were screened for eligibility (Fig 1). Two patients consumed up to 60 mL milk and were not randomized. Mean ± SD age of the ITT population was 3.82 ± 2 years (range, 10 months to 7 years, 8 months). Three patients were excluded from the PP population (1 lost to follow-up and 2 enrolled despite baseline CTD >67.1 mL).

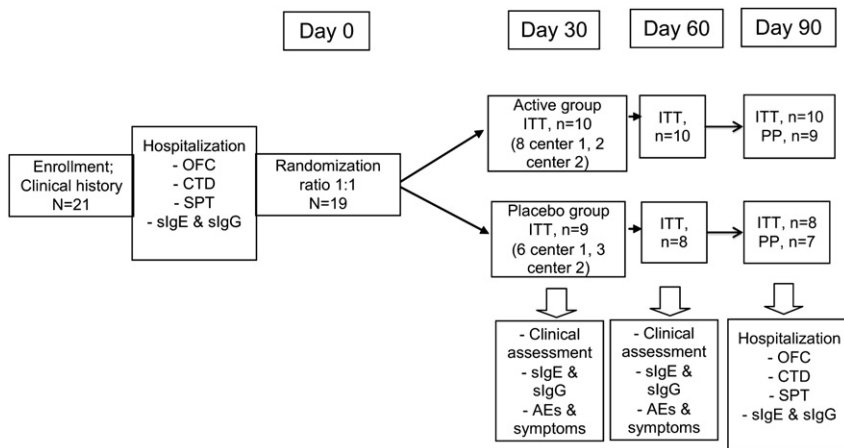


FIG 1. Study scheme (timelines) and tests performed during visits and hospitalizations. OFC, Oral food challenge; SPT, skin prick test.

TABLE I. Frequency and risk of AEs during epicutaneous desensitization in active and placebo groups, ITT patients (n = 18)

Adverse events	Active group			Placebo group			Active vs placebo OR (95% CI)	P value
	No. of patients with symptoms/total no. of patients*	No. of doses with symptoms/total no. of doses applied	Risk of symptom occurrence (%) (95% CI)	No. of patients with symptoms/total no. of patients*	No. of doses with symptoms/total no. of doses applied	Risk of symptom occurrence (%) (95% CI)		
Skin disorders	5/10	93/470	19 (16–23)	6/8	46/316	15 (11–19)	1.47 (0.95–2.08)	.07
Local pruritus	3	54/470	11 (8–14)	2	38/316	12 (8–15)	0.95 (0.61–1.48)	.81
Local eczema	2	39/470	8 (5–10)	1	3/316	1 (<0.5–1)	8.20 (2.72–24.5)	<.001
Cutaneous rash	0	0/470	—	1	3/316	1 (<0.5–1)	0.10 (0.01–1.95)	.03
Face oedema	0	0/470	—	1	1/316	1 (<0.5–1)	0.22 (0.01–5.45)	.22
Urticaria	0	0/470	—	1	1/316	1 (<0.5–1)	0.22 (0.01–5.45)	.22
Respiratory/ENT disorders	2/10	2/470	1 (<0.5–1)	4/8	5/316	2 (<0.5–1)	0.30 (0.07–1.35)	.09
Asthma	1	1/470	1 (<0.5–1)	2	3/316	1 (<0.5–1)	0.29 (0.04–1.97)	.15
Cough	0	0/470	—	0	0/316	—	—	—
Larynx pain	0	0/470	—	1	1/316	1 (<0.5–1)	0.22 (0.01–5.45)	.22
Bronchitis	1	1/470	1 (<0.5–1)	0	0/316	—	2.02 (0.08–49.40)	.41
Rhinitis	0	0/470	—	0	0/316	—	—	—
Sneezing	0	0/470	—	0	0/316	—	—	—
Conjunctivitis	0	0/470	—	1	1/316	1 (<0.5–1)	0.22 (0.01–5.45)	.22
Gastrointestinal disorders	1/10	16/470	3 (1–5)	0/8	0/316	—	22.98 (1.36–>100)	<.001
Diarrhea	1	16/470	3 (1–5)	0	0/316	—	22.98 (1.36–>100)	<.001
Vomiting/abdominal pain	0	0/470	—	0	0/316	—	—	—
Other disorders	1/10	6/470	1 (<0.5–1)	1/8	1/316	1 (<0.5–1)	2.94 (0.50–17.46)	.16
Fever	1	6/470	1 (<0.5–1)	1	1/316	1 (<0.5–1)	2.94 (0.50–17.46)	.16
Totals		117/470			52/316			

A total of 786 doses were applied (470, active group; 316, placebo group).

*Patients could present more than 1 symptom.

The values in boldface represent the total of cases per Class Organ.

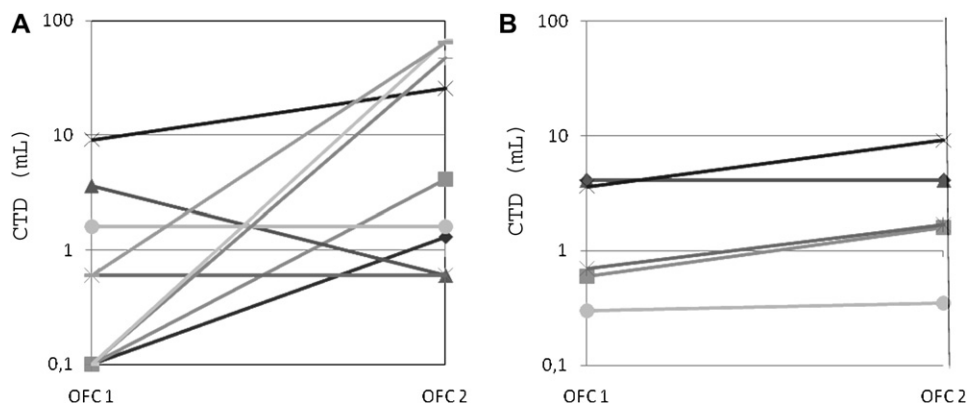


FIG 2. Individual evolution of CTD during the oral food challenges (OFCs) at D0 and D90 in the active (A) and placebo group (B) in the PP population. All values are in milliliters.

Symptoms leading to the diagnosis of cow's milk allergy were eczema (5 active, 5 placebo), chronic diarrhea (4 active, 1 placebo), skin rash and urticaria (4 active, 5 placebo), vomiting (7 active, 6 placebo), and other symptoms (2 active, 3 placebo).

Adverse events in the ITT population are described in Table I. Typically, local erythema occurred at the site of application and remained visible during 4 to 14 days. Local AEs were reported for 4 children in the active group and 2 in the placebo group. The estimated risk of local eczema was higher in the active group

than in the placebo group (Table I). Among the ITT population, 24 systemic AEs occurred in the active group and 8 in the placebo group, with no anaphylaxis (Table I). Local steroids for local eczema were used in 1 patient of each group. Treatment was well accepted by the patients. No child interrupted treatment because of an AE, and none received epinephrine or was seen at the emergency department or hospital.

In the PP population, EPIT treatment tended to increase the CTD, from a mean \pm SD of 1.77 ± 2.98 mL at day 0 to $23.61 \pm$

28.61 mL at day 90 ($P = .18$; Fig 2). In the active group, CTD slightly decreased in 1 patient and increased by more than 10-fold in 2 patients and more than 100-fold in 3 patients. Mean CTD did not vary in the placebo group (4.36 ± 5.87 mL at day 0 vs 5.44 ± 5.88 mL at day 90). The mean CTD increment was 12-fold in the active group versus 8% in placebo group ($P = .13$).

Epicutaneous immunotherapy did not increase cow's milk protein-sIgE. Mean \pm SD sIgE levels were 20.18 ± 23.27 KU_A/L in the active group and 12.19 ± 17.02 KU_A/L in the placebo group at day 0 and, respectively, 19.48 ± 17.44 KU_A/L and 20.99 ± 32.55 KU_A/L at day 90 ($P = .68$).

Epicutaneous immunotherapy may be a novel approach for allergen-specific immunotherapy and represents a promising alternative to the well established subcutaneous and sublingual methods of immunotherapy administration, as recently underlined by Werfel⁸ in the Journal. Without any skin preparation or adjuvant, the EDS Viaskin allows dissemination of the allergen to the immune cells of the stratum corneum without systemic diffusion of the intact allergen.⁶

This first investigation in children with cow's milk allergy shows that EPIT using the EDS is virtually devoid of serious systemic AEs, which differs from subcutaneous and oral immunotherapies.^{2,3} The active treatment was associated with more frequent complaints for local pruritus and discomfort than placebo, but this did not lead to treatment interruption. It was safe and most frequently well tolerated, even locally. Local reactions were twice less frequent with the placebo than with the active treatment, but lesions never exceeded grade II (International Contact Dermatitis Research Group classification)⁷ and were easily controlled by using local topical medications. Interestingly, local reactions largely varied between patients, even in the active group. Several reports suggested that cutaneous applications of allergen might trigger sensitization.⁹ In this study, only 1 child of the active group slightly decreased his CTD.

Although this preliminary study failed to demonstrate a statistically significant improvement of the CTD, recent food allergy oral immunotherapy studies suggest that the decrease in sIgEs and sIgGs becomes significant more than 1 year after treatment initiation.^{2,3,9} Considering the other desensitization techniques and the kinetics already known for the classic subcutaneous route, it is likely that 3 months represented a duration that is too short to show significant effects.

Following the recent study of Senti et al¹⁰ showing the potential efficacy of EPIT in patients with pollen allergy, this pilot study in childhood milk allergy suggests that EPIT is well tolerated, does not lead to sensitization, and exhibits a clear trend toward clinical efficacy. These results pave the way to further investigations of EPIT efficacy and suggest that longer treatment periods might be appropriate.

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Ozone activates pulmonary dendritic cells and promotes allergic sensitization through a Toll-like receptor 4-dependent mechanism

To the Editor:

Ozone is a highly reactive component of air pollution that is formed by the interaction of sunlight with oxygen, nitrous oxides, and volatile organic compounds. Human exposure to air pollution, including ambient ozone, is associated with several health problems, including increased incidence and severity of allergic airways disease. Ozone might exacerbate existing asthma by activating monocytes and macrophages,¹ which could in turn activate allergen-specific memory T cells. However, the ability of ozone to increase the prevalence of *de novo* asthma likely involves additional cell types because monocytes and macrophages are not efficient stimulators of naive T cells. Effective naive T-cell stimulation is generally thought to require activated dendritic cells (DCs),² which display very high levels of the MHC and also provide strong costimulatory signals, such as CD86 (B7.2). Recently, DCs residing in the airway were found to be activated by ozone,³ suggesting that these DCs might promote *de novo* asthma by stimulating naive T cells. Although naive T-cell stimulation might occur within the lung, a more widely held view is that antigen-bearing DCs migrate from the lung to the draining thoracic lymph nodes (LNs) for antigen presentation to naive T cells. However, the effect of ozone on LN DCs has not been reported, and it is not known whether ozone