"Allergie alimentaire: faut-il et quand faire une accoutumance ?"

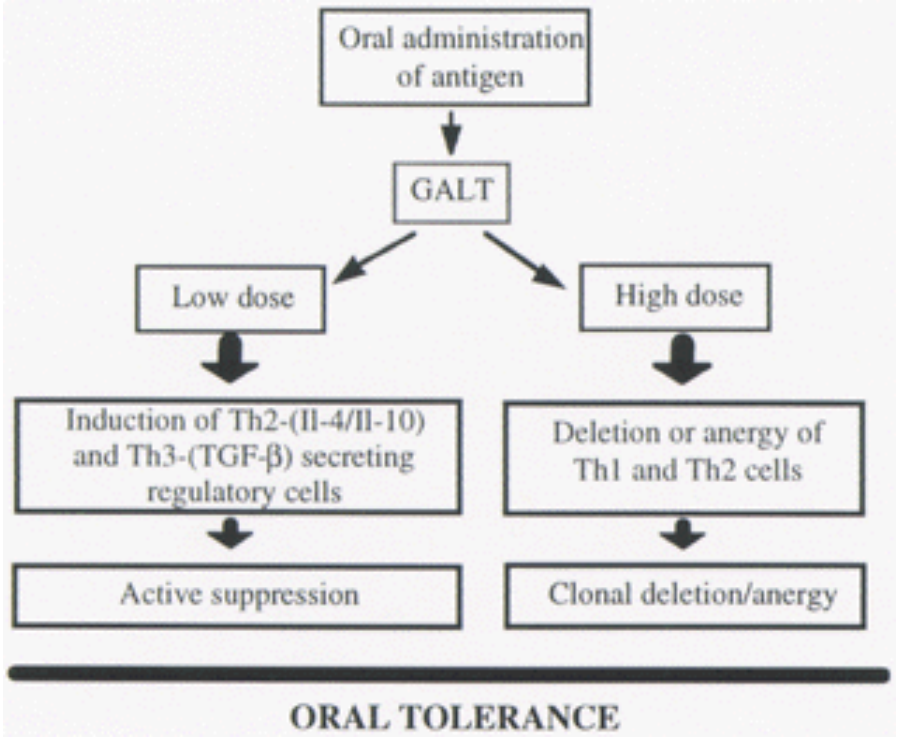
"Allergologie Pratique«

Ch DUPONT

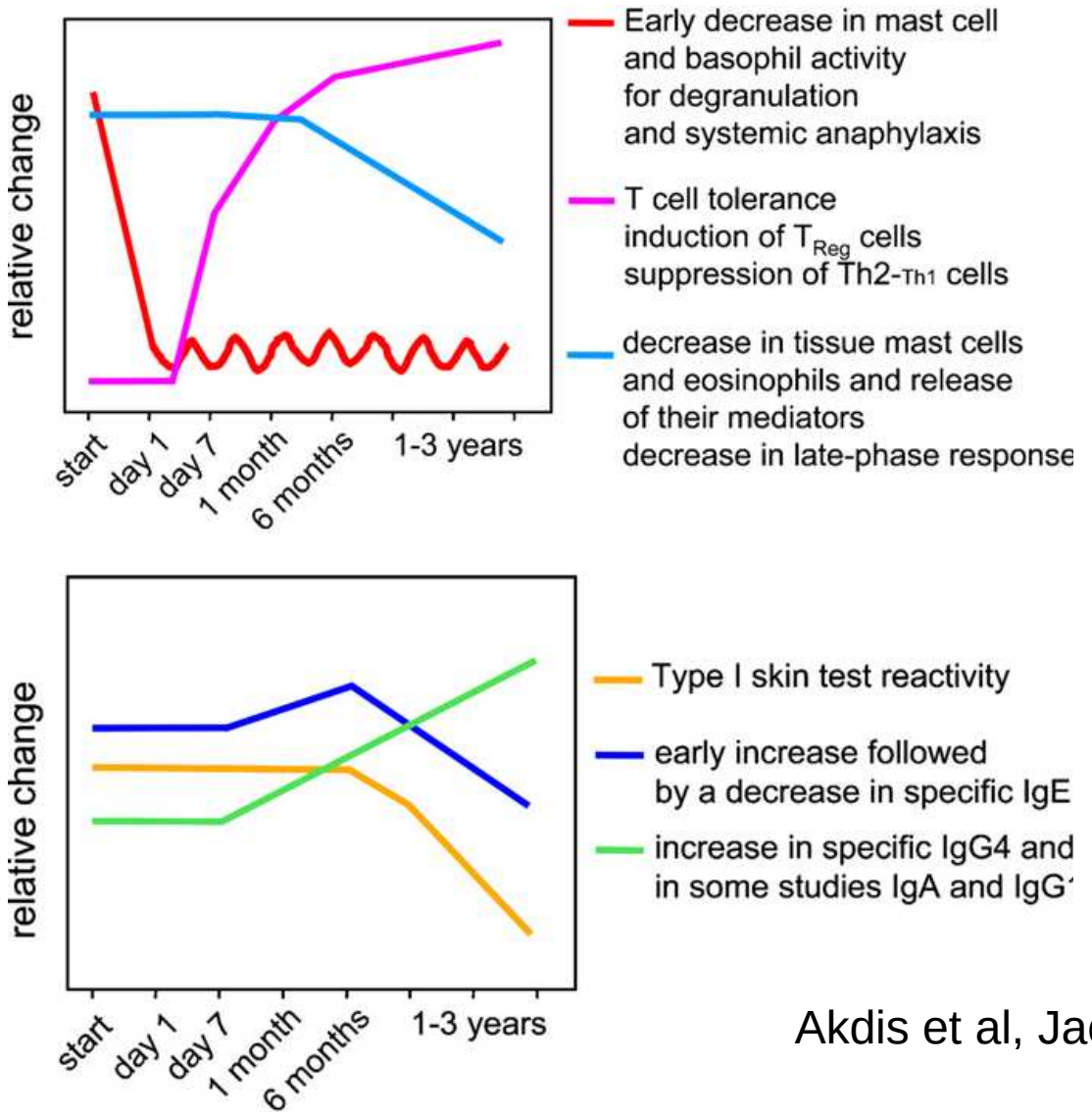
Mithridate VI musée du Louvre

- selon la légende, le roi Mithridate eut la vie sauve le jour où l'on tenta de l'empoisonner pour avoir pris la précaution d'ingérer préalablement régulièrement de petites doses de poison, on parle d'ailleurs de « mithridatisation »

Oral tolerance induction



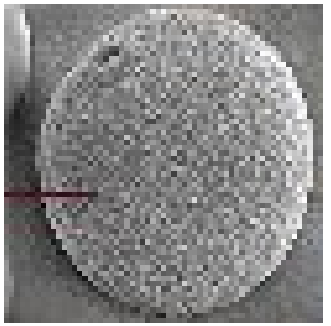
Immunotherapy

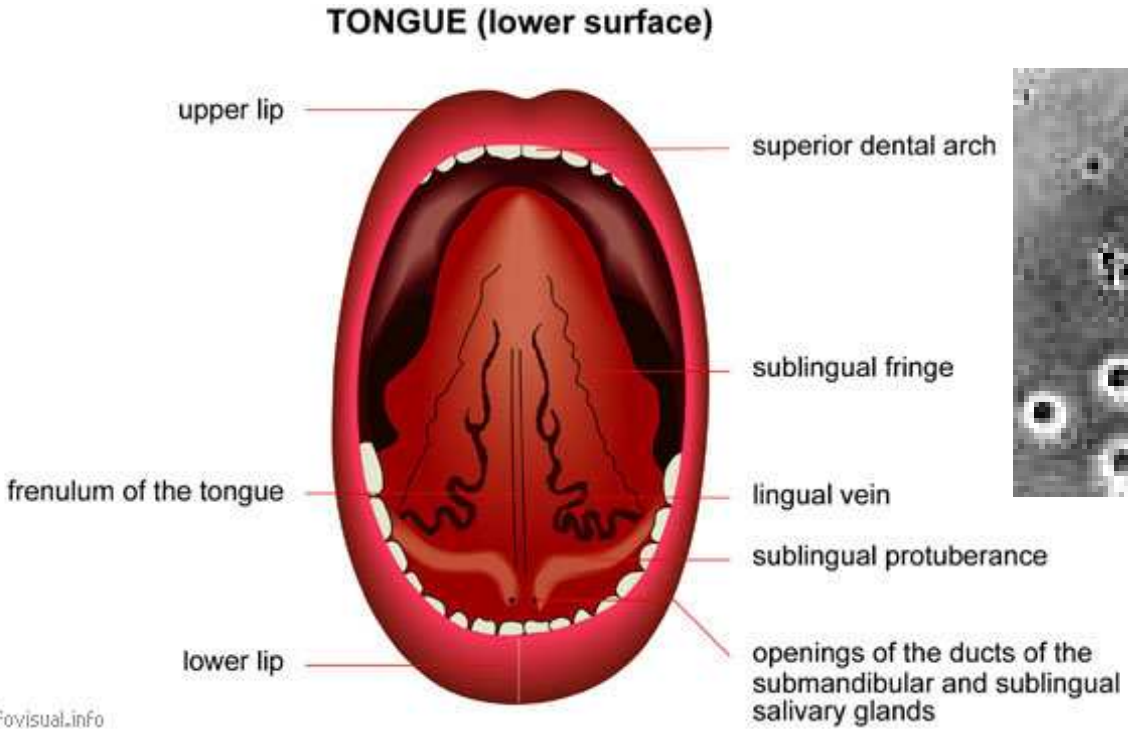


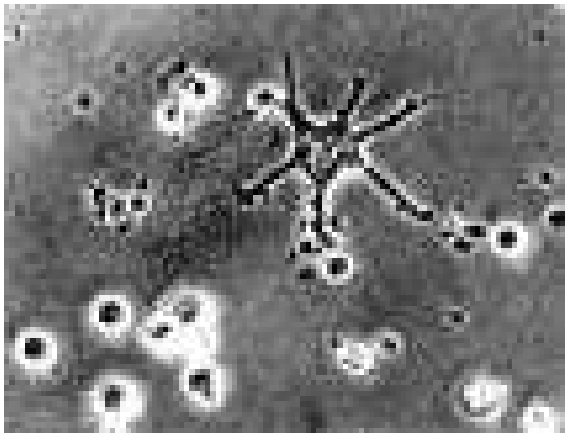
Akdis et al, Jaci 2007

Oral Immunotherapy

- desensitisation process using the sublingual route







Y a-t-il une différence?

- Certainement entre la voie sublinguale et la voie intestinale basse
  - Cellules immunocompétentes?
  - Disponibilité des allergènes (pas de digestion buccale, digestion dès le passage dans l'estomac par la pepsine puis dans le duodénum)
- Cela permet-il de différencier désensibilisation et tolérance orale?

patients desensitized or tolerized?

- Desensitization : the ability to tolerate more of an allergenic substance after treatment
  - requires ongoing exposure to be maintained, and it is completely unclear how long it would take before lack of continued exposure would result in loss of desensitization.
- Tolerance : permanent loss of reactivity to a previously allergenic substance.
  - proved by completely removing the relevant allergen from an individual's diet for a period of time.

Skripak JM et al, JACI, in press

Effet dose dans l'allergie alimentaire

- Allergie IgE et non IgE-médiée
- Tests de provocation montrant la variation de seuils de réactivité (NOAEL, eliciting dose) selon les sujets
- Augmentation du volume toléré avec l'âge lors que l'enfant devient tolérant
- Signification thérapeutique différente selon que le sujet tolère 1,5mL de lait (faire une désensibilisation?) ou qu'il en tolère 60mL (induire une tolérance orale?)?

Oral desensitizing treatment in food allergy: clinical and immunological results G. PATRIARCA Aliment Pharmacol Ther 2003; 17: 459–465

- Methods:
- 55 patients with food allergy, oral desensitizion (standardized protocols)
- Control group : age- and sex-matched subjects (strict elimination diet)
- Specific IgE and IgG4 at baseline and after 6, 12 and 18 months.

Oral desensitizing treatment in food allergy: clinical and immunological results G. PATRIARCA Aliment Pharmacol Ther 2003; 17: 459–465

- Results:
  - 83.3% successfully completed the treatment
  - 51.1% experienced some mild side-effects, oral antihistamines or sodium cromolyn
  - Specific IgE : significant decrease; specific IgG4: significant increase in all patients

Conclusions: may represent an effective alternative approach in food-allergic patients.

Egg oral immunotherapy in nonanaphylactic children with egg allergy

- Without anaphylaxis 24-month egg OIT rush, build-up, and maintenance phases
- Double-blind, placebo-controlled food challenges at conclusion
- Egg IgE and IgG

- Children (1-16 years) Duke and Arkansas
- Egg allergy: ≥ 7 kU/L (≥ 2 kU/L in≤ 2 years) or with allergic reaction to egg within 6 months

Buchanan A, … Burks W, Jaci, 2007,

Egg oral immunotherapy in nonanaphylactic children with egg allergy

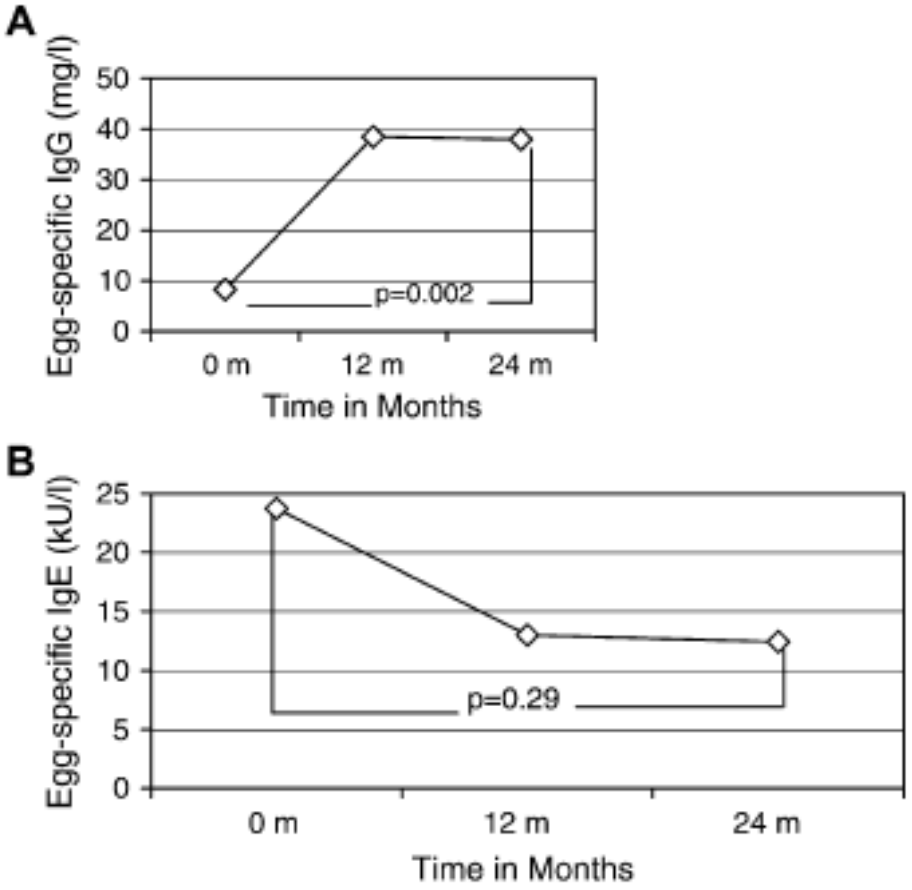


FIG 1. A, Mean egg-specific IgG levels (in milligrams per liter) over time. B, Mean egg-specific IgE levels (in kilounits per liter) over time.

TABLE IV. Outcomes of DBPCFCs with cumulative ingested egg protein amount at reaction

Subject no.	First challenge* (24 mo, during OIT)	Second challenge† (3 mo after OIT)
001	Pass	Pass
002	2 g	NA
003	Pass	24 mg
004	Pass	Pass
005	Pass	2 g
006	14.7 g‡	NA
007	8 g	NA

24-month egg OIT protocol involving modified rush, build-up, and maintenance phases. Double-blind, placebo-controlled food challenges were performed at study conclusion

Buchanan A, … Burks W, Jaci, 2007,

Egg oral immunotherapy in nonanaphylactic children with egg allergy

- Proof of concept : OIT safe for patients without anaphylaxis to egg.
- Egg OIT
  - does not heighten sensitivity to egg
  - might protect against reaction on accidental ingestion.
- OIT will induce clinical oral tolerance ?

- Use of allergen-specific OIT to protect subjects with food allergy from reaction on accidental ingestion would represent a significant paradigm change in the treatment of food allergy.

Buchanan A, … Burks W, Jaci, 2007,

COW'S MILK ALLERGY: A PILOT TRIAL OF SUBLINGUAL DESENSITIZATION

D de Boissieu, C Dupont

Department of pediatrics, Hôpital Saint Vincent de Paul

Persistent CMA

- IgE mediated cow’s milk allergy (CMA) disappears spontaneously in most cases
- CMA persists after age 8 yrs in 15%.
- The only current treatment is the elimination diet.
- Efficiency and of tolerance induction using increasing doses of cow‘s milk, given at home.
- Sublingual immunotherapy developing for pneumallergens (1st licence grass pollen, 2006).

COW'S MILK ALLERGY: A PILOT TRIAL OF SUBLINGUAL DESENSITIZATION

- T0 : Oral provocation test (OPT) in a hospital setting
- Milk desensitisation:
  - From the day after OPT
  - During 6 months
- T6 months : OPT in a hospital setting

COW'S MILK ALLERGY: A PILOT TRIAL OF SUBLINGUAL DESENSITIZATION

- Open, milk doses starting from 0,1mL and increasing progressively every 15', until an objective reaction.
- In case of difficulty in interpreting the symptoms: double blind OPT with soy + cocoa/ cow's milk + cocoa.
- Determination of the exact amount triggering a clinical reaction eg 1,5mL, 45 mL….

COW'S MILK ALLERGY: A PILOT TRIAL OF SUBLINGUAL DESENSITIZATION

- Beginning: the day after the first OPT
- Duration: 6 months until next OPT
- With half-skimmed milk, placed under the tongue for 2' during fast, every day
- Amounts of milk:
    - Initial : 0,1mL
    - Increase by 0,1mL every 15 days
    - Maximal dose: 1mL

COW'S MILK ALLERGY: A PILOT TRIAL OF SUBLINGUAL DESENSITIZATION

- During 1st OPT, one double blind was requested in patient n°7 due to recurrent subjective symptoms.

Following desensitisation :

- 1 drop-out after 5 months (tongue pruritus in the minutes following the deposition of milk under the tongue; 2nd OPT refused by the family
- 1 patient (n°6) did not comply, milk under his tongue only 3 - 4 times a week, 1 months stop during vacation

COW'S MILK ALLERGY: A PILOT TRIAL OF SUBLINGUAL DESENSITIZATION

- No side effect was seen
- Mean reactive dose (PP)
  - 39ml during the1st OPT
  - 143mL during the 2nd OPT, $p<0.01$
- 4 children: diet normalised (follow up 6 - 10 months).
- 2 children: the reactive dose increased.

- (ITT) child who did not respect the protocol: the reactive dose remained unchanged (68 to 70ml).

- Specific IgE decreased in 6 children and increased in 1

Oral tolerance induction

- **Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, Ventura A.**Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol 2008;121:343-7

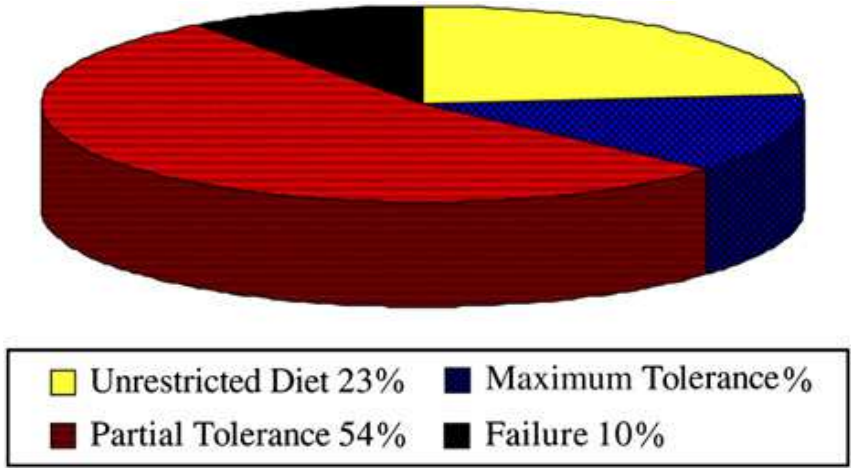
Specific oral tolerance induction in children with very severe cow's milk-induced reactions

TABLE IV. Group A: Symptoms and treatment required during SOTI in the hospital (10 days) and at home (1 year)

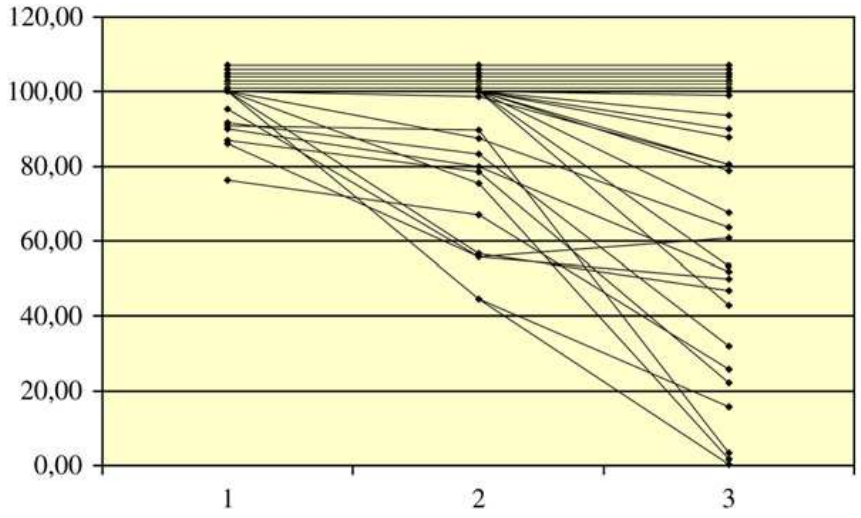
Symptoms	No. of in-hospital patients (total no. of reactions)	No. of at-home patients (total no. of reactions)
Lip or mouth pruritus	30 (355)	14 (85)
Perioral urticaria	28 (37)	17 (22)
Erythema or generalized urticaria	14 (17)	7 (13)
Abdominal pain with or without vomiting	23 (47)	14 (32)
Rhinoconjunctivitis	18 (23)	3 (8)
Mild laryngospasm	14 (15)	3 (5)
Mild bronchospasm	12 (28)	8 (19)

Longo et al, Jaci, 2008

Specific oral tolerance induction in children with very severe cow's milk-induced reactions



Outcome at 1 year in treatment group



Trend of cow’s milk–specific IgE values before starting desensitization (1) and after 6 (2) and 12 (3) months of follow-up.

Longo et al, Jaci, 2008

Oral immunotherapy

- **Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, Matsui EC, Burks AW, Wood RA.** A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol 2008 Oct 23

Milk oral immunotherapy for cow's milk allergy
Methods, Skripak JM, 2008

- 20(2:1) children randomized milk or placebo OIT
- 3 phases: build-up day (initial dose, 0.4 mg milk protein; final, 50 mg), daily doses (8 weekly in-office dose increases to 500 mg), continued daily maintenance doses for 3 to 4 months
- Double-blind, placebo-controlled food challenges
- Endpoint : titration skin prick tests
- Milk protein serology before and after OIT.

Milk oral immunotherapy for cow's milk allergy

Results, Skripak JM, 2008

TABLE I. OIT dosing in milligrams of CM protein

Initial build-up day	Every 1 to 2 week dose increases
0.4	75
0.8	100
1.5	130
3	170
6	225
12*	295
25	385
50	500

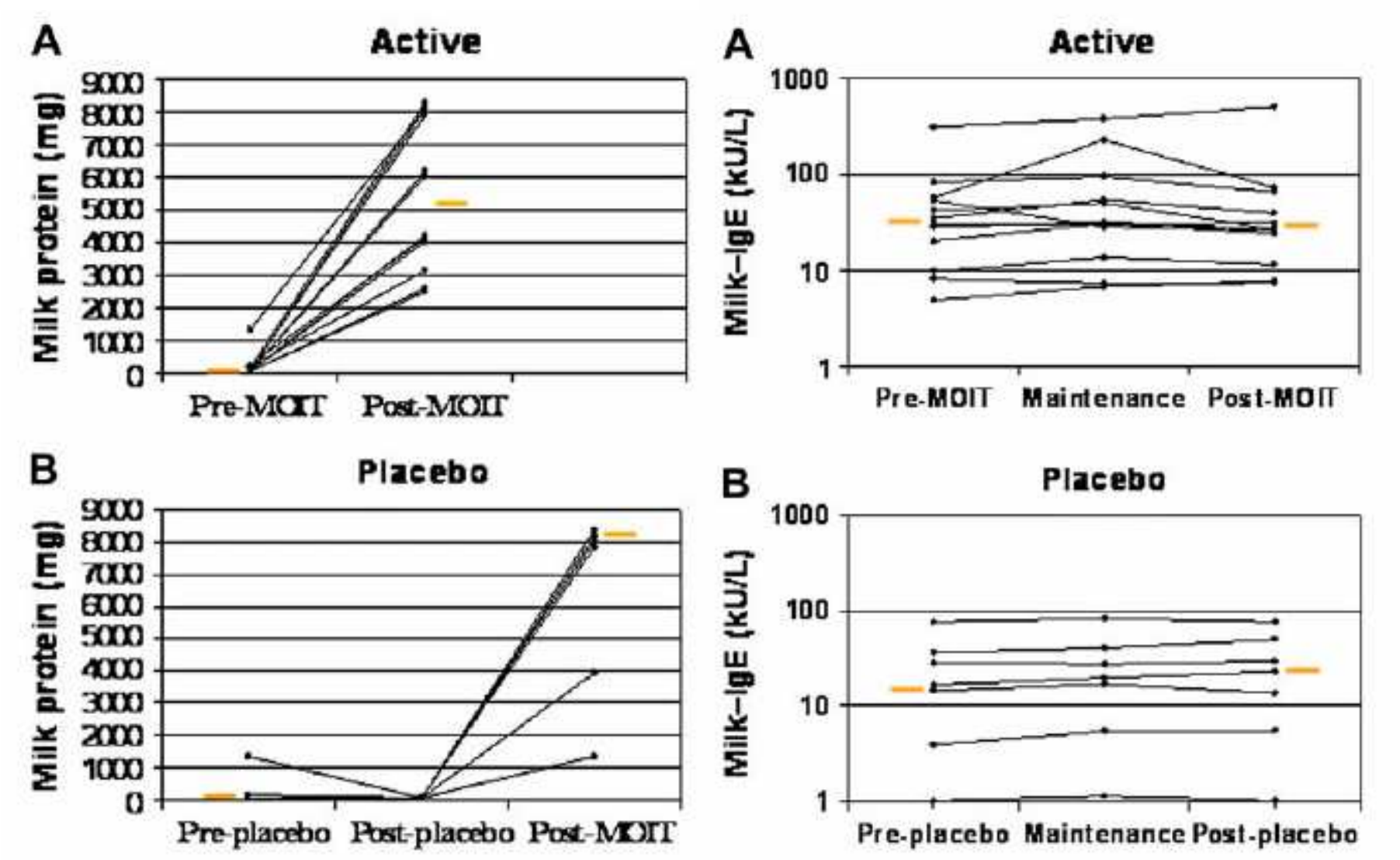
*Minimum dose tolerated to be taken at home.

Milk oral immunotherapy for cow's milk allergy
Results, Skripak JM, 2008

- 19 patients, 6 - 17 years, 12 active, 7 placebo 1 drop-out (persistent eczema during dose escalation)
- Baseline median milk IgE, active 34.8 kUa/L (4.86–314 Ua/L) vs placebo 14.6 kUa/L (0.93–133.4 kUa/L).
- Median milk threshold in both groups 40 mg (baseline)
- After OIT, median cumulative dose inducing reaction: active 5140 mg (range 2540-8140 mg), placebo 40 mg (P .0003)
- 2437 active OIT vs 1193 placebo,
- Reactions : 1107 active (45.4%) vs 134 (11.2%)
- Milk-specific IgE did not change significantly
- Milk IgG increased significantly (IgG4 level)

Milk oral immunotherapy for cow's milk allergy

Results, Skripak JM, 2008



Rush oral immunotherapy

- **Staden U, Blumchen K, Blankenstein N, Dannenberg N, Ulbricht H, Dobberstein K, Ziegert M, Niggemann B, Wahn U, Beyer K.** Rush oral immunotherapy in children with persistent cow's milk allergy. J Allergy Clin Immunol 2008;122:418-9

Rush oral immunotherapy in children with persistent cow's milk allergy

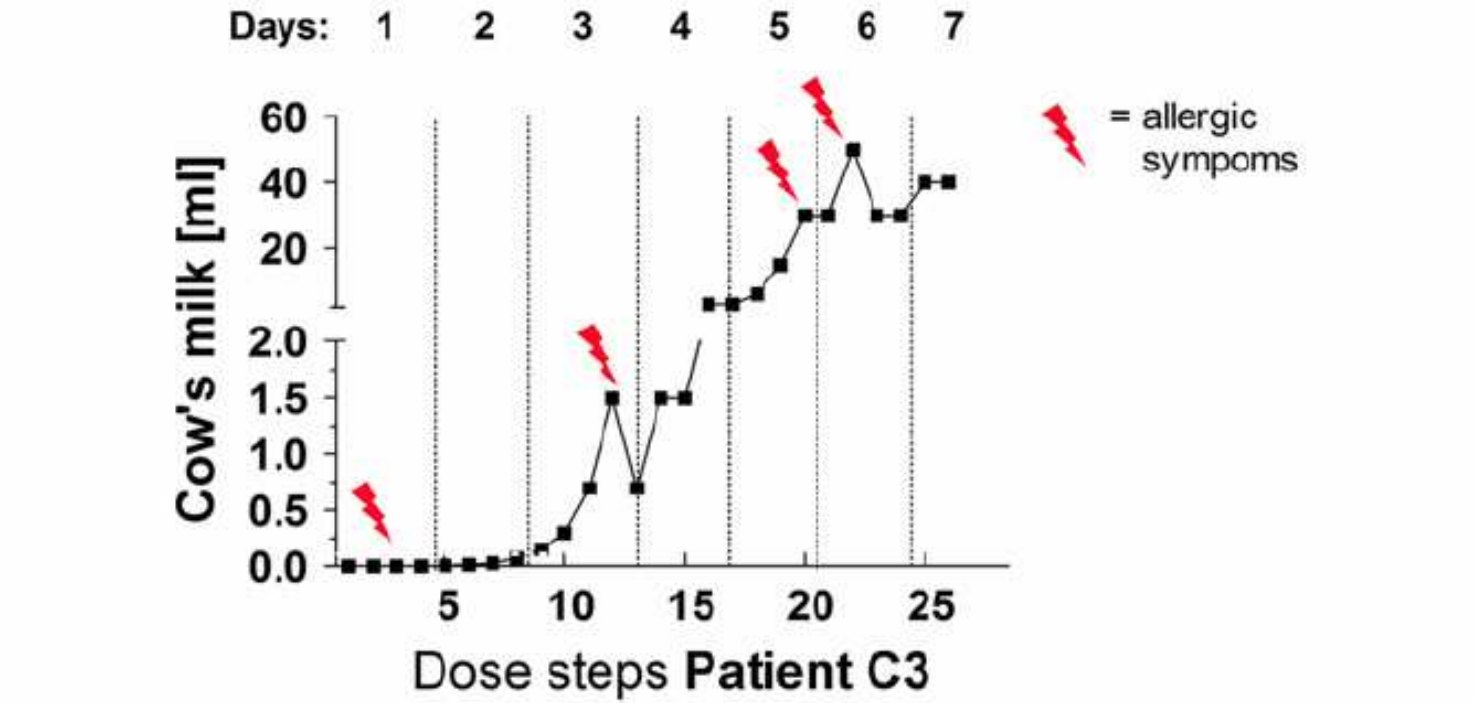


FIG 2. The individual course of patient C3, who was able to tolerate 40 mL of CM after 7 days of oral immunotherapy, is shown. The *red arrows* mark allergic reactions during the rush procedure, resulting in repeat or reduction of the dose.

Staden U et al, JACI, 2008)

Rush oral immunotherapy in children with persistent cow's milk allergy

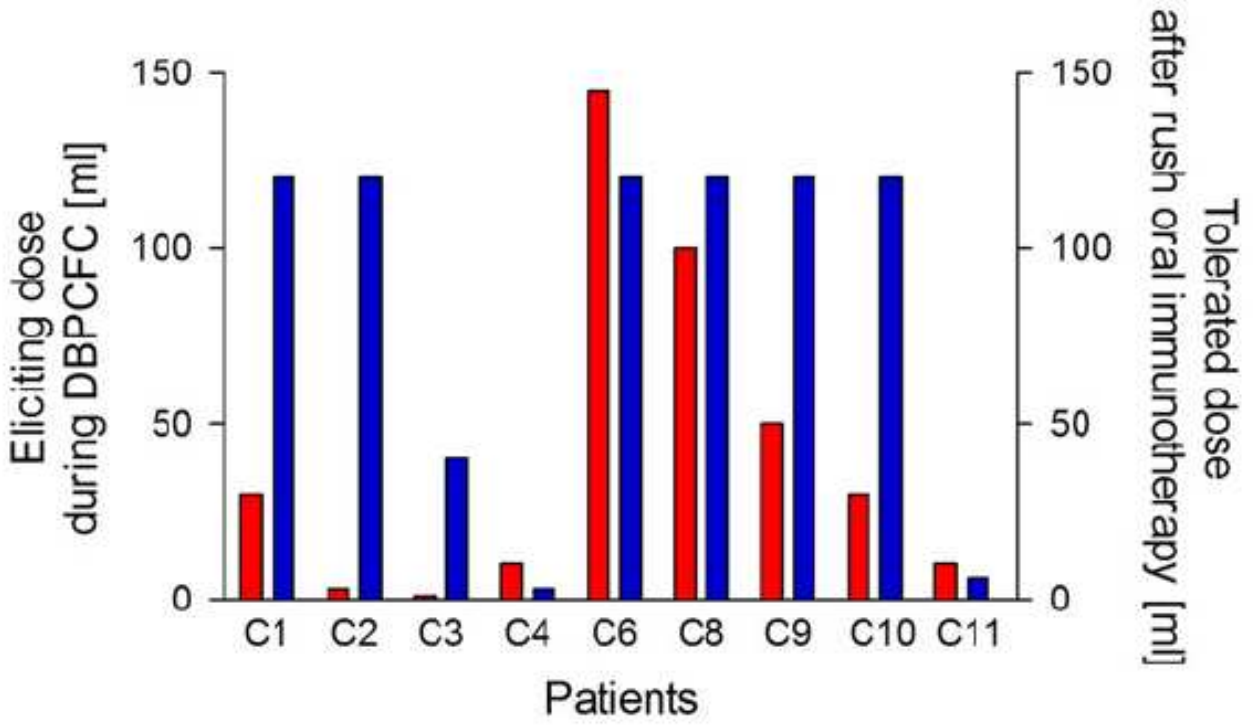


FIG 1. Shown are the EDs during DBPCFCs resulting in objective reactions *(red bars)* for each patient and the maximum dose that was tolerated after rush oral immunotherapy in a maximum of 7 days *(blue bars)*.

Staden U et al, JACI, 2008

Tentatives récentes

- Oral peanut immunotherapy, W Burks, AAAAI, 2008

Questions

- Aliments?
  - Lait, œuf, arachide?
- But?
  - Désensibiliser ou tolérance
- Faisabilité?
  - Enfant, adulte?

Qui?

- Risque anaphylactique?
- Pathologie durable?
- Enfant relativement âgé?

Conclusion

- Technique faisable, en cours d’évaluation
- PHRC en France, début des inclusions en septembre 2008
- Quid de la tolérance ou de la désensibilisation
- Quels critères de tolérance clinique au long cours
- Conséquences nutritionnelles, notamment avec le lait?