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### **Benefits of baked milk oral immunotherapy in French children with cow's milk allergy.**

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### **Cow's milk allergy and baked milk immunotherapy**

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### **Conflict of interest statement:**

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**Background:** Introduction and gradual incremental escalation of a low dose of baked milk may accelerate the resolution of severe cow's milk (CM) allergy for some children. The purpose of our study is to evaluate the efficacy and safety of baked milk oral immunotherapy (OIT) in children with CM allergy after a low-dose baked milk oral food challenge (OFC). **Methods:** In a retrospective analysis of OFC performed between 2013 and 2018 at the Children's Hospital of Toulouse (France), we identified 64 children with CM allergy and high milk and casein specific IgE levels, who underwent a total of 171 milk OFC. Mean age at 1<sup>st</sup> OFC was 4.8 years. Mean CM specific IgE was 47.9 kUA/l, and mean casein specific IgE was 42.3 kUA/l. **Results:** Most children were treated with baked milk OIT. Our study shows that 67.2% of the children did not react to 1<sup>st</sup> low dose baked milk OFC (168.6 mg of CM protein). Eighteen percent of children stopped the OIT at home. Finally, desensitization to fresh milk was achieved in 27 children (42.2% of children allergic to CM). Children with lower CM specific IgE levels have a significantly higher probability of becoming desensitized to unbaked CM. **Conclusion:** Most children with CM allergy and high milk and casein specific IgE levels tolerate the introduction of baked milk. However, the occurrence of anaphylactic reactions during OIT remains possible.

**Keywords:** Food Allergy, Cow's milk Allergy, Oral Immunotherapy, Baked food, Anaphylaxis, Pediatric, Oral Food Challenge

## Introduction

Food allergies (FA) in children have been increasing significantly over the past few years<sup>1, 2</sup>. Cow's milk (CM) and hen's egg allergies are the most frequent and the most disabling. It is estimated that CM allergy affects 0.5 to 3.8% of children<sup>3, 4</sup>. The prognosis for milk allergy has historically been considered good overall, with a reported resolution rate of 80% by the time children reach school-age. However, in more recent studies, the allergy was outgrown in only 50% of children who were school-aged<sup>5</sup> or sometimes even older<sup>6</sup>. Persistent CM allergy is associated with higher milk and casein specific IgE levels<sup>5, 7</sup>. Oral immunotherapy (OIT) is the only treatment currently available in FA. It is widely used in French hospitals; however, its side effects are frequent<sup>8</sup>. Using baked milk for OIT may reduce side effects and it may be tolerated better: 70% of children allergic to CM could tolerate baked milk<sup>9</sup>. If it has not yet been introduced at home, baked milk is usually introduced after an initial hospital oral food challenge (OFC). Thereafter, the regular ingestion of baked food helps accelerates resolution of the FA and improves the quality of life for a CM allergic child and his family<sup>10</sup>. The purpose of our study is to evaluate the implementation, efficacy and safety of baked milk OIT after a low-dose baked milk OFC in children with CM allergy. Our secondary purpose is to identify potential predictors of tolerance.

## Materials and Methods:

### a) Study overview

We carried out a retrospective chart review at the Children's University Hospital of Toulouse, from July 2013 to December 2018. All OFC to CM and baked milk performed during this period were analyzed. We included children with CM allergy, defined by a recent (< 6 months) history of a type I allergic hypersensitivity reaction after consumption of CM, associated with high specific IgE: CM specific IgE > 10 kUA/l, or casein specific IgE > 5 kUA/l<sup>11</sup>. Patients with high CM specific IgE (> 50 kUA/l) were also included. The exclusion criteria included: age ≥ 18 years, refusal to take part in the study, reaction to traces of CM or baked milk in the previous 6 months, tolerated consumption of baked milk (according to clinical history), negative skin prick tests (SPT) and negative specific IgE. We did not include cases in which there was not at least a 2<sup>nd</sup> OFC after implementation of the baked milk OIT (realisation after December 2018), and those without a 1<sup>st</sup> low dose baked milk OFC. A history of anaphylaxis was not an exclusion criterion. Before starting OIT, the patients underwent a low-dose OFC with Petit-Beurre (PB) (shortbread cookie)<sup>12</sup>. At

least one additional OFC with fresh milk at a higher dose was then performed, after OIT, to reassess the patients' tolerance.

#### b) Data collection on inclusion

For each patient, we collected clinical characteristics including age, sex, initial allergy symptomatology, presence of respiratory allergies, asthma, and associated FA. The diagnosis of allergy to other foods was made when these foods caused a type I allergic hypersensitivity reaction, associated with SPT and/or positive specific IgE. We collected the SPT results for fresh CM (performed with ALK® Lancet, using fresh milk rather than commercial CM extracts), as well as specific IgE tests: CM specific IgE and casein specific IgE (*Phadia Thermo Scientific Assay*). Allergic reactions were graded according to Ring & Messmer classification<sup>13</sup>:

I: Generalized cutaneous signs: erythema, urticaria, with or without angioedema

II: Moderate multi-organ involvement with cutaneous signs, hypotension and tachycardia, bronchial hyperreactivity: cough, difficulty to ventilate.

III: Severe life threatening multiorgan involvement: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm. Cutaneous signs may be present or may occur only after arterial blood pressure is restored.

IV: Cardiac and/or respiratory arrest

#### c) Oral food challenge

Various OFC were performed under the supervision of a senior physician from the Pediatric Pneumo-allergology team of the Children's Hospital of Toulouse. The first OFC included a total dose of 4.96 ml of baked milk (168.6 mg of CM protein) in the form of PB (shortbread cookie), which was administered sequentially according to the following scheme: 1/8<sup>th</sup> of PB (0.16 ml of CM, 5.4 mg of CM protein), then 1/4 of PB (10.9 mg), 1/2 of PB (21.8 mg), 1 PB (43.5 mg), and finally 2 PB (87.0 mg). The 2<sup>nd</sup> OFC, about one year later, consisted of sequential administration of a total dose of 254 ml of fresh milk (8.6 g of CM protein), according to the following scheme: 1 ml of fresh milk, then 3 ml, 5 ml, 10 ml, 20 ml, 40 ml, 75 ml, and 100 ml. Children who passed this test successfully were considered desensitized and this 2<sup>nd</sup> OFC was the last challenge for them. For the children who failed this 2<sup>nd</sup> OFC, because of clinical reactions the, baked milk OIT was continued, and a new OFC was performed one year later, with the same scheme as the 2<sup>nd</sup> one. Generally, doses were administered at 20 minutes intervals, and children were monitored at least 2 hours after the last dose of the OFC. The reactogenic dose and the type of clinical reaction

were detailed for the positive OFC, according to the Ring & Messmer classification<sup>13</sup>, as previously described.

#### d) Oral immunotherapy (OIT)

After the first OFC, we initiated baked milk OIT when it was possible. The family's commitment to follow the proposed OIT protocol was assessed. A dietician and a senior physician met with every family for an education session about allergic co-factors, the emergency kit, the use of adrenaline, and the conditions that would lead to its use. OIT involved the daily intake with progressive increase at home, of the food to be reintroduced. As per the baked milk OIT protocol, patients generally started with 1 PB per day (about 1 ml of baked milk). They started at a lower dose if they had shown a reaction before the last dose of the first OFC. Patients then increased their daily baked milk dose by one PB every month, until reaching 5 PB per day, except for those who reacted during the first OFC, and who did not exceed the reactogenic dose. At this point, patients were seen in medical consultation, and generally continued this same dose until the 2<sup>nd</sup> OFC, which was performed one year after the first OFC. When the 2<sup>nd</sup> OFC was still positive, we adjusted the OIT dosing by increasing it if possible until half the reactogenic dose, and a new OFC (same scheme as the 2<sup>nd</sup> one) was scheduled one year later. The dietitian and the senior physician could be contacted (telephone number and mail address were given to the family) if an allergic reaction occurred or in case of any other difficulty, and a medical consultation was carried out if necessary. The family was recommended to reduce the dosage during illness, to avoid non-steroidal anti-inflammatory drugs, and to avoid exercise before and after taking daily doses.

Data collected included the occurrence of reactions during baked milk OIT, the severity (or grade) of reactions, the presence of any allergic co-factors, and any treatment needed for OIT-related reactions, including whether adrenaline was administered. We also reviewed whether OIT was terminated for any reason.

#### e) Ethics

The study complies with the requirements of the French National Commission for Data Protection and Freedom and the General Data Protection Regulation. Non-opposition of patients and/or family was collected.

#### f) Statistical analysis

The statistical analysis was performed by a Chi-square test (or Fisher exact test according to the theoretical numbers) for the qualitative variables, and by a Student's t-test (or a Mann Whitney U test if the normality or the homoscedasticity of distributions were not verified) for quantitative variables. The statistical tests were performed with the STATA v13.1 software, and were conducted with a bilateral approach and a risk of error of the alpha risk set at 5%. We considered a  $p < 0.05$  statistically significant.

## Results

### a) Characteristics

We included 64 children for a total of 171 OFC. The clinical characteristics of children and their evolution are detailed in Table 1. We had 70.3% boys with an average age of 4.8 years (ranging from 2 to 16 years) at the 1<sup>st</sup> OFC. Most children had at least one associated FA (68.8%). The associated FA were: eggs (72.1%), peanuts (39.5%), tree nuts (39.5%), goat's and sheep's milk (32.6%), mustard (14%), wheat (11.6%), legumes other than peanuts (9.3%), fish and/or shellfish (9.3%), kiwi (4.7%), sesame (3.1%), and lamb meat (1.6%). Grade I allergy was the most common initial symptomatology (50%) related to CM. The mean diameter of the SPT with fresh CM during the first OFC was 10 mm (measured in 15 children (23.4%)).

### b) First OFC and OIT

The initial OFC was positive 32.8% of the time, with 14 grade I allergic reactions (66.7%), 1 grade II reaction (4.8%), and 6 grade III reactions (28.6%). On average, it was positive at a cumulative reactive dose of 3.4 ml of milk, *i.e.* 0.11 g of milk protein and 22 g of PB. Three reactions were treated with adrenaline. Baked milk OIT could be implemented in 63 children (98.4%). The child who did not start OIT had a severe (grade III) reaction to 2.4 mL CM during the OFC and required 2 injections of adrenalin and intravenous fluid hydration. The medical decision was to continue an elimination diet and to reevaluate the CM allergy later. Of the 63 children doing baked milk OIT at home, 21 (33.3%) had some reaction to home dosing, including oral itching (n=2, 9.5%), skin reactions (n=3, 14.3%), digestive reactions (n=10, 47.6%), asthma exacerbations (n=5, 23.8%), and anaphylaxis (n=1, 4.8%). Adrenaline was administered once for an OIT dose. OIT was interrupted (*i.e.* complete stop without resumption) in 11 children (18% of children following the baked milk OIT). These reactions and permanent interruptions are detailed in Table 2.

### c) Last OFC

The average age of the children at the time of their last OFC was 6.5 years. The mean diameter of the SPT for fresh CM was 9 mm (measured in 9 children (14.1%)). The OFC was positive for an average cumulative reactive dose of 57.9 ml of CM (1.85 g of CM protein), with 32.1% grade I allergies, 28.6% grade II allergies, and 39.3% grade III allergies. Thirty children needed more than 2 OFC to follow OIT program towards desensitization, because of reactions during the 2<sup>nd</sup>

OFC. Of the 171 OFC performed, 92 were negative (53.8%), and 79 were positive (46.2%), of which 42 were grade I allergies (53.2%), 16 grade II allergies (20.3%), and 21 grade III allergies (26.6%). Overall, desensitization was achieved in 27 children (rate of 42.2% for our entire population), after an average of 2.56 OFC, and an average duration of 521 days (1 year, 5 months, and 4 days) following the 1<sup>st</sup> OFC.

#### d) Initial characteristics of children achieving desensitization

Twenty-seven children achieved desensitization, as demonstrated by passing their last fresh milk OFC after completing baked milk OIT. Using the initial characteristics of these children, the initial mean specific IgE values were: CM: 36.8 kUA/l; casein: 35.8 kUA/l. In comparison, for the 37 children who did not achieve desensitization following the last fresh milk OFC, the initial mean specific IgE values were CM: 55.3 kUA/l; casein: 46.9 kUA/l. There is a statistically significant difference between those who achieved desensitized and the other children for the CM specific IgE level ( $p=0.043$ ). There is no statistically significant difference in the level of casein specific IgE ( $p=0.23$ ), the age of the children at the time of the 1<sup>st</sup> OFC ( $p=0.40$ ), or the presence of atopy (asthma, respiratory allergy, associated FA, and number of associated FA). These data are shown in Figure 1.

#### Discussion

In our study, the average age of CM allergic children at 1<sup>st</sup> OFC with baked milk was 4.8 years, which is altogether comparable to previous studies<sup>9, 14</sup>. Milk and casein-specific IgE levels among patients in our cohort were higher than those included in other studies<sup>14, 15, 16</sup>, as our intention was not to exclude children with severe CM allergy. Most of the children were atopic, with asthma. Most of the children have at least one associated FA.

We found that 42.2% of children allergic to CM were desensitized after completing a course of baked milk OIT. This rate is lower than in other studies. In the Kim study, 60% of the children were able to tolerate CM after an OFC of 240 ml<sup>3</sup>. The lower rate of desensitization achieved by our patients may be a result of inclusion of patients with a more severe milk allergic profile, with higher specific IgE levels.

Initially, the baked milk OFC was negative 67.2% of the time and marked the tolerance to baked milk (168.6 mg of CM protein). The Nowak-Wegrzyn study examining baked milk tolerance

among children with CM allergy (n=100, mean age 7.5 years) demonstrated that 77% tolerated baked milk (2.6 g of CM protein)<sup>9</sup>. This rate is higher than ours. It should be noted, however, that our specific IgE levels are higher (CM: 47.9 kUA/l and Casein: 42.3 kUA/l versus CM: 11.6 kUA/l and Casein: 14.5 kUA/l), than in the "Heated milk-reactive" group of Nowak-Węgrzyn<sup>9</sup>. In the prospective Perezabad study<sup>14</sup>, of 20 children allergic to CM (mean age 4.3 years), the cure rate after OIT was 70%, also higher than ours. Again, specific IgE levels were lower than in our study (CM: 27.38 kUA/l, and Casein: 26.45 kUA/l), patients possibly had less severe allergies. In another retrospective study of Bartnikas<sup>15</sup>, of 35 children with CM allergy (median age 8.1 years), 83% were able to tolerate baked milk (2.6 g of CM protein). The specific IgE levels (CM 1.96 kUA/l, and casein 1.93 kUA/l) were lower than in our study.

Our dose of CM ingested during the 1<sup>st</sup> OFC is much lower than in other studies<sup>9, 15</sup>, with 168.6 mg of CM protein, versus 1.3 g of CM protein in the muffin,  $\pm$  1.3 more g of CM protein in the waffle. A high dose ingested therefore does not seem essential for setting up an immunomodulation.

For the SPT and IgE, in the Nowak-Węgrzyn study<sup>9</sup>, CM-tolerant subjects had significantly lower SPT diameters with CM, and lower casein specific IgE. The thresholds recommended in this study to practice an OFC with baked milk are: CM specific IgE >5 kUA/l, SPT with CM between 5 and 15 mm. In the Caubet study<sup>11</sup>, the recommended thresholds for practicing OFC with baked milk are CM specific IgE >10 kUA/l, and Casein specific IgE >5 kUA/l. In the Kim study<sup>3</sup>, the proposed levels for an OFC with baked milk are CM specific IgE >5 kUA/l <2 years old, >15 kUA/l > 2 years old, or SPT CM >8 mm. We respected the thresholds recommended by Caubet, which were more selective than those proposed by Nowak-Węgrzyn.

Regarding the OIT procedure, daily ingestion of baked milk is usually well tolerated, with few serious allergic reactions<sup>3</sup>. However, moderate reactions are common, which may make it difficult to track OIT. Indeed, in our study, 33.3% of the children had reactions during OIT, with 18% OIT interruptions.

Only one reaction to OIT dosing at home required treatment with adrenalin. Although effective, OIT for CM seems quite difficult. The occurrence of anaphylaxis has already been raised in previous studies<sup>8, 16</sup>. Although these reactions remain rare, our study confirms that an anaphylactic reaction at home is possible during OIT. Families should be informed about the possibility of reactions, including anaphylaxis, to home OIT dosing and should be prepared to treat with adrenalin if needed. For this reason, we emphasize the availability of an emergency kit with auto-injectable adrenalin for all patients with FA on OIT<sup>17-18</sup>. Its use must be reviewed in

detail and parents/caregivers and patients must demonstrate proficiency with a training device (or demo pen). Patients need to be educated about cofactors that may promote a reaction to OIT dosing<sup>19</sup>.

Finally, we would like to highlight that even for children who did not achieve desensitization (i.e. the 35 children who did not pass the fresh milk exit OFC), we found an increase in the reactogenic dose between the 1<sup>st</sup> and last OFC challenges. Indeed, the average reactogenic dose increased from 3.4 ml of baked milk (116 mg of CM protein) to 57.9 ml [range 2.4-154.0 ml] of raw CM (1969 mg of CM protein).

One limit of our study is the absence of a control group. However, in France, the practice of OIT after OFC for FA (like CM, egg, peanut) is widespread, and it would not be ethical to exempt some children while they are eligible. This is also a monocentric retrospective study. Quality of life was not assessed; however, prior studies have already shown that OIT contributes to a better quality of life for FA children and their families<sup>20</sup>.

## Conclusion

In our study, 42.2% of children allergic to CM were desensitized after completing a course of baked milk OIT. The majority of children could introduce baked milk, even children who reacted during the 1<sup>st</sup> OFC. This introduction seems to be safe and well tolerated in most cases. A number of patients on OIT stop at home (18% in our retrospective study) for various reasons. Initially, 67.2% of CM allergic children did not react to the 1<sup>st</sup> low dose baked milk OFC (168.6 mg of CM protein). Children with a lower CM specific IgE level have a significantly higher probability of being desensitized. As with all OIT protocols in which individuals are exposed to their food allergens, it is necessary to keep in mind that allergic reactions, including anaphylaxis, can occur at any time during a desensitization protocol. Patients and their families need to be informed about it, and must be provided with an adrenalin auto-injector.

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**Table 1: Detailed clinical characteristics and patient evolution. The results are expressed in number (percentage), and average (standard deviation).**

|                                                   | <b>CM allergy</b> |
|---------------------------------------------------|-------------------|
| Number of patients                                | 64                |
| Number of OFC carried out                         | 171               |
| Gender (Male)                                     | 45 (70.3%)        |
| Atopic comorbidities:                             |                   |
| Asthma (Doctor diagnosed)                         | 33 (51.6%)        |
| Respiratory allergy                               | 21 (32.8%)        |
| Other FA                                          | 44 (68.8%)        |
| 1–2                                               | 25 (39.1%)        |
| 3–4                                               | 17 (26.6%)        |
| ≥ 5                                               | 2 (3.1%)          |
| Initial diagnosis made on:                        |                   |
| Sensitization                                     | 9 (14.1%)         |
| Grade I Allergy                                   | 32 (50%)          |
| Grade II Allergy                                  | 12 (18.8%)        |
| Grade III Allergy                                 | 11 (17.2%)        |
| Age (years) at 1 <sup>st</sup> OFC                | 4.8 (4.13)        |
| Specific IgE (kUA/I) at 1 <sup>st</sup> OFC       |                   |
| CM                                                | 47.9 (34.9)       |
| Casein                                            | 42.3 (35.8)       |
| 1 <sup>st</sup> positive OFC (n=)                 | 21 (32.8%)        |
| Grade I Allergy                                   | 14 (21.9%)        |
| Grade II Allergy                                  | 1 (1.6%)          |
| Grade III Allergy                                 | 6 (9.4%)          |
| Age (years) at last OFC                           | 6.5 (4.31)        |
| Specific IgE (kUA/I) at last OFC                  |                   |
| CM                                                | 32.4 (31.9)       |
| Casein                                            | 25 (30.3)         |
| Last positive OFC (n=)                            | 37 (57.8%)        |
| Average time for achieve desensitization (months) | 17.1 (4.6)        |

**Table 2: Detailed characteristics of the 21 children reacting during OIT, including the 11 OIT permanent interruptions.**

| Patient N° | Age (years) | Reaction                                | Dose†       | Cofactors                      | Medication used                                 | Time since starting OIT | Decision of interruption |
|------------|-------------|-----------------------------------------|-------------|--------------------------------|-------------------------------------------------|-------------------------|--------------------------|
| 1          | 8           | Asthma                                  | 5 ml        | No                             | Salbutamol, prednisolone                        | 6 months                | By family                |
| 2          | 6           | Asthma                                  | 0,3 ml      | Grass pollen allergy           | Salbutamol, prednisolone                        | 3 days                  | By doctor                |
| 3          | 3           | Vomiting, abdominal pain                | 2,2 ml      | No                             | Desloratadine, prednisolone                     | 3 months                | By family                |
| 4          | 14          | Abdominal pain                          | 3,2 ml      | No                             | No                                              | 3 months                | By family                |
| 5          | 7           | Abdominal pain                          | 5 ml        | No                             | Desloratadine, prednisolone                     | 6 months                | By family                |
| 6          | 4           | Vomiting                                | 1 ml        | No                             | No                                              | 2 days                  | By family                |
| 7‡         | 6           | Asthma                                  | 2,5 ml      | No                             | <b>Adrenalin x 2</b> , salbutamol, prednisolone | 3 months                | By doctor                |
| 8          | 3           | Anaphylaxis (urticaria, asthma, pallor) | 4 ml        | No                             | Desloratadine, prednisolone                     | 3 months                | By family                |
| 9          | 4           | Asthma                                  | 0,3 ml      | No                             | Salbutamol                                      | 1 week                  | By doctor                |
| 10         | 2           | Vomiting                                | 1 ml        | No                             | No                                              | 2 days                  | By family                |
| 11         | 10          | Vomiting, abdominal pain                | 1 ml        | No                             | Prednisolone                                    | 2 days                  | By family                |
| 12         | 10          | Urticaria                               | 10 ml       | No                             | Desloratadine                                   | 4 months                | No                       |
| 13         | 2           | Vomiting                                | 5 ml        | No                             | No                                              | 6 months                | No                       |
| 14         | 6           | Asthma                                  | 55 ml of CM | Grass pollen allergy, exercise | Desloratadine, prednisolone                     | 5 months                | No                       |
| 15         | 17          | Oral itching                            | 20 ml of CM | No                             | No                                              | 9 months                | No                       |

|    |    |                |             |                      |             |          |    |
|----|----|----------------|-------------|----------------------|-------------|----------|----|
| 16 | 16 | Oral itching   | 1 ml        | Grass pollen allergy | No          | 6 months | No |
| 17 | 4  | Abdominal pain | 15 ml of CM | No                   | No          | 3 months | No |
| 18 | 2  | Abdominal pain | 5 ml        | No                   | No          | 2 months | No |
| 19 | 4  | Vomiting       | 1 ml        | No                   | No          | 5 days   | No |
| 20 | 7  | Urticaria      | 3,5 ml      | No                   | Mequitazine | 4 months | No |
| 21 | 4  | Urticaria      | 4 ml        | No                   | No          | 4 months | No |

† For the dose, if no precision, this is baked milk.

‡ Acute severe asthma, hospitalisation in intensive care unit for 48 hours.

Figure 1: Evolution of the children with severe CM allergy.

