



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

Vianney Gruzelle¹ | Agnès Juchet¹ | Audrey Martin-Blondel¹ | Marine Michelet¹ | Anne Chabbert-Broue¹ | Alain Didier²

¹Pediatric Pneumo-allergology Department, Children's Hospital, University Hospital Centre of Toulouse, Toulouse, France

²Department of Respiratory Medicine and Allergic Diseases, University Hospital Centre of Toulouse, Toulouse, France

Correspondence

Vianney Gruzelle, Pediatric Pneumo-allergology Department, Children's Hospital, 330 Avenue de Grande Bretagne, TSA 70 034, 31059 Toulouse Cedex 9, France.
Email: gruzelle.v@chu-toulouse.fr

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Abstract

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 was 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 1st 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 1st 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

anaphylaxis, baked food, cow's milk allergy, food allergy, oral food challenge, oral immunotherapy, pediatric

1 | INTRODUCTION

Food allergies (FA) in children have been increasing significantly over the past few years.^{1,2} 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.^{3,4} 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-aged⁵ or sometimes even older.⁶ Persistent CM allergy is associated with higher milk and casein-specific IgE levels.^{5,7} Oral immunotherapy (OIT) is the only treatment currently available in FA. It is widely used in French

hospitals; however, its side effects are frequent.⁸ 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.⁹ 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 accelerate the resolution of the FA and improve the quality of life for a CM-allergic child and his family.¹⁰ The purpose of our study was 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.

2 | MATERIALS AND METHODS

2.1 | 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.¹¹ Patients with high CM-specific IgE (>50 kUA/L) were also included. The exclusion criteria included the following: 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 2nd OFC after implementation of the baked milk OIT (realization after December 2018), and those without a 1st 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).¹² At least one additional OFC with fresh milk at a higher dose was then performed, after OIT, to reassess the patients' tolerance.

2.2 | 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 and Messmer classification¹³:

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

Key Messages

It is already known that frequency of cow's milk (CM) allergy is increasing in children, including more and more severe and persistent forms. Most of the children can tolerate baked milk after oral food challenge, even if the allergy is severe. Introduction and gradual incremental escalation of a low dose of baked milk may accelerate the resolution of severe CM allergy for these children. Our study included CM-allergic French children, with high specific IgE levels. Most of them could start baked milk oral immunotherapy (OIT). Eighteen percent of children stopped OIT at home, mainly because of mild reactions. Desensitization to fresh milk was achieved in 42.2% of CM-allergic children. Children with lower CM-specific IgE levels have a significantly higher probability of becoming desensitized to fresh milk.

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

III: Severe life-threatening multi-organ 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.

2.3 | Oral food challenge

Various OFC was 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: 1/8th of PB (0.16 mL of CM, 5.4 mg of CM protein), then ¼ of PB (10.9 mg), ½ of PB (21.8 mg), 1 PB (43.5 mg), and finally 2 PB (87.0 mg). The 2nd 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, 5, 10, 20, 40, 75, and 100 mL. Children who passed this test successfully were considered desensitized, and this 2nd OFC was the last challenge for them. For the children who failed this 2nd 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 2nd one. Generally, doses were administered at 20-minute 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 and Messmer classification,¹³ as previously described.

2.4 | 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 cofactors, 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 2nd OFC, which was performed one year after the first OFC. When the 2nd 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 2nd 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 cofactors, and any treatment needed for OIT-related reactions, including whether adrenaline was administered. We also reviewed whether OIT was terminated for any reason.

2.5 | 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.

2.6 | 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 whether the normality or the homoscedasticity of distributions was 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 $P < .05$ statistically significant.

3 | RESULTS

3.1 | 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 1st OFC. Most children had at least one associated FA (68.8%). The associated FA were as follows: 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%)).

TABLE 1 Detailed clinical characteristics and patient evolution

	CM allergy
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 (y) at 1st OFC	4.8 (4.13)
Specific IgE (kUA/L) at 1st OFC	
CM	47.9 (34.9)
Casein	42.3 (35.8)
1st 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 (y) at last OFC	6.5 (4.31)
Specific IgE (kUA/L) at last OFC	
CM	32.4 (31.9)
Casein	25 (30.3)
Last positive OFC (n=)	37 (57.8%)
Average time for achieve desensitization (mo)	17.1 (4.6)

Note: The results are expressed in number (percentage) and average (standard deviation).

3.2 | 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, ie, 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 two 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 (ie, 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.

3.3 | 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 nine 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 two OFC to follow OIT program toward desensitization, because of reactions during the 2nd 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 1st OFC.

3.4 | 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 as follows: 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 and 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 ($P = .043$). There is no statistically significant difference in the level

of casein-specific IgE ($P = .23$), the age of the children at the time of the 1st OFC ($P = .40$), or the presence of atopy (asthma, respiratory allergy, associated FA, and number of associated FA). These data are shown in Figure 1.

4 | DISCUSSION

In our study, the average age of CM-allergic children at 1st OFC with baked milk was 4.8 years, which is altogether comparable to previous studies.^{9,14} Milk and casein-specific IgE levels among patients in our cohort were higher than those included in other studies,¹⁴⁻¹⁶ 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.³ The lower rate of desensitization achieved by our patients may be a result of the 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).⁹ 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 vs CM: 11.6 kUa/L and casein: 14.5 kUa/L), than in the "Heated milk-reactive" group of Nowak-Wegrzyn.⁹ In the prospective Perezabad study,¹⁴ 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,¹⁵ 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 ingestion during the 1st OFC is much lower than in other studies,^{9,15} with 168.6 mg of CM protein, vs 1.3 g of CM protein in the muffin, ± 1.3 more gram of CM protein in the waffle. A high dose ingestion therefore does not seem essential for setting up an immunomodulation.

For the SPT and IgE, in the Nowak-Wegrzyn study,⁹ 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 as follows: CM-specific IgE >5 kUa/L, SPT with CM between 5 and 15 mm. In the Caubet study,¹¹ 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,³ the proposed levels for an OFC with

TABLE 2 Detailed characteristics of the 21 children reacting during OIT, including the 11 OIT permanent interruptions

Patient N°	Age (y)	Reaction	Dose ^a	Cofactors	Medication used	Time since starting OIT	Decision of interruption
1	8	Asthma	5 mL	No	Salbutamol, prednisolone	6 mo	By family
2	6	Asthma	0.3 mL	Grass pollen allergy	Salbutamol, prednisolone	3 d	By doctor
3	3	Vomiting, abdominal pain	2.2 mL	No	Desloratadine, prednisolone	3 mo	By family
4	14	Abdominal pain	3.2 mL	No	No	3 mo	By family
5	7	Abdominal pain	5 mL	No	Desloratadine, prednisolone	6 mo	By family
6	4	Vomiting	1 mL	No	No	2 d	By family
7 ^b	6	Asthma	2.5 mL	No	Adrenalin x 2 , salbutamol, prednisolone	3 mo	By doctor
8	3	Anaphylaxis (urticaria, asthma, pallor)	4 mL	No	Desloratadine, prednisolone	3 mo	By family
9	4	Asthma	0.3 mL	No	Salbutamol	1 wk	By doctor
10	2	Vomiting	1 mL	No	No	2 d	By family
11	10	Vomiting, abdominal pain	1 mL	No	Prednisolone	2 d	By family
12	10	Urticaria	10 mL	No	Desloratadine	4 mo	No
13	2	Vomiting	5 mL	No	No	6 mo	No
14	6	Asthma	55 mL of CM	Grass pollen allergy, exercise	Desloratadine, prednisolone	5 mo	No
15	17	Oral itching	20 mL of CM	No	No	9 mo	No
16	16	Oral itching	1 mL	Grass pollen allergy	No	6 mo	No
17	4	Abdominal pain	15 mL of CM	No	No	3 mo	No
18	2	Abdominal pain	5 mL	No	No	2 mo	No
19	4	Vomiting	1 mL	No	No	5 d	No
20	7	Urticaria	3.5 mL	No	Mequitazine	4 mo	No
21	4	Urticaria	4 mL	No	No	4 mo	No

^aFor the dose, if no precision, this is baked milk.

^bAcute severe asthma, hospitalization in intensive care unit for 48 h.

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-Wegrzyn.

Regarding the OIT procedure, daily ingestion of baked milk is usually well tolerated, with few serious allergic reactions.³ 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.^{8,16} 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.^{17,18} 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.¹⁹

Finally, we would like to highlight that even for children who did not achieve desensitization (ie, the 35 children who did not pass the fresh milk exit OFC), we found an increase in the reactogenic dose between the 1st 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)

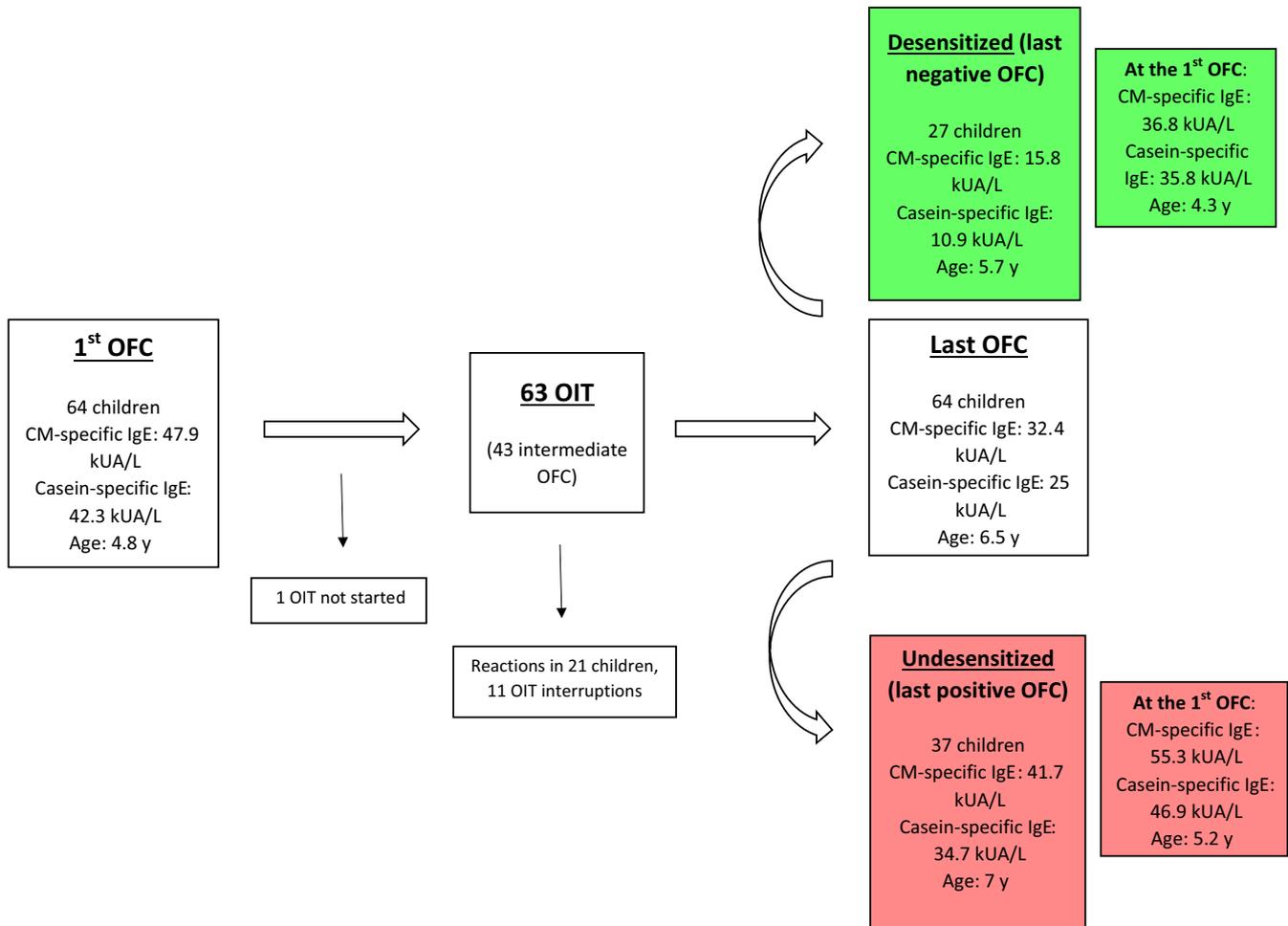


FIGURE 1 Evolution of the children with severe CM allergy [Colour figure can be viewed at wileyonlinelibrary.com]

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.²⁰

5 | 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 1st 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 1st 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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CONFLICT OF INTERESTS

There is no conflict of interest to declare.

ORCID

Vianney Gruzelle  <https://orcid.org/0000-0001-7024-2118>

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