



As soon as possible in IgE-cow's milk allergy immunotherapy

Javier Boné Calvo¹ · Marcos Clavero Adell¹ · Isabel Guallar Abadía¹ · Sara Laliena Aznar¹ ·
María Luisa Sancho Rodríguez¹ · Angela Claver Monzón² · Yolanda Aliaga Mazas¹

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Abstract

Oral immunotherapy is a common treatment in cow's milk protein allergy. The Department of Pediatric Allergology at the Children's Hospital of Zaragoza performed a retrospective analysis of 335 infants under 1 year of age diagnosed with IgE-mediated cow's milk and early treated. Clinical evaluation, skin prick test, and serum-specific IgE level control were performed before starting and after finishing treatment. Upon completion of treatment, more than 98% of patients became tolerant to milk and no one presented serious adverse reactions. Nowadays, the remaining non-tolerant patients (1.8%) can take milk or derivatives daily—as prophylaxis—to a certain maximum dose and still remain asymptomatic. After immunotherapy, both positive skin prick tests and a progressive decrease in specific IgE levels were found, as desensitization to milk increased.

Conclusion: Oral immunotherapy is a safe and effective treatment against allergy to cow's milk proteins in infants. Such treatment should be offered to the children's families from the first moment of diagnosis.

What is known:

- Cow's milk proteins are responsible for the earliest IgE-mediated allergic reactions in children.
- Oral immunotherapy (OIT) is commonly used as cow's milk allergy treatment and it is proposed at different ages.

What is new:

- OIT it is an effective and safe method with no severe reactions at early ages.
- The number of reaching successful treatments is awesome so we believe that immunity response can be molded at the first months of life, so the probability of success with infants is greater than in older children.

Keywords “Cow's milk allergy” · “Oral immunotherapy” · “Oral food challenge” · “Children”

List of abbreviation

CEICA Clinical Research Ethics Committee of Aragón
CMA Cow's milk allergy
CMA-IgE IgE-mediated cow's milk allergy

FSD Fixed starting dose
OIT Oral immunotherapy
OCT Oral challenge test

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✉ Marcos Clavero Adell
m.claveroadell@gmail.com

Javier Boné Calvo
javierbone@gmail.com

Isabel Guallar Abadía
iguallara@salud.aragon.es

Sara Laliena Aznar
saralaliena@gmail.com

María Luisa Sancho Rodríguez
mlsr.sancho@gmail.com

Angela Claver Monzón
claverangela@gmail.com

Yolanda Aliaga Mazas
yolaaliaga@hotmail.com

¹ Pediatric Allergy Unit, Miguel Servet University Hospital, Paseo Isabel La Católica 1-3, 50009 Zaragoza, Spain

² Pediatrics, Hospital Universitari Dexeus, Barcelona, Spain

Introduction

Cow's milk proteins are typically the first food allergen to which children are exposed and, as such, these proteins are responsible for the earliest IgE-mediated allergic reactions (CMA-IgE) [1]. The natural course of this type of allergy is favorable, and progressive tolerance tends to appear spontaneously and develop in the medium to long term [2]; thus, temporary avoidance to allergen exposure is often recommended. However, a strict exclusion diet has negative consequences in patients such as risk of poor nutrition, increased levels of anxiety, and possible unjustified restrictions to further foods, with an increased immunological risk of non-acquiring tolerance. Besides, in non-tolerant infants, CMA-IgE is one of the main causes of anaphylaxis during childhood and adolescence, even just through skin contact, and it is sometimes deadly [3]. In this way, oral immunotherapy (OIT) can be proposed at different ages as an effective and safe treatment [4, 5]. The objective of this study was to analyze the safety and effectiveness of OIT in infants under 1 year of age, with treatment starting to be applied since the moment of diagnosis. We strongly believe that a diagnosed child should be automatically treated.

Material and methods

Between the years 2007 and 2018, we performed a retrospective analysis of infants under 1 year of age diagnosed with CMA-IgE. Patients with cutaneous symptoms (erythema, urticaria), gastrointestinal symptoms (immediate vomiting), respiratory symptoms (cough, stridor, wheezing), or systemic (anaphylaxis) symptoms consistent with CMA-IgE after taking infant formula were evaluated within less than 48 h from getting notice in the allergology unit of our hospital. OIT was immediately proposed for children diagnosed with CMA-IgE, after their parents had received exhaustive information and signed informed consent. Sensitized infants were defined as those who presented a positive result in the skin prick test (values equal/more than histamine) and/or positive specific IgE levels for milk and/or its fractions (casein, alpha-lactalbumin, beta-lactoglobulin) [3]. The Clinical Research Ethics Committee of Aragón (CEICA) approved the working model. Between January 2007 and June 2011, before immunotherapy was introduced, an in-hospital oral challenge test (OCT) was performed, with gradual increases in infant formula doses, seeking the threshold dose for the start of treatment (OCT group). From July 2011 to June 2018, OIT was introduced with a fixed starting dose (FSD = 0.5 ml), without prior challenging (FSD group). There were no exclusion criteria for the fixed starting dose. Once the initial dose was determined, the corresponding dose was administered at home at least twice a day for a week (Annexed 1). Families were instructed to administer the dose of infant formula (initial or continuation formula) diluted in

any other food, depending on the age of the child (hydrolyzed formula, cereals, fruits, vegetables, etc.). An in-hospital dose increase was scheduled every 7 days. A pattern adapted to each patient's tolerance was followed: patients who did not suffer any adverse reactions were proposed to make dose increments every half week, whereas patients who suffered frequent adverse reactions were proposed to make a 2-week dose increase. Parents were alerted that adverse reactions were more likely to appear on patients suffering from any undercurrent illnesses, and they were advised to return to the previous week dose. After reaching a dose of 150–200 ml of infant formula, the treatment was considered successfully completed.

Results

A total of 335 infants under 12 months of age were included in this study: 68 in the OCT group and 267 in the FSD group. No infants were excluded from initiating immunotherapy because of medical reasons (elevated IgE levels, serious adverse reactions at the onset, or concomitant pathologies). Three families refused to start OIT. The average age of starting treatment was 168 days (range 12–360) with no differences between groups. During immunotherapy, 152 patients (45.4%) presented some type of adverse reaction, 136 of them (89.4%) were Clark grade 1, 2 were grade 2 (1.3%), 12 were grade 3 (7.9%), and 2 were grade 4 (1.3%) [6] (Annexed 2). No patients showed grade 5 reactions, none of them required treatment with adrenaline, and no one showed reactions at the administration of the starting dose at FSD group. Most of these reactions happened in the hospital during the up-dosing visit. Furthermore, no patient required to be attended at the Emergency Room after home treatment. A total of 67 patients in the OCT group (98.5%) and 262 (98.1%) in the FSD group completed the treatment successfully and now consume dairy products regularly. Median duration of immunotherapy was 106 days (range 27–269) in the OCT group and 77 days (range 77–254) in the FSD group, showing significant difference between groups (p value 0.001). Six patients (one from the OCT group and five from the FSD group) did not complete the protocol due to adverse reactions: four discontinued due to persistent vomiting, one due to marked rhinorrhea and sneezing, and one due to cough with no impact on respiratory function. These six patients did not have relevant clinical differences at the onset compared to the others (same symptoms, same prick tests results, and similar specific IgE levels). These children are now between 3 and 8 years old. After the failure of the first treatment, they were offered a new subsequent OIT, and to the date, they can take milk or milk-derivatives daily—as prophylaxis—to a certain maximum dose and still remain asymptomatic [7]. Although some data are unavailable because parents did not permit their children to perform new diagnostic tests (most of who were asymptomatic), the trend after the end of immunotherapy was towards

Table 1 Progress of skin prick tests and specific IgE serum levels before and after oral immunotherapy

	Overall population				OCT group				FSD group			
	Before treatment		After treatment		<i>p</i> value	Before treatment		<i>p</i> value	Before treatment		<i>p</i> value	<i>p</i> value
	(<i>n</i> = 335)	(<i>n</i> = 316)	(<i>n</i> = 316)	(<i>n</i> = 316)		(<i>n</i> = 68)	(<i>n</i> = 59)		(<i>n</i> = 268)	(<i>n</i> = 257)		
Positive skin prick test												
Cow milk, <i>n</i> (%)	239 (71.3%)	102 (32.2%)	102 (32.2%)	102 (32.2%)	< 0.001*	62 (91.2%)	13 (22%)	0.90*	177 (66.2%)	89 (34.6%)	0.003*	
Casein, <i>n</i> (%)	244 (72.8%)	133 (42.1%)	133 (42.1%)	133 (42.1%)	< 0.001*	60 (88.2%)	15 (25.4%)	0.17*	184 (68.9%)	118 (45.9%)	0.001*	
ALA, <i>n</i> (%)	283 (84.4%)	153 (48.4%)	153 (48.4%)	153 (48.4%)	< 0.001*	57 (83.6%)	16 (27.1%)	0.24*	226 (84.6%)	137 (53.3%)	0.02*	
BLG, <i>n</i> (%)	279 (83.2%)	(44.3%)	(44.3%)	(44.3%)	< 0.001*	62 (91.2%)	17 (28.8%)	0.39*	177 (66.2%)	121 (47.1%)	0.04*	
IgE serum levels, median (IQR) ^a												
Cow milk	1.7 (0.6–5.7)	0.8 (0.3–3.1)	0.8 (0.3–3.1)	0.8 (0.3–3.1)	< 0.001**	1.3 (0.6–6)	0.7 (0.3–3.5)	0.03**	1.9 (0.7–6.2)	1.1 (0.3–4.2)	< 0.001**	
Casein	0.1 (0–0.8)	0.2 (0–1.1)	0.2 (0–1.1)	0.2 (0–1.1)	0.9**	0.2 (0–0.8)	0.2 (0–0.4)	0.07**	0.2 (0–0.9)	0.2 (0–1.4)	0.40**	
ALA	0.3 (0–1.4)	0.1 (0–0.8)	0.1 (0–0.8)	0.1 (0–0.8)	< 0.001**	0.2 (0–0.7)	0.1 (0–0.8)	0.26**	0.4 (0–1.5)	0.2 (0–1.1)	0.001**	
BLG	0.9 (0.2–3)	0.3 (0–1.1)	0.3 (0–1.1)	0.3 (0–1.1)	< 0.001**	0.7 (0.1–3.1)	0.4 (0–2.3)	0.12**	0.9 (0.3–3.1)	0.4 (0–1.3)	< 0.001**	

Differences were considered statistically different in all the tests when the *p* value was less than 0.05

n number, ALA alpha-lactalbumin, BLG beta-lactoglobulin, IQR interquartile range

p* value refers to the chi-squared test on the difference between skin prick test before and after treatment; *p* value refers to the Wilcoxon signed rank test on the difference between median IgE serum levels before and after treatment

^a Specific IgE serum levels are measured by kU/L, normal ranges are 0–0.3 kU

desensitization to skin prick tests and a progressive decrease in specific IgE levels (Table 1).

Discussion

We believe that our method is a simple, safe, and effective way of performing early oral immunotherapy. We know that the natural course of CMA-IgE generally culminates in spontaneous dairy tolerance [8]. However, as Berti et al. demonstrate [9], early immunotherapy helps anticipate the disease course, not only nudging less sensitized patients towards an early cure but also identifying the candidates who present more severe reactions in the early stages of life and offering prophylaxis against severe anaphylaxis. As reasonably expected at an early age, the study shows quite low specific IgE levels on patients (coinciding with other authors studies), generating a favorable environment to induce tolerance [2, 10]. In fact, imposing avoidance behaviors until the allergy has been confirmed, before starting treatment, diminishes the quality of life of children and their families, and it involves the prolonged use of hydrolyzed formulas with the extra added cost. Martorell et al. demonstrate safety of oral immunotherapy in cow's milk allergy in the first years of life (children between 2 and 3 years of age), thus avoiding severe problems in adulthood [11]. Despite being an uncommon allergen in Europe (except from UK), Vickery et al. also showed that this practice can be useful in allergy to peanuts [12]. Given the fact that the probability of suffering a severe allergic reaction is low or almost inexistent in the first months of life, it allows us to confirm the safety of this therapy. We believe that the allergic immunity response can be modulated during the months of life, so the probability of successful regulation of the immune system in infants is greater than in older children.

Conclusion

This pragmatic retrospective report suggests feasibility of early cow's milk protein reintroduction in a large cohort of infants with previous systemic reactions in a safe manner, suggesting that induction to tolerance may be easier to achieve in the first year of life.

Limitations

The retrospective nature of this study is a limitation by itself, despite the longitudinal follow-up of patients after treatment. Also, no control group was studied so there is no chance for randomization, which would have allowed us to draw stronger conclusions. In order to minimize the former limitations, the authors might have tested real tolerance in children who were less sensitized or those who allowed increasing dose of OIT

quickly. We also recognize that early OIT may be a burden on the family's daily life schedule, but it is worth the benefits in the long term, in order to avoid anaphylaxis.

Point of strength

In a scenario with very limited data available about this specific approach, our study shows a relevant number of patients and a consistently long follow-up period.

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Authors' contribution JBC made substantial contributions to the study, including the design, methodology, investigation, supervision, data curation, formal analysis, writing the manuscript, and reviewing the manuscript.

MCA made substantial contributions to the study, including the design, methodology, investigation, supervision, data curation, formal analysis, writing the manuscript, and reviewing the manuscript.

IGA made substantial contributions to the study, including the design, methodology, investigation, and reviewing the manuscript.

SLA made substantial contributions to the study, including the methodology, investigation, data curation, and reviewing the manuscript.

MLSR made substantial contributions to the study, including the methodology, investigation, data curation, and reviewing the manuscript.

ACM made substantial contributions to the study, including the design, supervision, and reviewing the manuscript.

YAM made substantial contributions to the study, including the design, methodology, investigation, supervision, and reviewing the manuscript.

Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed parental consent was obtained from all individual participants included in the study. The Clinical Research Ethics Committee of Aragón (CEICA) approved the working model.

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Table 2 Severity grading of worst reaction before referral

Reaction grade	Clinical features
1. Mild	Localised cutaneous erythema/urticaria/angioedema/oral pruritus
2. Mild	Generalised erythema/urticaria/angioedema
3. Mild	At least 1 or 2 plus gastrointestinal symptoms/ rhinoconjunctivitis
4. Moderate	Mild laryngeal oedema (voice change/tightening of throat)/mild asthma
5. Severe	Marked dyspnoea/hypotensive symptoms (collapse/loss of consciousness)

'/' = and/or.

- 1 **Annexed 1.** Proposed dose increase schedule in oral immunotherapy (FSD
2 group). A 16-week scheme is suggested that can be adapted and modified
3 according to the patient's tolerance and situation.

Week of treatment	Infant formula (mL) [†]	Week of treatment	Infant formula (mL) [†]
1	0.5	9	25
2	1	10	35
3	2	11	50
4	4	12	75
5	7	13	100
6	11	14	125
7	15	15	150
8	20	16	200

- 4 [†]Dose of infant formula (initial or continuation) measured in milliliters should be administered at
5 least twice a day.