Early oral immunotherapy in infants with cow's milk protein allergy

To the Editor,

Cow's milk allergy (CMA) is the most frequent food allergy in the first years of life, with prevalence rates estimated in the range of 2%-3%.[1,2] With the aim of reducing the risk of allergic reactions for accidental exposures to cow's milk (CM) proteins and of favouring the regain of clinical tolerance, strategies of controlled oral exposure to CM have been developed as immunotherapy for the treatment of children with established food allergy.[3-5] However, available data on the use of oral immunotherapy in infants with food allergy are very limited.

This report investigates the feasibility of an oral immunotherapy protocol for infants with CMA, started in their first year of life.

Between March 2015 and June 2017, we prospectively enrolled children <12 months of age who were admitted to the department for Allergy and Asthma of the tertiary level, university teaching, children's hospital, Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy, because of symptoms of immediate hypersensitivity, including skin (urticaria, angioedema and/or erythema), digestive tract (acute vomiting), respiratory system (bronchospasm, rhinitis and/or voice change), central nervous system (anxiety, drowsiness or loss of consciousness) and cardiovascular system (collapse) to CM. Infants have had typical clinical manifestations in the first hour after CM ingestion and evidence of sensitization to CM proteins on both skin prick test and specific IgE levels for whole cow's milk and at least one CM major protein.

We excluded children younger than three months of age; children with not IgE-mediated clinical manifestations; and children with a known immunodeficiency.

In order to test whether infants have had a minimal clinical tolerance that allows starting oral immunotherapy, eligible patients underwent an open "low-dose" oral food challenge (OFC). Infants took three increasing doses of 1, 5 and 10 ml of CM every 30 minutes. During the OFC, clinical reactions were recorded using Clark's classification.[6] OFC was stopped at 10ml of CM even if no clinical reactions occurred. Examining clinical symptoms during the OFC, children with a class 2 or more reaction at the first CM dose (1 ml) and children with a class 5 reaction at any CM dose were considered not suitable candidates for home oral immunotherapy.

The home oral immunotherapy protocol was conceived as follows.

From the day after the OFC, every suitable infant took at home, everyday for three to four weeks, the higher dose of milk already tolerated in hospital.

We suggested to parents diluting the CM in a small amount of liquid or food commonly consumed by the infant. Parents were instructed on possible clinical reactions and their management and to communicate to our department every possible reaction or mistake in administration. We provided families with a dedicated telephone number for urgent needs or doubt.

Infants were re-evaluated at our department every three to four weeks. At every hospital evaluation, if parents reported a steady tolerance of the dose of milk offered at home, a doubling dose of milk was administered, under medical supervision. If the doubling dose was tolerated in hospital, parents were instructed to continue offering the same doubled dose at home for other three to four weeks until the next hospital evaluation.

Every increase in the dose of milk was initially tested in hospital, in order to favour child safety, until a tolerance of 40 ml of milk was stably achieved by infants.

Once the infant had reached tolerance to 40 ml of CM without reactions at home for at least two weeks, families were instructed to increment the dose by 5 ml every week, up to 50 ml tolerated, then to increment the dose by 10 ml every week, up to 100 ml and then 10 ml every 3 days up to 150 ml of milk. A list of equivalent doses of dairy products was also provided. Families were contacted by telephone every 2 weeks.

The target of the protocol was considered to be achieved when children were able to take a dose of 150ml of CM or a corresponding dose of dairy products without reactions. Determination of IgE- and IgG4-specific CM and CM proteins was performed at baseline and repeated approximately two months after the start and at the completion of the protocol.

We investigated the feasibility of the above-mentioned oral immunotherapy protocol in terms of the number of children who completed the protocol, of number and types of clinical reactions experienced at home and of trends in serum levels of specific IgE and IgG4 between baseline and the end of the protocol.

We enrolled 73 infants. Table 1 shows their main characteristics at enrolment.

Among them, 46 (63%) reacted during the low-dose OFC. Five patients (11%) had a class 2 reaction at the CM dose of 1 ml, and they were not considered suitable for the home oral immunotherapy. Of the 41 infants suitable for oral immunotherapy, 38 infants (93%) had a class 1-3 reaction and 3 infants (7%) had a class 4 reaction during the OFC.

TABLE 1 Patient's characteristics

Patient's characteristics (n = 73)	
Age in month, mean (ranges)	7.3 (3-11)
Male sex, number (%)	50 (68)
History of atopic dermatitis, number (%)	42 (58)
Familiar history positive for allergy, number (%)	35 (48)
Age of the allergic reaction leading up to diagnosis in months, median (IQR)	2 (1-3)
Severity grading of the allergic reaction that leads to the diagnosis, based on Clark's classification, reference,[6] number (%):	
Class 1 (localized cutaneous erythema/urticaria/ angioedema/oral pruritus)	18 (25)
Class 2 (generalized erythema/urticaria/ angioedema)	28 (38)
Class 3 (at least 1 or 2 plus gastrointestinal symptoms/rhinoconjunctivitis)	18 (25)
Class 4 (mild laryngeal oedema (voice change/ tightening of throat)/mild asthma)	9 (12)
Class 5 (marked dyspnoea/hypotensive symptoms [collapse/loss of consciousness])	0
Patients evaluated at the emergency department for the allergic reaction at the moment of diagnosis, number (%)	22 (30)
Patients who received intramuscular epinephrine injection for the allergic reaction at the moment of diagnosis, number (%)	1 (1)

A total of 68 infants (41 with a positive OFC and 27 with a negative OFC) started the home oral immunotherapy protocol.

Sixty-six infants (97%) reached the target of the protocol. Two patients (3%), being part of the group of infants positive to the OFC, abandoned the protocol because of recurrent vomiting.

The target of the protocol was achieved in a median time of 5.5 months (IQR: 4.5-7, range: 3.5-16).

During in-hospital administration of doubled dose, seven children (10%) presented at least an allergic reaction and we recorded a total of 13 allergic reactions, classes 1-3. All reactions were controlled with oral medications when necessary, with one infant needing an epinephrine inhalation aerosol. During the home phase of the protocol, 29 infants (43%) experienced at least an allergic reaction. In total, 40 allergic reactions occurred. The severity of the reactions was mainly class 1, with 5 reactions being of classes 2-3, and successfully managed by caregivers with oral medications. No patient required emergency department evaluation, hospital admission or epinephrine injection due to an allergic reaction during home oral immunotherapy. The number and types of the allergic reactions experienced during the protocol are available online in Table S1.

Table 2 shows the trend of the serum levels of IgE and IgG4 specific for CM and CM major proteins, between baseline and the end of the protocol.

We found that this protocol had a high rate of families' compliance and an acceptable rate of adverse events. Considering that the majority of infants spontaneously acquires tolerance in a few years, any intervention at this age should have a very high safety profile, should be very easily manageable at home and highly acceptable by families. In our series, most of the infants reached the target of the protocol in a brief period of time. Throughout the protocol, we found that IgE levels tend to decrease, while IgG4 levels tend to increase. This trend allows us to speculate that the reintroduction of allergen in infancy could favour the regain of biologic tolerance, similarly to what was previously reported in older children[7,8] and in infancy.[9] Our experience had some limitations. At baseline, we did not perform a diagnostic OFC. Although diagnostic OFC is the gold standard according to current guidelines,[10] it is rarely performed and difficult to complete in infancy. We included also children who did not react at the low-dose OFC, therefore we cannot exclude that some of the infants may have already achieved tolerance spontaneously, even considering such a short time lapse between diagnosis of CMA and OFC. Finally, we did not enrol a control group of infants maintained

TABLE 2 Distribution of the IgE and IgG4 serum levels in the three periods of the protocol

	Baseline visit	Two-month visit	The end of the protocol visit	
IgE serum levels (kUA/L)	Median (IQR)			*P*-value[a]
Milk	1.81 (0.75-7.17)	1.89 (0.60-7.33)	1.04 (0.28-2.42)	<0.0001
ALA	0.91 (0.20-2.73)	0.87 (0.32-2.96)	0.53 (0.17-1.22)	0.0002
BLG	4.11 (0.97-13.55)	2.48 (1.01-10.16)	1.44 (0.68-4.57)	<0.0001
Casein	0.87 (0.28-3.46)	1.20 (0.21-4.05)	0.63 (0.13-2.55)	0.0247
	Baseline visit	**Two-month visit**	**The end of the protocol visit**	
IgG4 serum levels (mgA/L)	**Median (IQR)**			***P*-value**
ALA	0.06 (0.01-0.21)	0.38 (0.10-1.25)	2.22 (0.40-8.63)	<0.0001
BLG	0.19 (0.03-0.66)	1.18 (0.35-4.03)	4.61 (1.37-17.35)	<0.0001
Casein	0.13 (0.08-0.29)	0.37 (0.17-1.51)	1.63 (0.41-8.20)	<0.0001

Abbreviation: IQR, interquartile range.

[a]*P*-value is referred to the Wilcoxon signed ranks test on the difference between baseline and the end of the protocol.

on a milk-free diet; thus, we were not able to differentiate induction of tolerance secondary to early oral immunotherapy and natural resolution of allergy.

The majority of infants with CMA develop tolerance before school age spontaneously. Therefore, waiting for the natural acquisition of spontaneous tolerance before starting an allergen immunotherapy is recommended.[11] However, a considerable proportion of children may experience a long persistence of CMA,[2] with a relevant risk of severe allergic reactions for accidental exposure to CM proteins[4] or during allergen immunotherapy started after 4-5 years of age.[12] For these patients, an early oral immunotherapy could be a potentially curative therapy, allowing to increase the amount of milk that the child can tolerate and reducing the risk of potentially life-threatening allergic reactions. Even in patients candidate to a spontaneous achievement of tolerance in the first years of life, a safe and easy to manage protocol may offer the advantage of an earlier unrestricted diet, reducing possible food avoidance-related nutritional risks and improving families' quality of life by limiting parents' anxiety for the risk of reactions related to accidental food ingestion. Future randomized controlled studies are needed to confirm these preliminary findings.

CONFLICT OF INTEREST

The authors have no conflict of interest in relation to this work.

AUTHORS' CONTRIBUTIONS

GL, IB, LB and AV contributed to the conception of the work. CB and LB contributed to the acquisition of the data. MG and LR contributed to the statistical analysis of the data and reviewed the final version of the paper. GC, LB and EB wrote down the draft of the paper and contributed to the critical revision of the work. All the authors read and approved the final manuscript.

ETHICAL APPROVAL

The protocol was approved by the Independent Bioethic Committee of the Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy. All children's parents or legal guards provided written informed consent for their participation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.