

Cow's Milk Allergy in Children, from Avoidance to Tolerance

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Abstract: Food allergy is the primary cause of anaphylaxis in paediatric age affecting roughly 4% of children and their families worldwide, and requiring changes in dietary habits. The prognosis for food allergy in children has traditionally been regarded as good for the most frequent allergens, however the prognosis for cow's milk allergy in the pediatric age is currently considered to be worse than previously believed. There is now enough evidence that measures of avoidance for children at risk did not have any preventive effect whatsoever, but they still came to be counterproductive by avoiding the physiological interaction between food allergens and gastrointestinal mucosal immune system. Programs of specific oral tolerance induction (SOTI) have obtained interesting results in the treatment of food allergy supporting the idea that antigen exposure through gastrointestinal section is important to allow the development of tolerance. Nevertheless this approach is not yet considered "ready" for community recommendations. In this paper we describe our experience in the field of SOTI in children with cow's milk allergy.

Keywords: Anaphylaxis, avoidance, cow's milk, food allergy, SOTI, tolerance.

BACKGROUND

Food allergy is the primary cause of anaphylaxis in paediatric age affecting roughly 4% of children and their families worldwide, and requiring changes in dietary habits. In Europe cow's milk proteins (CMPs) and hen's egg proteins are the main offenders [1-4]. In developed countries the prevalence of true food allergy diagnosed by oral food challenge is about 3–8% in children [5-8]. These rates vary between countries and have increased in recent years [9-11] so that some investigators consider food allergy as an evolving public health issue [12].

The prognosis for food allergy in children has traditionally been regarded as good for the most frequent allergens, with almost all children outgrowing their food allergy. For cow's milk allergy about twenty years ago one study reported resolution rates of about 45–50% at age 1 year, 60–75% at age 2 years, and 85–90% at age 3 years [13]. However, in 2007 another study reported about a fifth of non-tolerating children aged 16 years; these children had increased concentrations of cow's milk IgE at all ages [14]. Also due to this new epidemiologic data, the prognosis for cow's milk allergy in this population is currently considered to be worse than previously believed so that a possible persistent allergy to cow's milk and the effect of specific IgE concentrations on prognosis should be taken into account in the management of these children.

There is now enough evidence that measures of avoidance for children at risk (elimination diet in breastfeeding mothers,

hydrolyzed formulas, cow's milk free diet) did not have any preventive effect whatsoever, but they still came to be counterproductive by avoiding the physiological interaction between food allergens and gastrointestinal mucosal immune system and preventing the development of normal regulatory mechanisms [10, 15-16].

Still now, according to existing guidelines [17], in children with documented sensitization (history of reactions, presence of specific IgE, positive challenge) food avoidance should be recommended and a follow-up visit and assessment every 12 months should be provided. This approach does not consider the actual evidence suggesting that contact with allergen could play a pivotal role in the acquisition of tolerance [18-19] and that tolerance is likely to develop gradually, and that long before the child tolerates normal amounts, he or she can tolerate small amount of the offending food.

Data from observational studies suggest low-dose challenge protocols suited to young children outgrowing their food allergy to prove that a child can eat small amounts of the food without an allergic reaction [20]. Programs of specific oral tolerance induction (SOTI), the gradual monitored administration of an allergen over months and years, have obtained interesting results in the treatment of food allergy [21-29] supporting the idea that antigen exposure through gastrointestinal section is important to allow the development of tolerance. Nevertheless this approach is not yet considered "ready" for community recommendations [30]. The main criticism expressed by avoidance supporters is that the benefits of SOTI have not been measured in largely subjective outcomes (*i.e.* enhancement or worsening of quality of life with validate instruments) and may be counterbalanced by possible serious adverse effects [30-31].

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The immunologic mechanisms underlying SOTI are still unclear and whether SOTI induces long-term tolerance or only transient desensitization remains to be established. In food-sensitized children Th-2 polarized immune response leads to increased levels of allergen-specific IgE and IgG1 levels [32]. It is not already known if SOTI is able to induce a long-lasting immunity shift (no longer TH2 oriented) or whether tolerance is obtained through temporary reduction of specific IgE levels. In the latter case tolerance would disappear if antigen intake is suspended for any reason, so we recommend to our patients a constant intake of CMP for years after SOTI to promote a durable decrease of specific IgE levels. Actually we know that after a few months of oral immunotherapy, clinical improvement is accompanied by a decrease in effector T-cell populations and an increase in regulatory T cells and hypoproliferative and non-reactive CD4+ T cells [32]. The hypothesis is that oral tolerance is first achieved through an antigen-specific mast cell desensitization, followed by a TH-mediated process with normalization of IgE levels.

OUR EXPERIENCE

Specific oral tolerance induction (SOTI) is a promising approach in the treatment of severe food allergy. Recent reports have demonstrated the efficacy of different oral desensitization protocols in the treatment of cow's milk (CM) allergy [21-25]. Nevertheless, the number of children who have undergone these protocols is still small and SOTI is considered an experimental approach to be limited to highly defined settings. Data regarding the incidence and severity of adverse reactions during SOTI show a wide range varying from infrequent, mild reactions [33] to frequent, severe ones [34]. This was likely due to the variability in patients' specific IgE levels as well as in SOTI protocols adopted.

Our experience in the field of SOTI started some years ago, initially dedicated to children with severe allergy. In the following years, also in the light of new knowledge about mechanisms of tolerance, programs of induction of tolerance had been extended to children with history of less severe reactions and infants with early documented sensitization to cow-milk.

In this paper we briefly describe our experience in these three categories of patients.

Children with Very Severe Cow's Milk Allergy

Commonly, children with very severe cow's milk allergy show very high levels of specific IgE12 and have severe reactions after the ingestion of, inhalation of, or even skin contact with trace amounts of antigen [35-39]. For them, the risk of fatal reactions is real and increases with age as a result of reduced parental control over their diet.[40] The possibility of spontaneous recovery is quite rare in patients 6 years or older with very high levels of specific IgE [41-44]. Currently, standard management for these subjects consists of strict antigen avoidance combined with instructions for recognizing symptoms, prescription for self-injectable epinephrine for emergency use, and information on access to emergency services [2]. This approach has a negative effect on the child's behavior and compromises the quality of life

of the entire family because of the fear of unexpected or life-threatening reactions [45]. Indeed, it is difficult to avoid completely a common food, and the likelihood of unintended exposure is considerable [40, 46-47].

In our service challenge with CM was performed by offering progressive increasing amounts of pure fresh pasteurized CM, starting with one drop up to a maximal dose of 150 ml (Table 1). To children unable to tolerate at a challenge a single dose of at least 2 ml or with a history of severe reactions occurring within the previous year and requiring emergency room care, and with high specific IgE levels (greater than 70 kUA/l) we routinely propose a program of tolerance induction that starts with an intra-hospital rash phase.

In the intra-hospital SOTI, CM administration was developed based on small initial doses, increased every day for about 10 days admission [48]. The raise in CM was regulated according to the patient's symptoms and reactions. As a rule, the number and severity of reactions did not change the length of admission, but might have changed the amount of single CM dose reached at discharge (the more severe the reactions, the slower the increase and lower the dose of CM at discharge). Patients who did not experience any adverse symptoms during the first few days of SOTI were given increasing doses of CM until symptoms were provoked. In these cases, admission could last less than ten days, and the patient was discharged with a higher tolerance of CM, resulting in a larger initial dose during the home phase. Adverse reactions during this in-hospital SOTI protocol were frequent but always easily manageable. Once the patients were released, the protocol was continued at home with slow increase in the amount of milk. As reported in a previous study [49] at 1 year after discharge between the patients who started SOTI more than 1/3 of children had become completely tolerant, about 1/2 of children could take limited amounts of milk (5-150 mL), and about 10% of children were not able to complete the protocol because of persistent respiratory or abdominal complaints (Fig. 1). Patients in control group kept on milk-free diet underwent to placebo-controlled food challenge after a year and it was positive in all. Allergic symptoms were common during the increasing dosage phase, but symptoms typically were managed effectively by educated parents. During the course of the study, all the parents were highly motivated because of their awareness of the child's problem and of the very poor quality of life deriving from antigen avoidance. The parents

Table 1. Cow' milk challenge scheme at our institute.

Dose	Time	Dose	Time
1 drop	0	4 ml	70 minutes
2 drops	10 minutes	8 ml	85 minutes
4 drops	20 minutes	16 ml	100 minutes
8 drops	30 minutes	32 ml	120 minutes
16 drops	40 minutes	64 ml	140 minutes
2 ml	55 minutes	150 ml	160 minutes

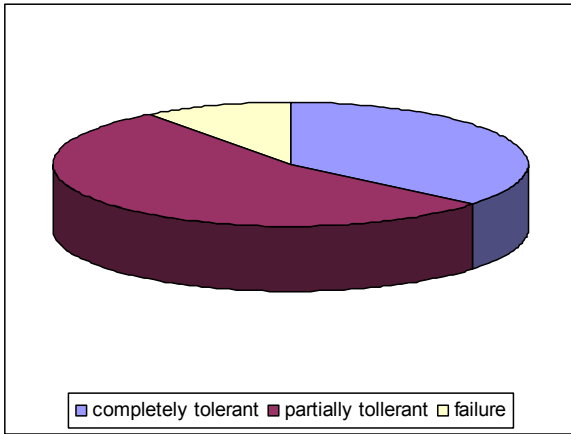


Fig. (1). Outcome at 1 year in treatment group A. Completely tolerant: Patients who could tolerate at least 150 mL of cow's milk daily. Partial tolerance: Patients who could tolerate a limited amount (5-150 mL) of cow's milk daily. Failure: Patients who stopped the protocol and restarted an avoidance diet

of treated children expressed great satisfaction, including those whose children had experienced major symptoms and achieved only partial success.

These results had been substantially confirmed by the recent data in this group of patients.

Children with "Partial Tolerance" to Cow's Milk

Since 2002 we empirically started to offer a home SOTI protocol to all patients able to tolerate during a food challenge at least 2 mL of whole milk, but not reaching the maximal dose because of reaction.

After oral challenge each patient was discharged with written instructions on how to gradually increase the dose of CM (Table 2). Empirically we decided that the starting dose from the day after the challenge, corresponded to that prior to the last tolerated dose without symptoms.

The increase in CM was flexible and could be adapted to the patient's tolerance and symptoms by slowing down the rate of increase or keeping it a fixed dose for weeks or even months at a time, in the case of recurring symptoms.

According to our protocol [49] parents were told to keep the child under observation for 3 hours following the ingestion of CM and to avoid physical activity during this 3 hours period. In case of a respiratory infection, they were instructed to decrease the dose of CM by 30% and in the case of gastroenteritis or asthma by 50%, until a complete resolution of the symptoms was seen. At the time of discharge parents received oral and written instructions on how to deal with the various reactions associated with the home phase of SOTI.

During the period between January 2005 and April 2010 245 patients were enrolled for CM challenge. Among the 125 subjects with a positive challenge who were able to tolerate a minimum dose of 2 mL, 122 were enrolled for home SOTI. At one year follow up among 118 subjects who completed the study 89 (75.4%) patients were in an

Table 2. Cow's milk dosage in home SOTI.

Period	CM Dose
between 1° and 20° day	1 ml for five days
	1.5 ml for five days
	2 ml for five days
	3 ml for five days
between 21° and 40° day	4 ml for five days
	5 ml for five days
	6 ml for five days
	7 ml for five days
between 41° and 60° day	9 ml for five days
	11 ml for five days
	13 ml for five days
	15 ml for five days
between 61° and 80° day	19 ml for five days
	23 ml for five days
	27 ml for five days
	31 ml for five days
between 81° and 100° day	40 ml for five days
	50 ml for five days
	60 m for five days
	70 ml for five days
between 101° and 120° day	90 ml for five days
	110 ml for five days
	130 ml for five days
	150 ml for five days

The starting dose corresponded to that prior to the last tolerated dose without symptoms during the open CM challenge (examples: a child reacting to 4 mL would start with 1 mL, a child reacting to 32 mL with 8 mL).

unrestricted diet, 19 (16.1%) ("partially tolerants") were able to tolerate significant amounts of milk (between 5 and 150 mL) and 10 (8.5%) had suspended the protocol because of recurrent minor adverse effects or refused of child or parents to continue.

During the home phase 36 (30.5%) subjects presented some adverse effects. An admission to the local emergency department was required for 5 (4.2%) patients (Table 3). No patient was hospitalized. No child was treated with intramuscular epinephrine.

At follow-up at one year, considering all the 118 subjects who completed the study, approximately 79.7% of parents were satisfied or very satisfied with the SOTI, 6.8% of parents were partially satisfied because they felt the shelter of severe reactions to accidental contact but hoped for a

Table 3. Adverse effects during the home phase.

Adverse Effects	
Number of patients (%)*	36 (30.5%)
Hospital admission (%)	5 (4.2%)
Minor adverse effects (throat and/or tongue itching, mild rhinitis and/or conjunctivitis, urticaria, abdominal pain)	25 (21.2%)
Major adverse effects (respiratory symptoms)	11 (9.3%)

*no more than 10 reaction for any patient (range 1-10)

better outcome and 13.5% of parents were unsatisfied due to the lack of complete liberalization of the diet or because of the repeated occurrence of adverse effects, although not severe.

In our series the absence of a control group should lead to a cautious interpretation of the results but the difference in the percentage of children acquiring tolerance between our series (76%) and the average rate of spontaneously acquired tolerance (20%) reported by the literature [14] can be considered as relevant.

Early SOTI

It is now suggested that the normal development of oral tolerance is an antigen dependent process requiring an early and repeated exposure to foods and that delaying complementary feeding after the age of six months could be self-defeating in terms of sensitization to foods [50]. Some studies have also suggested the existence of a relatively narrow window, probably between 3-4 months to 6-7 months of life, of immunological opportunity to expose children to allergenic foods and induce tolerance [51-54]. Some randomized controlled trials (RCTs) are currently in progress to evaluate whether early introduction of allergenic foods may lead to tolerance and protect against the development of IgE mediated food allergy [55-57]. Preliminary data from an ongoing study at our institution of early introduction of CM in infants with proved sensitization are encouraging in this sense. In the past two years we have enrolled about fifty children aged less than 18 months with mild reactions (urticaria, angioedema) after taking CM and specific IgE. Of these children, about 90% were on an unrestricted diet after an average of 6 months.

DISCUSSION

Over the past few years new data that challenge many old dogmas about allergies have been published. Delayed weaning and prolonged exclusive breastfeeding as well as other strategies based on avoidance of solid foods have thought to be ineffective and probably harmful. Moreover complete avoidance of food allergens is difficult [57-58] and the risk of accidental and severe reactions can create anxiety and diminish quality of life among children and caregivers [59-61]. There is now strong and repeated evidence from the most recent literature [18-19] that the prerequisite for the

development of tolerance is repeated exposure to antigen and that contact with antigen induces tolerance. On the other hand it is now strongly suggested that in the proper development of tolerance food avoidance can even be deleterious and prevent the development of normal regulatory mechanism and that in many children the partial tolerance could be broken when the child is put on an elimination diet [18, 62].

In infants with an atopic constitution, sensitization to foods, particularly milk and eggs, usually begins during the first year of life before these foods are introduced into the diet. In the majority of cases, if these allergens are not introduced, sensitization reaches its peak during the 2nd or 3rd year of age [14]. Recommendations that increase the risk of food allergy such as the common habit to remove a food from the diet of an eczematous child after a prior ingestion without acute IgE-mediated symptoms should be abandoned. Indeed, this is not effective in controlling the eczema and could lead to an increased risk of anaphylaxis upon re-exposure to the offending food after a period of elimination.

Considering SOTI, one should always think that by the age of 6 years the majority of children with less severe food allergy spontaneously acquire tolerance; the prognosis in older children with severe allergy is clearly worse and the risk of fatal or near-fatal reactions should always kept in mind. The benefit of intervention, that is the possibility of introducing even small amounts of the incriminated food getting out of the risk of reactions from contamination or in adverted contact, is perceived by families as a major improvement in their quality of life. This benefit must be weighted case by case with the costs of family engagement for milk administration and risk of reactions. Furthermore this approach is time consuming and requires a defined level of commitment by the staff involved.

Data about the cost benefit ratio of SOTI are still limited in the literature but different groups showed that SOTI has high efficacy and very limited side effects (no need of intramuscular epinephrine) in series of children with lower IgE levels [21-25, 26, 29]. Recent papers have also shown the safety and efficacy of an oral desensitization in 2-year-old children with allergy to CM proteins, as a treatment alternative to elimination diet (diet free of milk and derivatives) [63].

Our experience confirms the idea that "partially tolerant" children can be successfully treated by the very day of the challenge with a home SOTI protocol, with high efficacy and limited side effects. We believe that the safety record of this series and of the others published reports [21-25, 26, 29], dealing with children with mild allergy, justifies this approach and that guidelines should be reviewed considering that partially tolerant children should not straight forwardly undergo through an exclusion diet, especially children with lower specific IgE levels tolerating significant milk amounts.

In children with severe cow's milk protein (CMP) allergy our data support the hypothesis that tolerance can be achieved through a progressive increase of oral administration of cow's milk in a significant percentage of patients. Even a partial tolerance (*i.e.*, ingestion of limited amounts of cow milk) resulted in a striking improvement in quality of life.

Clearly the risk of fatal or near-fatal anaphylaxis during SOTI compared with the risk of fatal anaphylaxis after accidental exposure in untreated patients still needs to be determined on the basis of larger numbers of patients and longer follow-up periods. Considering the need for careful management of this kind of patients this procedure should only be conducted in highly controlled settings.

FUTURE TRENDS AND RESEARCH

The major allergens from cow's milk have been found to be β -lactoglobulin, α -lactalbumin and caseins. Strategies for destroying or modifying these allergens to eliminate milk allergy are being sought by different scientists. Heating is an important process in the manufacturing of most dairy products. During the heating processes, important structural and chemical changes in proteins occur [64]. These alterations may have significant impacts on the antigenicity of milk protein allergens. In addition to heating, milk protein allergenicity may also be decreased through interaction with other food proteins in a complex food, such as in a wheat matrix in a baked muffin or cupcake, due to delayed gastrointestinal digestion and epithelial transport of food allergens [65]. Analysis of serum samples of children with persistent cow's milk allergy demonstrates significantly higher ratio of sIgE to linear versus conformational epitopes compared to children who have achieved tolerance [65]. Some authors have suggested that tolerance of baked-milk is a marker of transient IgE-mediated CM allergy whereas reactivity to baked-milk portends a more severe phenotype. The same authors have also suggested that the addition of baked-milk to the diet of children tolerating such foods could accelerate the development of tolerance for unheated-milk compared to strict avoidance [66]. This interesting hypothesis remains to be proved. To our knowledge actually only few studies with small numbers of children on SOTI with baked-milk were done and large clinical trials are necessary to validate this approach. Moreover as far as milk allergy is concerned, the acquisition of tolerance for the unprocessed raw food is a priority in real life since contact with raw milk can be frequent. For these reasons, at the present time, our practice remains to proceed with the SOTI with the raw milk.

CONCLUSION

Cow's milk allergy remain an important cause of anaphylaxis in paediatric age. Data that challenge many old dogmas about allergies have been published and strategies based on avoidance of solid foods have thought to be ineffective and probably harmful. Actual evidence suggests that contact with allergen could play a pivotal role in the acquisition of tolerance and programs of specific oral tolerance induction (SOTI) have obtained interesting results in the treatment of food allergy. Our experience confirms the idea that SOTI, conducted in highly controlled settings, can be considered as the first line treatment in CM allergy in children.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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