A practical focus on milk oral immunotherapy

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ABSTRACT

Cow's milk allergy (CMA) is a common childhood food allergy associated with a significant burden for those children who are affected and their families, including unintentional exposures that result in allergic reactions, severe allergic reactions, and anaphylaxis. In young children, cow's milk is one of the most frequent food triggers in anaphylactic episodes, and fatalities have also been described as a result of unintentional exposures, which reinforces the notion that milk allergy can be severe in some individuals. The natural history of CMA is favorable, with the allergy resolving over time in the majority of individuals, although some will have persistent allergy that does not resolve. The standard management approach for CMA consists of strict avoidance of milk and carriage of emergency medication for use in accidental exposures. Recently, a novel approach has emerged as an alternative option for management in patients with CMA in the form of oral immunotherapy (OIT). The aim of milk OIT is to protect patients from accidental exposures to milk-containing foods and allow patients to introduce larger amounts of milk into their diet. The goal of this article was to review the available evidence, discuss key studies that focused on milk OIT, and provide practical information and useful tips related to this novel treatment.

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Cow's milk allergy (CMA) is a common food allergy in childhood, which affects 2.5% of infants.[1] CMA poses a significant burden on individuals who are affected, including unintentional exposures that result in allergic reactions, severe allergic reactions and anaphylaxis, dietary restrictions, psychosocial limitations, and financial issues.[2–6] Milk is used in a wide variety of food products, which makes strict avoidance a difficult task. Milk oral immunotherapy (OIT) presents a newer option for management in patients with CMA, especially those who are unable to outgrow their allergy. The aim is to protect individuals from accidental exposures to milk-containing foods. This raise in the threshold is more significant if the patient achieves desensitization to the top dose, which is usually defined as the ability to consume a full serving of milk (~200 mL) without any allergic reactions. The goal of this article was to discuss key studies that focus on milk OIT and provide practical information and useful tips related to this novel treatment.

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EFFICACY AND SAFETY

A seminal research trial on milk OIT by Skripak *et al.*[7] evaluated the efficacy and safety of this intervention with a double-blind placebo controlled design. Treatment duration is reported as 10 weeks of escalation, followed by 13 weeks of maintenance (total duration, 23 weeks). The study showed that children who received active treatment (milk OIT, in the form of milk powder) were able to raise their median threshold from 40 mg at study entry to > 5 g after OIT (for reference, a full 250-mL serving of cow's milk contains 8 g of protein). In the placebo group, there was no change from baseline threshold at the study exit. Allergic reactions were seen in 45.6% of the active doses, with > 90% of these consisting of local (oral itching) or gastrointestinal (abdominal pain) symptoms.[7] A total of four doses of epinephrine were administered during the trial in the active group: two during the initial escalation day and two with home doses.[7]

In a separate research study, Longo *et al.*[8] reported on 60 children, 5–17 years old, with severe milk allergy, defined as previous systemic reactions to cow's milk and very high cow's milk specific immunoglobulin E (IgE) levels (>85 kUA/L). The participants were either undertaking milk OIT (n = 30) or were following a dairy-free diet (n = 30) for 1 year.[8] A total number of four participants were treated with epinephrine for in-hospital anaphylaxis, and one participant was treated with epinephrine for at-home anaphylaxis.[8] All received a single dose of epinephrine.

The investigators reported that more than one-third of the participants (36%) were able to consume > 150 mL of cow's milk, 54% tolerated ingestion of 5–150 mL of cow's milk, and 10% in whom the intervention failed due to persistent respiratory or abdominal symptoms during OIT.[8] In practical terms, milk OIT allowed a significant proportion of OIT participants on OIT (more than one-third) to consume a full serving of milk without allergic reactions.

Meglio *et al.*[9] performed an open study in their cohort of 21 children (ages ≥ 6 years) with severe IgE-mediated CMA for a 6-month treatment period. A total of 71.4% of the participants were successfully desensitized to 200 mL of cow's milk, 14.3% were able to tolerate 40–80 mL of cow's milk, and the intervention failed in 14.3%.[9] Allergic reactions during treatment were successfully managed with oral antihistamines, and epinephrine was not required in any subject.[9]

After the publication of the above and other research studies that showed benefit from the use of OIT in individuals with milk allergy, a systematic review was performed to assess the evidence that supports the use of OIT in IgE-mediated CMA.[10] The review included both randomized controlled trials and observational studies, with a total of 301 patients (218 in the randomized control trials and 83 in the observational studies).[10] The results derived from the systematic review confirmed the benefit of milk OIT compared with a milk-free diet alone.[10] It was shown that the probability of achieving successful desensitization to cow's milk was 10-fold greater with the use of milk OIT compared with the elimination diet. However, it was recommended that the benefits of milk OIT should be assessed together with the risks; it was shown that adverse events occur frequently in children who received OIT, with a reported 16% of doses associated with local reactions and a fivefold greater risk of requiring epinephrine during treatment.[10]

Outside the research environment, Luyt *et al.*[11] reported on a cohort of 50 children (ages 5–16 years; all received active treatment with milk OIT), treated in the clinic setting in the United Kingdom with a specific tolerance induction program to cow's milk. The program involved slow updosing up to a full dose of 250 mL, with 23 of 50 of the participants (46%) who achieved this dose, defined as full desensitization.[11] A further 9 of 50 (18%) achieved partial desensitization and milk OIT failed in 18 of 50 of the participants (36%).[11] The rate of epinephrine administration was low (2/50 [0.04%]), with the majority of adverse events described as mild to moderate.[11]

PRACTICAL IMPLICATIONS

It is clear that milk OIT successfully raises the threshold of reactivity to cow's milk and allows at least one-third of the participants to consume a full serving of milk without allergic symptoms. Adverse reactions occur during treatment, and, to safely administer milk OIT, patients and families must be educated on how to recognize, treat, and promptly report allergic reactions, including anaphylaxis. A written management plan must be provided, which includes step-by-step instructions on how to manage allergic reactions and report them to the attending physician. In addition, exercise avoidance for 2 hours after dosing, dosing changes during illness, menstruation, or tiredness need to be highlighted to families undergoing OIT.

PUBLISHED DOSING SCHEDULES

Multiple dosing schedules have been published by different investigators in a variety of studies of milk OIT. Examples from key published studies are described here. Skripak *et al.*[7] used an initial rush day, when doses were increased from 0.4 mg to a maximum of 50 mg of cow's milk protein. This was followed by increases every one or every 2 weeks in doses from 75 mg to 100, 130, 170, 225, 295, 385, and 500 mg of cow's milk protein.[7] Longo *et al.*[8] followed a more stepwise and cautious approach for their severely allergic population, with a 10-day rush phase starting with dilution of 1 drop of cow's milk in 10 mL of water, up to a maximum of 20 mL of undiluted cow's milk. This was followed by at-home dosing, when children would have their dose increased by 1 mL every second day, based on individual response. The full serving dose was defined as 150 mL of cow's milk (undiluted).

Meglio *et al.*[9] used an updosing schedule that started from 1 drop of whole cow's milk diluted 1:25 with water (~0.06 mg of cow's milk protein), with doses doubled every week for 7 weeks, followed by undiluted drops of cow's milk for another 3 weeks (5, 10, 20 drops). After this period, doses (in mL of undiluted cow's milk) would be doubled every 16 days (doses: 2, 4, 8, 16, 32, 64, 128, and 200 mL) with the aim to reach a total daily dose of 200 mL (equivalent to 6.4 g of cow's milk protein).

For their clinical program, Luyt *et al.*[11] used the slow updosing protocol of Staden *et al.*,[12] which spans 67 days and has three stages. In the first stage, 1 drop of milk is diluted in 99 drops of water (1% solution, 0.02 mg of milk).[12] The first dose (day 1) is 1 drop of the above solution increased in a further 11 steps up to 20 drops (equivalent to 0.33 mg of milk protein).[12] In the second stage, 1 drop of milk is diluted with 10 drops of water (10% solution, 0.2 mg of milk protein).[12] A dose of 3 drops (0.50 mg of milk protein) is given initially, followed by eight incremental increases to 20 drops (3.3 mg of milk protein).[12] The third and last stage uses undiluted whole milk, starting with 3 drops (5 mg of milk protein), increasing gradually to 20 drops at day 30 (33 mg), then to 13 mL (429 mg) by day 40, and all the way up to 250 mL (8.250 mg) by day 67.[12] Modifications may be required, depending on individual patient response.

Table 1 **Amount of milk protein in different products and foods**

Food or Product	Amount of Food or Product	Approximate Amount of Cow's Milk Protein, g*
Cow's milk	250 mL (8.4 oz)	8
Yogurt (Greek)	100 g (3.5 oz)	10
Yogurt (fruit variety)	100 g (3.5 oz)	4.4
American cheese	100 g (3.5 oz)	18
Cheddar cheese	1 slice (28 g or 1 oz)	7
Parmesan cheese (shredded)	100 g (3.5 oz)	38
Feta cheese	100 g (3.5 oz)	14
Baked milk muffin	1 muffin	1.3

**Protein content may vary by brand.*

Practical Implications

There is not a single standardized protocol for use in milk OIT, instead a variety of different approaches that may be used to achieve the desired outcome of desensitization in patients with CMA. Results may vary, depending on the population treated and the severity of CMA at baseline (before the intervention). When comparing different protocols, the main consideration is safety. Generally, slower updosing protocols allow more time for adaptation to dose increases and are likely to be associated with fewer adverse events. However, this approach usually results in a longer duration of OIT escalation and in reaching maintenance. For milk, most protocols would aim for a maintenance dose of 150–250 mL of fresh milk, considered a full, age-appropriate portion. For patients who are unable to reach this dose, smaller maintenance doses can be considered, which allow safe exposure to smaller amounts of milk protein, including baked milk (see Table 1 for protein amounts in different milk-based products).

DOSE PREPARATION AND MASKING

Doses should be prepared in a clean area, free from contamination with any potential food allergens. For milk OIT, both milk powder[7] and liquid cow's milk[8,9] (diluted and/or undiluted) were used in research studies. The amount of cow's milk protein is the same in skim, 1%, 2%, or whole milk. The shelf life of various products differs. Cow's milk–free vehicles (for dose mixing and disguising taste) that have been used successfully include apple sauce, soy milk, and rice milk flavored with chocolate or strawberry syrup.[7]

MILK REINTRODUCTION INTO THE DIET

After successful desensitization, cow's milk may be reintroduced into the diet on a regular basis. The daily amount will depend on the maintenance dose achieved, but a variety of products can be used in addition to fresh cow's milk (Table 1). If the taste of milk or yogurt is an issue, then flavoring agents may be used, *e.g.,* chocolate- or strawberry-flavored milk is often preferred by young children. For those who tolerate small-to-medium amounts of milk protein, baked products are also an option, *e.g.,* baked egg muffins or store-bought products with milk listed as a third ingredient or less. It is important to note that the allergenicity of different milk-containing foods is variable and that these are supplementary foods that do not replace OIT dosing (*e.g.,* a baked milk product cannot be used interchangeably with fresh milk). However, used appropriately, these products would likely be tolerated, add variety to the diet, and reduce the burden of avoidance for patients with CMA.

BAKED MILK OIT

For patients who are reactive to baked milk, a form of baked OIT has been investigated. In a U.S. study,[13] 15 participants (ages 3–18 years) were randomized to receive baked milk OIT or placebo for 12 months. At study exit, 11 of 15 (73%) were tolerating 4044 mg of baked milk protein compared with 0 of 15 (0%) on the placebo arm. Dose-related reactions were common, but > 95% of these were mild, which suggests that baked milk OIT was well tolerated and induced a substantial level of desensitization after 12 months of treatment.[13] In contrast, a different study, from Israel, described 15 patients ages > 4 years for whom milk OIT was previously unsuccessful and who participated in baked milk OIT. Only 3 of 14 patients (21%) tolerated the targeted 1.3 g of the baked milk dose. Baked milk OIT failed in a total of 8 of 11 participants because of IgE-mediated reactions and in 3 because of non–IgE-mediated factors. An increase in challenge threshold to unbaked milk was noted in those who continued until 12 months. The investigators concluded that baked milk OIT should be administered in a cautious manner due to the risk for anaphylaxis. In addition, only a limited benefit in terms of an increase in threshold was

found.[14] Results of the above studies suggest that, although baked milk OIT seems to be a promising therapy for some, care must be taken in patient selection and treatment administration due to adverse effects and potentially limited benefit in certain patient populations.

LONG-TERM MILK OIT AND CLINICAL FOLLOW UP

In terms of long-term efficacy and safety of milk OIT, a prospective study of 42 children and adolescents who underwent milk OIT and successfully reached a maintenance dose of 200 mL daily were followed up for at least 36 months after reaching the maintenance dose.[15] Of the 42 patients, 36% had a history of anaphylaxis and 57% had a history of asthma.[15] The median time of follow-up was 69 months (range, 39–105 months).[15] A total of 92% were on an unrestricted diet (at least 200 mL of cow's milk daily), 14% had transient interruptions of milk ingestion, and 7% had stopped ingesting milk completely.[15] During maintenance, 45% developed mild-to-severe allergic reactions at least once, with a positive correlation seen between allergic reactions and a history of anaphylaxis or asthma diagnosis, which suggests that daily intake is not entirely protective of symptoms in these patients.[15]

A different follow-up study, of 24 children who were previously successfully desensitized to cow's milk, reported that 14 of these children (58.3%) continued to consume milk (≥200 mL) or milk products (protein ≥ 6400 mg) daily for 7 years after reaching maintenance.[16] However, three of these children (21.4%) still reported symptoms associated with milk consumption.[16] Of the 10 remaining children, 2 continued ingestion of milk products daily but consumed less than the target maintenance amount due to symptoms; 8 (33.3%) had discontinued milk consumption.[16]

Clinic follow up (every 3 to 6 months) of individuals who were successfully desensitized is recommended to monitor safety of long-term maintenance, evaluation of adherence to regular dosing, and management of adverse events (if these occur). For those individuals who were unable to achieve desensitization to the full dose, regular follow up is also important to maximize the benefit of partial desensitization, discuss any further available management options, and monitor for compliance and adverse events. Monitoring for eosinophilic esophagitis is also important because cases have been described in patients undergoing OIT.[17]

MILK OIT AND OMALIZUMAB

The addition of a biologic to OIT is an area of interest. U.S. researchers investigated the addition of omalizumab to milk OIT with 57 participants (children and young adults) randomized to either omalizumab or placebo.[18] Open-label milk OIT was initiated after 4 months of omalizumab or placebo, with escalation to maintenance over 22 to 40 weeks, followed by daily maintenance until month 28. The use of omalizumab in combination with milk OIT resulted in significant improvements in safety, but efficacy of the intervention remained unchanged.[18] In practical terms, omalizumab is currently not indicated for food allergy, but it is used in patients with asthma and urticaria. Therefore, it is worth noting the potential for improved safety during desensitization in this subgroup.

SPECIFIC CHALLENGES AND CONSIDERATIONS

It is important to note that milk OIT is recommended for IgE-mediated CMA; patients with non-IgE CMA are not candidates for OIT. The timing of milk OIT is an important consideration. When considering the high rate of natural resolution, it may be prudent in infants and toddlers to wait a few years and offer OIT if it is likely that the milk allergy will be persistent rather than transient. However, if a patient is having multiple allergic reactions due to accidental exposures, OIT may be considered at a younger age. Although it may not be possible to predict with absolute certainty if a toddler will ever outgrow his or her milk allergy, it is reasonable to assume that if the milk specific IgE is high at age 1 year and keeps increasing yearly by age 5 years, the patient is unlikely to outgrow his or her milk allergy within the next several years and may be considered a candidate for OIT.

In any circumstance, shared decision-making plays a key role in this process. Milk OIT is not a cure, but it does provide benefits, including fewer dietary restrictions and protection from unintentional exposures. Patients may also feel less anxious about the possibility of accidental exposures to milk-containing products and experience improved social interactions.[19–23] These benefits have to be balanced against the risks of undergoing milk OIT, which include the possibility of severe reactions and anaphylaxis. The patient's preferences, values, and individual circumstances will shape shared decision-making[24] and lead to the final decision with regard to undertaking milk OIT or choosing a different management option, such as dietary elimination of milk.

CLINICAL PEARLS

- OIT for milk allergy is effective, although not all individuals will achieve desensitization to the full dose (defined as an age-appropriate portion); there are risks associated with milk OIT that should be discussed in detail with patients and families as part of the shared decision-making process.

- There currently is no standardized approach for milk OIT, but multiple protocols have been published with variable results in terms of efficacy and risk. Shared decision-making is key when considering both participation in the intervention and choice of protocol.

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