

COCHRANE META-ANALYSIS IN ALLERGY

Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and meta-analysis

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Summary

Cow's milk is a common cause of food allergy in children. Children usually outgrow cow's milk allergy by the age of 3–5 years, but some will have persistent symptoms beyond childhood. We performed a systematic review of randomized controlled trials (RCTs) and observational studies to assess the evidence supporting the use of oral immunotherapy in IgE-mediated cow's milk allergy to inform the World Allergy Organization guidelines. Of 1034 screened articles published until May 2011, five RCTs and five observational studies fulfilled *a priori* specified inclusion criteria. RCTs including 218 patients showed that oral immunotherapy, compared to elimination diet alone, increased the likelihood of achieving full tolerance of cow's milk [relative risk: 10.0 (95% CI: 4.1–24.2)]. Adverse effects of immunotherapy include frequent local symptoms (16% of doses), mild laryngospasm [relative risk: 12.9 (1.7–98.6)], mild asthma [rate ratio: 3.8 (2.9–5.0)], reactions requiring oral glucocorticosteroids [relative risk: 11.3 (2.7–46.5)] or intramuscular epinephrine injection [rate ratio 5.8 (1.6–21.9)]. Results of observational studies were consistent with those of RCTs. Despite the availability of RCTs, the overall low quality of evidence leaves important uncertainty about anticipated effects of immunotherapy due to very serious imprecision of the estimates of effects and the likelihood of publication bias for some of the critical outcomes. A potentially large benefit of oral immunotherapy in patients with cow's milk allergy may be counterbalanced by frequent and sometimes serious adverse effects. Additional, larger RCTs measuring all patient-important outcomes are still needed.

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Introduction

Cow's milk allergy

The IgE-mediated food allergy affects 2–4.5% of children (with a prevalence of self reported food allergy of 9% [range: 2.5% to 38%]) [1]. Cow's milk is one of the most common causes of food allergy among children [2] with a self reported prevalence of 1.2% to 17% and the prevalence of IgE sensitization from 2% to 9% with ca. 0.6% (95% CI: 0.3–1.0) being sensitized and symptomatic [1].

Clinical manifestations of IgE-mediated cow's milk allergy (CMA) include urticaria, angioedema, rhinitis,

conjunctivitis, asthma, oral allergy syndrome, gastrointestinal symptoms and generalized anaphylaxis. IgE-mediated reactions are rapid in onset, typically beginning within minutes to 2 hours from the time of ingestion. Anaphylactic reactions to cow's milk can be severe and fatal cases have been described [3, 4]. In contrast, non-IgE-mediated food allergy usually presents as subacute or chronic symptoms that are generally limited to skin or the gastrointestinal tract.

Patients usually outgrow CMA throughout childhood and adolescence achieving tolerance that most frequently occurs around the age of 3–5 years. Studies investigating natural history of achieving tolerance to cow's milk in

children with CMA provide very inconsistent estimates. Earlier studies showed that 87% of children with non-IgE-mediated CMA achieve tolerance to cow's milk by the age of 3 years [5] and 78% of children with IgE-mediated and non-IgE-mediated CMA outgrow it by the age of 6 years [6]. However, more recent larger studies suggest that only 12–37% of children outgrow CMA before reaching school age and that IgE-mediated mechanism is a predictor of persistence of symptoms [7, 8].

The mechanisms by which CMA resolves are not well understood and involve not only specific IgE but also IgG₄ and IgA [9]. Spontaneous resolution of IgE-mediated CMA is less frequent than that of non-IgE-mediated allergy [5, 10, 11]. In most patients with CMA milk-specific IgE levels tend to fall over time being the best-known predictor of achieving the tolerance [9]. However, loss of milk-specific IgE is not a requirement for the resolution of CMA, since some patients become clinically tolerant even with persistently elevated IgE levels [12]. In general, the higher the level of cow's milk-specific IgE in serum at the time of diagnosis the longer is the duration of disease [12] and the less likely the child is to become tolerant over time [7]. Strict elimination of cow's milk proteins from diet is difficult, if at all possible. Hence, accidental ingestions of cow's milk are frequent, especially in processed foods, posing a high risk of severe allergic reactions in a proportion of milk allergic subjects [13].

Oral immunotherapy for CMA

Several observational studies suggested that oral immunotherapy is a promising treatment of CMA [14–17]. The approach generally follows the same principles as immunotherapy of other allergic disorders. Oral immunotherapy of CMA involves administering small, increasing doses of cow's milk during an induction phase followed by a maintenance phase with regular intake of a maximum tolerated amount of cow's milk. So far, no uniform protocol has been developed.

The mechanisms involved in oral immunotherapy of CMA are not understood. This uncertainty about the immunological mechanism is reflected in the discussions about the best nomenclature – oral desensitization, specific oral tolerance induction (SOTI) or oral immunotherapy.

The World Allergy Organization (WAO) has recently identified CMA as an area in which clinicians might benefit from evidence-based guidance. The Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines panel developed specific clinical recommendations about the diagnosis and management of IgE-mediated CMA [18, 19]. The guideline development process followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE)

approach that calls for a systematic review of current research evidence to inform guideline panel's decisions [20–22]. As the panel did not identify any comprehensive up-to-date systematic review of the diagnosis or treatment of CMA, we performed a systematic review of the studies of oral immunotherapy in the management of IgE-mediated CMA to inform the guidelines [23].

Methods

Criteria for considering studies

We developed a protocol for the guideline and systematic assessment of the literature and determined *a priori* to include randomized trials and observational studies with an independent control group that enrolled patients – children and adults – with CMA as defined by the study authors. The intervention of interest was the oral immunotherapy with cow's milk.

Types of outcome measures

Outcomes of interest for this review were specified *a priori* by the DRACMA guideline panel: symptoms of CMA (mild: erythema, urticaria, angioedema, pruritus, vomiting, diarrhoea, rhinitis, conjunctivitis; moderate: mild laryngeal oedema, mild asthma; severe: severe laryngeal oedema, severe asthma, anaphylaxis), duration of CMA, atopic eczema, quality of life of a patient and/or carers, allergic reaction to cow's milk protein during immunotherapy, and resource utilization (i.e. cost, hospital visits, availability of trained personnel, availability of resuscitation equipment, etc.) [19].

Search methods for identification of studies

We searched electronic bibliographical databases: MEDLINE, EMBASE, The Cochrane Library (including Cochrane Central Register of Controlled Trials/CENTRAL, Cochrane Database of Systematic Reviews (CDSR), DARE, and NHS EED) until May 2011. A professional librarian in collaboration with content, clinical and methodology experts developed specific search strategies without any methodology or language restrictions (Appendix S1). In addition, we reviewed the references of identified studies and of selected narrative review articles.

Data collection and analysis

We extracted data about methodological quality, participants, interventions and outcomes of interest using a standardized data collection form. Two reviewers independently examined titles and abstracts of all identified citations for exclusion criteria. Subsequently, two reviewers evaluated full text reports of all poten-

tially eligible studies for compliance with *a priori* specified eligibility criteria for considering studies for this review. Studies that did not fulfil the inclusion criteria were excluded and reasons for exclusion were recorded. Any disagreements were resolved by consensus. We corresponded with investigators of primary studies, where appropriate, to clarify study eligibility and to request further information about missing results.

We assessed the risk of bias using standard criteria suggested in the Cochrane Handbook for Systematic Reviews of Interventions [24] and assessed the overall quality of evidence using the GRADE system [25, 26]. We calculated relative risks and corresponding confidence intervals (CI) for the dichotomous outcome of achieving tolerance and rate ratios for count data about adverse effects that each participant could experience more than once [27]. We used Review Manager version 5.1 to conduct meta-analyses of relative risk and rate ratio [28], StatsDirect version 2.7.8 [29] to calculate incidence rate difference and GRADEpro version 3.6 to produce evidence profiles [30].

Results

Included studies

Our electronic searches identified 1034 distinct records (all study designs), of which we excluded 987 on the basis of title and abstract screening. We assessed the full text of the remaining 48 articles for eligibility (Fig. 1). We found six randomized trials [31–36] and five observational studies [16, 17, 37–39] that examined specific tolerance induction to cow's milk proteins in patients with CMA and compared oral immunotherapy with elimination diet alone; one study used soy formula as the control intervention [35]. We were not able to include one randomized trial in this review

since it was published only as a conference abstract and we have not been able to obtain additional information about the outcomes of interest from the authors [34].

Table 1 presents characteristics of the included randomized trials. Four trials [31, 32, 35, 36] included children aged 2–17 years in whom CMA was confirmed with a blinded placebo-controlled food challenge test. Longo and colleagues [31] used oral immunotherapy with whole milk for 40 weeks in children with a history of at least one severe allergic reaction and milk-specific IgE levels >85 kUA/L who were not able to tolerate more than 0.8 mL of milk during the challenge test. Martorell and colleagues [32] used oral immunotherapy with whole milk for 16 weeks in children with a history of immediate-type clinical manifestations after ingestion of cow's milk and a positive skin prick test (SPT) to milk or milk-specific IgE > 0.35 kU/L. Pajno and colleagues [35] used oral immunotherapy with whole milk in patients with clinical history of CMA and a positive SPT to milk or serum milk-specific IgE. Skripak and colleagues [36] used a preparation of dry, non-fat powdered milk for 6 months in children with a history of IgE-mediated milk allergy (no history of anaphylaxis requiring hospitalization, intubation, or severe asthma), a positive SPT result to milk extract or milk-specific IgE level greater than 0.35 kU/L who were not able to tolerate more than 75 mL of milk during the challenge test.

The fifth trial included children aged 1–7 years of whom 90% had atopic eczema and either a positive result of labial or oral food challenge test or a positive skin prick test or serum milk-specific IgE [33]. Because a diagnosis of CMA in the included children was uncertain (25% of children probably had a non-IgE mediated CMA and all included children were able to tolerate at least 60 mL of milk), we did not combine the results of this study with the results of the other four studies and we

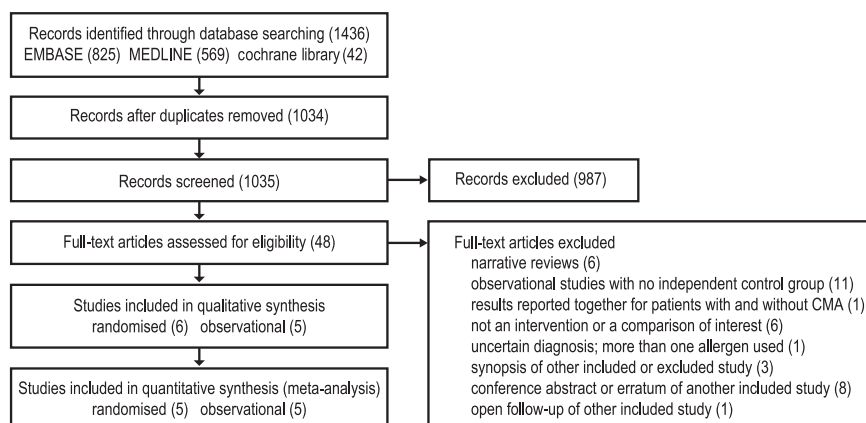


Fig. 1. Flow of information through the different stages of the systematic review (for details about the excluded studies see online appendix S2).

Table 1. Characteristics of the included randomized trials

	Longo 2008	Martorell 2011	Morisset 2007	Pajno 2010	Skripak 2008
Number of patients (SOTI/control)	30/30	30/30	28/32	15/15	13/7
Age*	8 years (5–17)	2 years (2–3)	2 years (1–7)	10 years (4–13)	10 years (6–16)
Inclusion criteria	• history of ≥ 1 severe allergic reaction • milk-specific IgE levels > 85 kUA/L[†] • not able to tolerate > 0.8 mL of milk	• immediate-type clinical manifestations in the first two hours after cow's milk ingestion • positive food challenge • positive SPT to milk or milk-specific IgE > 0.35 kU/L[†]	• positive SPT to milk or milk-specific IgE • positive labial or oral food challenge or complete recovery from symptoms after 3 weeks of avoidance of milk	• clinical history of CMA • positive SPT to milk or milk-specific IgE • positive food challenge	• history of IgE-mediated milk allergy • positive SPT to milk or milk-specific IgE > 0.35 kU/L[†] • not able to tolerate > 75 mL of milk
Exclusion criteria	• history of unreliable management of complications and treatments • limited availability of emergency facilities in the area where family lived • uncontrolled asthma	• history of anaphylactic shock • non-IgE-mediated or non-immunological adverse reactions to cow's milk • primary or secondary immune deficiency	• not able to tolerate 60 mL of milk	• positive clinical history or suspected adverse reactions to soy formula • positive SPT or serum specific IgE levels to soy	• history of anaphylaxis requiring hospitalization or intubation • severe asthma
Treatment	Oral immunotherapy with whole milk + elimination diet	Oral immunotherapy with whole milk + elimination diet	Oral immunotherapy with whole pasteurized milk + elimination diet	Oral immunotherapy with whole milk + elimination diet	Oral immunotherapy with dry nonfat powdered milk + elimination diet
Control	Elimination diet	Elimination diet	Elimination diet	Oral administration of soy formula + elimination diet	Placebo powder + elimination diet
SOTI duration[weeks]	~40	16	26	18	26

*Age is presented as mean and range, when information was available.

[†]Fluorescence enzyme immunoassay (FEIA).

did not consider its results when presenting the results for decision making (Fig. 5).

Five small observational studies including altogether 83 patients (Table 2) used oral milk immunotherapy in children aged 3 months to 15 years with CMA confirmed by a blinded placebo-controlled food challenge test [16, 17, 37, 39]. In one study, available only as a conference abstract, confirmation of diagnosis was not specified [38].

Quality of evidence from the included studies

Tables 3 and 4 present our assessment of the risk of bias in five randomized trials and five observational studies included in the review. Because of the small number of available studies we did not use funnel plots or other statistical methods for detecting publication bias. However, we believe that publication bias is very likely because there are only few small studies showing large effects on beneficial outcomes and inconsistently reporting adverse effects.

Effects of interventions

No study measured resource utilization or the quality of life of children and their parents.

Benefits. Four randomized trials showed that the probability of achieving a full tolerance of cow's milk (i.e. being able to tolerate at least 150 mL of milk and eat dairy and milk-containing products) was 10 times higher (95% CI: 4.1–24.2) in children receiving immunotherapy compared to elimination diet alone (Fig. 2) [31, 32, 35, 36]. The probability of achieving partial tolerance (i.e. being able to tolerate at least 5 but less than 150 mL of milk) was also higher with immunotherapy (relative benefit: 5.3; 95% CI: 1.2–24.5; Fig. 3). These effects were similar in the five observational studies (the relative benefit of achieving tolerance was 4.0; 95% CI: 2.1–7.5; Fig. 4) [16, 17, 37–39].

A randomized trial in children with atopic eczema who initially were able to tolerate up to 60 mL of milk showed a relative benefit of achieving full tolerance (>200 mL of milk) of 1.44; 95% CI: 0.98–2.11 (Fig. 2) [33].

Downsides

Local reactions. Local symptoms were the most frequent adverse effects of immunotherapy that occurred during the administration of 16% of doses. Lip and/or mouth pruritus was the most frequent adverse effect occurring almost exclusively in children receiving immunotherapy (relative risk: 34.4; 95% CI: 4.8–244.7 [studies [31, 32], 120 patients]) with most events pre-

Table 2. Characteristics of the included observational studies

	Patriarca 1998	Patriarca 2002	Patriarca 2007	Reche 2011	Rodriguez-Alvarez 2009
Number of patients (SOTI/control)	6/5	4/4	15/5	10/10	14/10
Age*	8 years (4–14)	10 years (5–15)	8 years (4–15)	3 months	>4 years
Inclusion criteria	• history of food allergy • positive SPT with cow's milk (>3 mm) • positive oral food challenge with cow's milk	• history of allergy to cow's milk	• history of allergy to cow's milk • positive SPT to milk or milk-specific IgE or oral food challenge	• cow's milk allergy†	• cow's milk allergy confirmed by oral food challenge
Exclusion criteria	Not reported	Not reported	Not reported	Not reported	Not reported
Treatment	Oral immunotherapy with whole milk + elimination diet	Oral immunotherapy with whole milk + elimination diet	Oral immunotherapy with whole milk + elimination diet	Oral immunotherapy + elimination diet	Oral immunotherapy + elimination diet
Control	Elimination diet	Elimination diet	Elimination diet	Elimination diet	Elimination diet
Study duration [months]	12	18	18	12	12

*Age is presented as mean and range, when information was available.

†Cow's milk allergy not further specified (conference abstract only).

Table 3. Summary of the methodological quality of the included randomized controlled trials – review authors' judgements about the risk of bias based on the Cochrane Collaboration risk of bias tool [44]

	Longo 2008	Martorell 2011	Morisset 2007	Pajno 2010	Skripak 2008
Adequate sequence generation	Yes	Yes	Yes	Yes	Yes
Allocation concealment	Yes	Yes	Unclear	Yes	Unclear
Incomplete outcome data addressed	Unclear	Yes	Unclear	Yes	Yes
Free of selective reporting	Yes	Yes	No	Yes	Yes
Blinding					
Patients/parents	No	No	Unclear	Yes	Yes
Personnel	No	No	Unclear	Yes	Yes
Outcome assessors	Yes	No	Unclear	Yes	Unclear
Data collectors	No	Yes	Unclear	Yes	Unclear
Data analysts	No	Yes	Unclear	Yes	Unclear
Other threats to validity	No	No	No	No	No

senting during the initial phase of rapid increase of milk dosage. Risk of perioral urticaria was also higher in the immunotherapy groups (relative risk: 8.2; 95% CI: 1.2–55.0 [two studies [31, 32], 120 patients]). Two studies reported the rate of perioral urticaria events during immunotherapy that were more frequent in the immunotherapy groups (rate ratio: 9.9; 95% CI: 4.3–22.9)[31, 36].

Mild generalized reactions. Generalized adverse reactions also occurred more often in children receiving immunotherapy. Relative risk of generalized erythema or urticaria with oral immunotherapy was 12.1 (95% CI: 3.0–49.1) based on three studies [31, 32, 35] including 147 patients. Two studies reported the rate of generalized erythema or urticaria events during immunotherapy (rate ratio: 16.9; 95% CI: 4.5–63.3) [31, 36]. Risk of gastrointestinal symptoms (abdominal pain, vomiting, diarrhoea) was also higher with active treatment (relative risk: 16.6, 95% CI: 4.1–66.9 [three studies [31, 32, 35], 150 patients]). Gastrointestinal symptoms were also more frequent in the immunotherapy groups (rate ratio: 25.8; 95% CI: 5.9–113.9) [31, 36]. Pooled

Table 4. Methodological quality summary: review authors' judgements about the risk of bias in the included observational studies (based on the Newcastle-Ottawa quality assessment scale [45])

	Patriarca 1998	Patriarca 2002	Patriarca 2007	Roche 2011	Rodriguez-Alvarez 2009
Selection					
Representativeness of the exposed cohort	Probably yes*	Unclear†	Probably yes*	Unclear‡	Unclear‡
Selection of the non-exposed cohort	Same community§	Same community§	Same community§	Same community§	Same community§
Ascertainment of exposure	Yes	Yes	Yes	Unclear‡	Yes
Demonstration that outcome of interest was not present at start of study	Yes	Yes	Yes	Unclear‡	Yes
Comparability					
Comparability of cohorts on the basis of the design or analysis	No adjustment¶	No adjustment	No adjustment	Unclear‡	Unclear‡
Outcome					
Assessment of outcome	Likely adequate**	Likely adequate**	Adequate††	Unclear††	Unclear‡
Was follow-up long enough for outcomes to occur	Yes	Yes	Yes	Yes	Yes
Adequacy of follow-up of cohorts	No‡‡	Yes	Yes§§	Unclear‡	Unclear‡

*Consecutive children suffering from food allergy.

†No description of the derivation of the cohort.

‡Limited information based on the conference abstract only.

§Drawn from the same community as the exposed cohort.

¶Study reported that patients were randomly assigned to groups, however, some patients were arbitrarily assigned to particular groups.

**Independent blind assessment and self report for some patients.

††Blinded food challenge test.

‡‡Two of six treated patients dropped out from the study.

§§Three of 18 patients discontinued treatment.

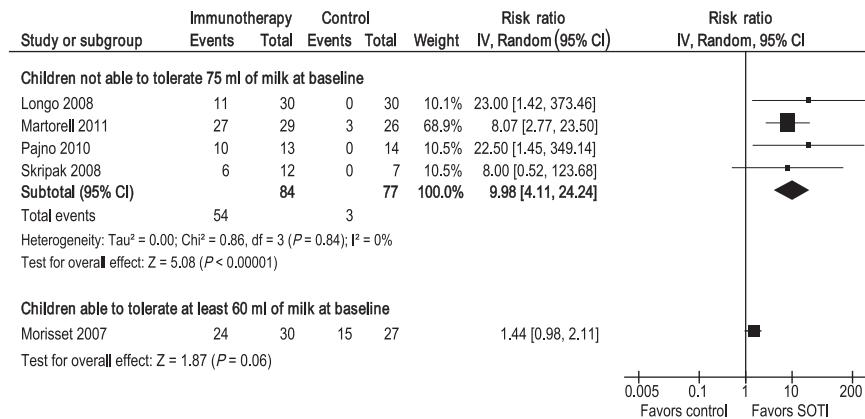


Fig. 2. Randomized controlled trials showing the probability of achieving full tolerance of cow's milk (i.e. being able to tolerate ≥ 150 mL of milk during a challenge and/or drink milk and eat dairy products with no problems) with oral immunotherapy, compared to placebo or elimination diet, in patients with CMA.

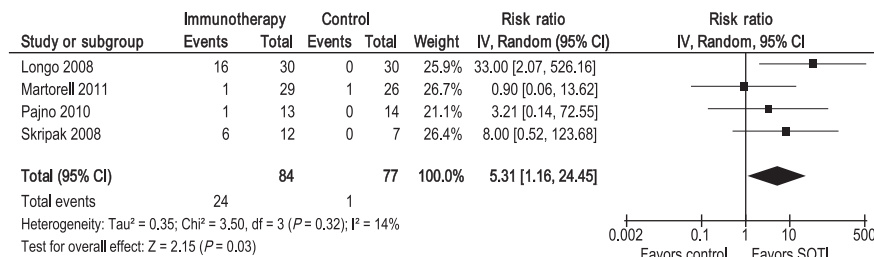


Fig. 3. Randomized controlled trials showing the probability of achieving partial tolerance of cow's milk (i.e. being able to tolerate 5–150 mL of milk during a challenge) with oral immunotherapy, compared to placebo or elimination diet, in patients with CMA.

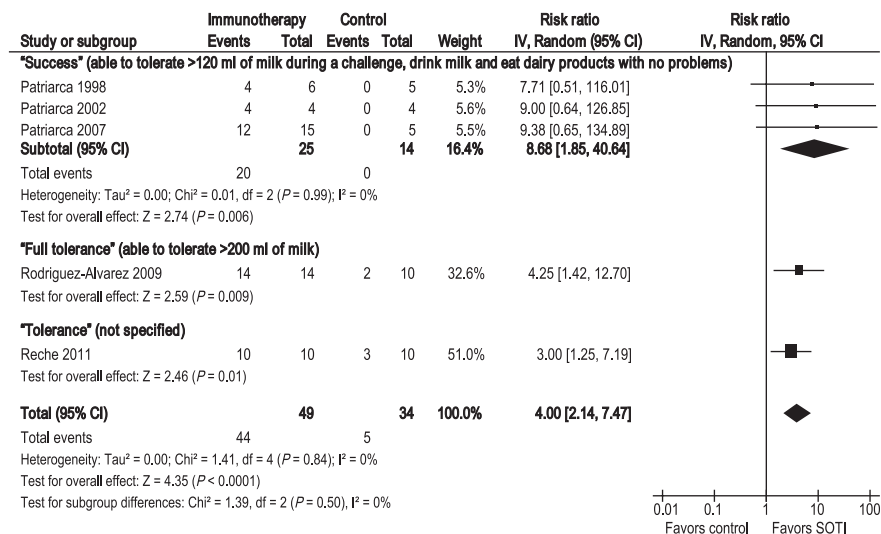


Fig. 4. Observational studies showing the probability of achieving tolerance of cow's milk with oral immunotherapy, compared to placebo or elimination diet alone, in patients with CMA. Tolerance was defined variably in those studies as ability to tolerate >120 mL of milk during a challenge and/or drink milk and eat dairy products with no problems, ability to tolerate more than 200 mL of milk; definition of tolerance in one study was not available (conference abstract only).

relative risk of rhinoconjunctivitis with oral immunotherapy, compared to elimination diet alone was 15.9 (95% CI: 4.0–63.8) in three studies including 150 patients [31, 32, 35]. One study (60 patients) also

reported the rate of rhinitis and/or conjunctivitis that were 15 times more frequent with oral immunotherapy (rate ratio: 15.5, 95% CI: 3.7–64.8)[31]. Risk of mild laryngospasm was higher in the oral immunotherapy

groups (relative risk: 12.9, 95% CI: 1.7–98.6 [two studies [31, 32], 120 patients]). Longo and colleagues also reported higher frequency of mild laryngospasm in those patients (rate ratio: 40.9; 95% CI: 2.5–673.7) [31]. Risk of mild bronchospasm was also higher with active treatment (relative risk: 10.0 (95% CI: 2.4–41.4 [3 studies [31, 32, 35], 150 patients])). Two studies also reported higher frequency of bronchospasm in immunotherapy groups (rate ratio: 47.0; 95% CI: 6.5–340.2) [31, 36].

Severe generalized reactions. One small study in which 17 of 20 patients had a history of asthma reported higher rate of asthma exacerbations with oral immunotherapy (rate ratio: 3.8; 95% CI: 2.9–5.0) [36]. Three studies reported increased need for oral glucocorticosteroids (relative risk: 11.3, 95% CI: 2.7–46.5; Fig. 5) [31, 32, 35] and four studies reported higher rate of the need for administration of intramuscular epinephrine (rate ratio: 5.8, 95% CI: 1.6–21.9; Fig. 5) [31, 32, 35, 36].

Discussion

We conducted a systematic review and meta-analysis of randomized controlled trials and observational studies investigating the effects of oral immunotherapy in patients with cow's milk allergy. The available studies suggest that in children with CMA oral immunotherapy increases the probability of achieving tolerance of cow's milk compared to elimination diet alone. However, this effect is very uncertain due to the low confidence in the estimated effects (quality of the supporting evidence). Local adverse effects as well as systemic, potentially serious reactions during the course of oral immunotherapy are common.

Strengths and limitations

Our very broad search criteria make it unlikely that we missed any relevant information and our findings probably represent the current best evidence about the use of oral immunotherapy with cow's milk for IgE-mediated CMA. Although Fisher and colleagues have recently performed a systematic review of randomized trials of SOTI in a broad population of children with any food allergy [40] they reported the effect of SOTI on all food allergies combined. They found three randomized trials of which two enrolled patients with CMA and were included in our analysis [31, 36]. The third trial included in that review, enrolled patients with CMA or hen's egg allergy [41] and reported the results for all patients together precluding inferences about the effect in patients with CMA alone. Hence, it was excluded from our analyses. We also included two additional more recently published studies [32, 35]. Fisher and colleagues focused only on one outcome of

achieving tolerance and did not examine the findings of the observational studies. We investigated and report the effect of oral immunotherapy on all *a priori* specified patient-important outcomes required for decision-making, including adverse effects. We also explored the likelihood of achieving different degrees of tolerance that provides information useful in clinical practice – full tolerance (being able to tolerate at least 150 mL of milk and/or drink milk and eat dairy products permitting a virtually unrestricted diet) or a partial tolerance (being able to tolerate 5–150 mL of milk).

The exact reactions during the initial challenge tests as well as the history of the most severe prior reaction have not been consistently reported in the studies. Hence, at least for some studies, it is difficult to make judgements about the underlying severity of CMA and representativeness of the included population. It is possible, at least theoretically, that the children included in the studies represented some subgroup of patients with CMA more likely to benefit from oral immunotherapy. However, at least one study [32] reported enrolling consecutive patients seen the allergy clinics participating in the study and the results of that study were consistent with the results of other studies. This makes it more likely that the observed effects do apply to most children in IgE-mediated CMA irrespective of the severity of prior reactions. The purpose of this systematic review was to inform decision about using or not using immunotherapy in patients with CMA. Since it has not yet been established whether “tolerance” – as defined by lack of symptoms when eating a relevant amount of cow's milk or milk products – represents true immunological tolerance with a long-lasting effect or a temporary desensitization (tachyphylaxis). Therefore, achieving tolerance, as defined in this review, seems not to depend on the severity of clinical symptoms at presentation.

The evidence supporting the use of oral immunotherapy in CMA, however, is of low quality (i.e. our confidence in the estimated effects is low) because of a high likelihood of publication bias and a serious imprecision of the estimates of effects (Fig. 5). Although the presence or absence of publication bias generally cannot be proven, especially when only few studies are available, we believe it is highly probable that some studies showing less extreme effects remained unpublished and thus the observed benefit of immunotherapy in patients with CMA may have been systematically overestimated. Low quality of available evidence allows setting priorities for further research.

It is possible that the observed very large effects of immunotherapy on achieving tolerance of cow's milk were actually due to chance. Although, in theory, a CI around the pooled estimate that excludes no effect should capture this imprecision, the very small number of events in the studies makes the results very fragile.

Oral immunotherapy with cow's milk compared to elimination diet alone in children with IgE-mediated cow's milk allergy**Patient or population:** patients with IgE-mediated cow's milk allergy**Settings:** specialist pediatric allergy units**Intervention:** oral immunotherapy with cow's milk**Comparison:** elimination diet alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Elimination diet alone	Corresponding risk Oral immunotherapy with cow's milk				
Full tolerance of cow's milk (able to drink >150 ml of milk) Follow-up: 6 to 12 months	4 per 100	39 per 100 (16 to 94)	RR 9.98 (4.11 to 24.24) ¹	161 (4 studies)	⊕⊕○○ low ^{2,3,4,5,6}	Those patients would be able to drink milk and eat dairy products.
Partial tolerance of cow's milk (able to drink 5 to 150 ml of milk) Follow-up: 6 to 12 months	1 per 100	7 per 100 (2 to 32)	RR 5.31 (1.16 to 24.45)	161 (4 studies)	⊕⊕○○ low ^{2,3,5,7}	Those patients would not achieve full tolerance, but would have no symptoms when accidentally ingesting small amount of milk or dairy products.
Anaphylaxis (rate of epinephrine injections) Follow-up: 6 to 12 months	The mean rate of adrenaline injections in the control groups was 0 per 100 patients per year ⁸	The mean rate of adrenaline injections in immunotherapy groups would be 23 per 100 patients per year (5 to 40) ⁸	Rate ratio 5.82 (1.55 to 21.86)	170 (4 studies)	⊕⊕○○ low ^{5,9,10,11}	
Need for systemic glucocorticosteroids Follow-up: 6 to 12 months	1 per 100	15 per 100 (4 to 62)	RR 11.29 (2.74 to 46.47)	150 (3 studies)	⊕⊕○○ low ^{5,9,12,13}	
Quality of life of children not measured	See comment	See comment	Not estimable	—	See comment	Quality of life was not measured in any of the experimental and observational studies.
Quality of life of caregivers not measured	See comment	See comment	Not estimable	—	See comment	Quality of life was not measured in any of the experimental and observational studies.
Exacerbation of eczema Follow-up: 6 months	14 per 100	8 per 100 (1 to 100)	RR 0.54 (0.04 to 7.36)	20 (1 study) ¹⁴	⊕○○○ very low ^{5,15,16}	There were only 2 events reported in one very small study. Other studies did not report this outcome.

*The basis for the **assumed risk** was the incidence of an outcome in the control groups of the included studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Relative risk

GRADE working group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Three studies (Martorell 2011, Pajno 2010 and Skripak 2008) also measured ability to tolerate >200 ml of milk during a food challenge and/or drink milk and eat dairy products with no problems. The relative effect of this outcome was RR: 8.7 (95% CI: 3.4 to 22.3).

² Two studies did not blind patients and personnel, however it is unlikely to have affected this outcome since tolerance was assessed in a blinded food challenge.

³ There is some uncertainty if the single challenge with milk reflects long term tolerance.

⁴ There were only 57 events, despite the confidence interval suggesting a precise estimate.

⁵ There are only 4 small studies showing very large effect on beneficial outcomes.

⁶ The large effect was observed, however, we did not upgrade the quality of evidence due to the serious limitations of the body of evidence.

⁷ There were only 25 events and the pooled confidence interval does not exclude a large benefit or no effect.

⁸ There were no events in control groups; 95% CI around the absolute difference in rates was estimated using incidence rate difference meta-analysis. There was statistical heterogeneity in the absolute results of individual studies ($I^2 = 69\%$) but we did not downgrade the quality of evidence for this outcome since the 95% CI around I^2 was very wide (0% to 87%) and the confidence intervals of individual studies overlapped.

⁹ Two studies were not blinded. There is some uncertainty to what extent this might have influenced the results, especially reporting of adverse effects. However, we did not downgrade the quality of evidence for this outcome because of increased risk of bias, since we already downgraded it for imprecision and likelihood of publication bias.

¹⁰ There is some uncertainty to what extent epinephrine injections reflect severe anaphylactic reaction.

¹¹ There were only 13 events.

¹² There is some uncertainty to what extent short-term administration of systemic glucocorticosteroids relates to adverse effects important for patients. However, it likely reflects the severity of adverse effect for treatment of which they were used.

¹³ There were only 25 events.

¹⁴ One more study (Martorell 2011) reported no exacerbations of eczema, but it enrolled only 3 patients with atopic eczema (out of 60 in the trial).

¹⁵ Only one study enrolling patients with atopic eczema reported exacerbations. No study reported any other measure of the severity of eczema.

¹⁶ Only 2 events; results do not exclude an appreciable benefit or appreciable harm.

¹⁷ Only 20 patients.

Fig. 5. Summary of findings table for a question: Should oral immunotherapy be used in children with IgE-mediated cow's milk allergy? Table includes all outcomes deemed to be critical for making decision about using oral immunotherapy [19].

The concept of fragility of results relates to the observation that a small shift in the number of events between the immunotherapy and control groups would change the statistical significance of the results [42]. For instance, only one additional child achieving partial tolerance in the control group of one of the four randomized trials would make the statistical significance of the pooled effect on partial tolerance disappear.

Clinical implications

Figure 5 summarizes the findings for all outcomes deemed to be critical for making a decision about using oral immunotherapy for in children with IgE-mediated cow's milk allergy. Given the overall low quality of the evidence and very imprecise estimates of the benefits and downsides, the true effect of oral immunotherapy in patients with CMA remains uncertain. Consequently, those patients and clinicians who place a relatively high value on avoiding possibly serious adverse effects during oral immunotherapy may choose to continue the elimination diet and re-evaluate the possibility of oral immunotherapy when more robust and precise data are available. On the other hand, those who place a relatively high value on achieving tolerance (being able to drink milk and eat dairy products or at least to loosen the tight elimination diet) and a relatively low value on avoiding possibly serious adverse effects of the treatment may choose to undergo immunotherapy with milk. Clinicians and patients would also need to consider the need for a long-term compliance and significant commitment of the child's family, the need for round-the-clock availability of medical emergency support, and resources needed to immediately treat adverse effects during immunotherapy. Although severe reactions happen rarely, once they develop they pose a serious problem, since they may occur at home. The DRACMA guideline panel recommended that clinicians do not

administer oral immunotherapy with cow's milk in patients with IgE-mediated CMA, unless this is done in the context of formal clinical research [19].

Research implications

The immunological mechanism of immunotherapy for CMA is not known. It still has to be established whether a true tolerance with a long-lasting effect or a temporary desensitization is achieved. There is also a need for rigorously designed and executed randomized trials of immunotherapy in children and adults with CMA that measure and properly report [43] patient-important outcomes, including quality of life of children and their parents and adverse effects.

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Authors Contributions

JLB and HJS developed an outline of this article based on numerous discussions with all co-authors. JLB wrote the first draft and all co-authors critically revised it. All authors read and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Electronic search strategies.

Appendix S2. Characteristics and references of excluded studies.

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