Safety and Efficacy Profile and Immunological Changes Associated With Oral Immunotherapy for IgE-Mediated Cow's Milk Allergy in Children: Systematic Review and Meta-analysis

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Abstract

Background: Cow's milk allergy (CMA), one of the main types of childhood allergy, considerably impairs patient quality of life. Allergen avoidance is difficult, and mistakes are common. Therefore, new treatment strategies such as oral immunotherapy (OIT) have been sought for patients with CMA. Our objective was to review current evidence on immunological changes, efficacy, and safety when using OIT as an alternative to an avoidance diet in the treatment of children with IgE-mediated CMA.
Methods: We performed a systematic review and subsequent meta-analysis of all randomized controlled studies published to date in which OIT is used to treat CMA in children. We evaluated immunological effects, acquisition of desensitization, and adverse events. Immunological changes were examined by means of a meta-analysis of individual patient data.
Results: Desensitization using OIT to cow's milk is 10.2 times more likely than in non–OIT-treated patients. The decrease in cow's milk–specific IgE levels was found to differ by 8.1 kU_A/L between OIT-treated patients and those on an avoidance diet. This difference was not statistically significant (P=.318). Although side effects are common, they usually involve mild reactions that are easy to manage without parenteral epinephrine.
Conclusion: OIT can be considered safe and effective (in terms of acquiring desensitization) and reasonably safe (mild-to-moderate adverse events, little need for parenteral epinephrine) in patients with CMA. Although OIT leads to changes in cow's milk–specific IgE levels, the differences between OIT-treated and non–OIT-treated patients are not significant. More studies are needed to evaluate other immunological changes that may occur, such as the increase in IgG4 levels.

Key words: Avoidance diet. Children. Cow's milk allergy. Food allergy. Meta-analysis. Oral desensitization. Oral immunotherapy. Systematic review.

Resumen

Antecedentes: La alergia a la leche de vaca (LV) es una de las principales causas de alergia en la infancia, que altera la calidad de vida de los pacientes y su familia. La evitación del alérgeno es difícil y pueden producirse reacciones adversas graves por ingesta accidental. Esto ha impulsado a la investigación de nuevas estrategias terapéuticas como es la inmunoterapia oral (ITO) para la alergia a LV.
Objetivo: Determinar la evidencia actual acerca de los cambios inmunológicos, la eficacia y seguridad de la ITO como alternativa a la dieta de exclusión en el tratamiento del niño con alergia IgE-mediada a LV.
Métodos: Revisión sistemática y posterior meta-análisis de todos los estudios controlados aleatorizados publicados hasta el momento actual en los que se emplea la ITO para el tratamiento de la alergia a la LV en niños, evaluando los cambios inmunológicos, la adquisición

de desensibilización y los efectos adversos. Los cambios inmunológicos se evaluaron realizando un meta-análisis de los datos individuales de cada paciente.
Resultados: La adquisición de desensibilización empleando la ITO con LV es 10.2 veces más frecuente que en los pacientes no tratados. Se observa una diferencia en el descenso de los niveles de IgE específica frente a LV en los pacientes tratados con ITO y los que llevan a cabo una dieta de evitación de 8.1, que no es estadísticamente significativa (p=0.318). Aunque los efectos secundarios son frecuentes, se trata en la mayoría de las ocasiones de reacciones leves de fácil manejo que no requieren el uso de adrenalina parenteral.
Conclusión: Existe evidencia suficiente para poder considerar que la ITO es efectiva (en términos de adquisición de desensibilización) y razonablemente segura (efectos adversos leves-moderados, con escasos requerimientos de adrenalina parenteral) para el tratamiento de la alergia a LV. Produce modificaciones inmunológicas en cuanto a los niveles de IgE específica frente a LV, sin embargo, las diferencias no resultan significativas a corto plazo. Hacen falta más estudios para valorar otras cambios inmunológicos que pueden producirse, como es el incremento de los niveles de IgG4.

Palabras clave: Dieta de evitación. Niños. Alergia a la leche de vaca. Alergia alimentaria. Meta-análisis. Desensibilización oral. Inmunoterapia oral. Revisión sistemática.

1. Introduction

Food allergy is defined as an adverse event resulting from a specific immune response that is reproducible under the same conditions of exposure to a food [1]. The prevalence of food allergy is increasing, and the disease currently affects 2-3% of adults and 6% of children [2]. Cow's milk protein (CMP) is a major cause of food allergy in children and is often the first allergy to manifest [3]. Food allergy has traditionally been treated by avoiding the offending food, although this approach poses great difficulty in the case of CMP allergy, because milk is one of the staple foods in early childhood and is also present in many prepared foods.

The problems arising from avoidance diets are diverse and common. They include dietary obsession and fear on the part of parents and other caregivers of accidental ingestion, leading to a state of anxiety and stress that affects the quality of life of both patients and their families [4]. Food allergies can also have social consequences and cause nutritional and financial problems. Consequently, alternative treatments (eg, subcutaneous immunotherapy [5], anti-IgE antibody [6], oral immunotherapy (OIT) or oral desensitization [7], and sublingual immunotherapy [8]) are aimed at shortening the time to reach tolerance or increasing the threshold dose needed to produce the reaction and thereby reduce the risk of severe reactions due to accidental exposure. OIT involves progressive introduction of increasing amounts of the food allergen so that the patient develops tolerance [9]. The concept of desensitization is not new. The first successful case was published in 1908 [10]. Although evidence is limited, recent publications show that OIT is a feasible intervention [11-18]. However, the safety and efficacy of this approach must be confirmed before it can be added to recommendations on the management of this condition [19]. It is also necessary to study in depth the immunological mechanisms that support this tolerance.

The main objectives of this meta-analysis are to review published data from clinical trials conducted with OIT to treat cow's milk allergy, assess whether there is evidence that it is an effective and reasonably safe option in routine clinical practice, and to analyze the evidence on the immunological changes resulting from this procedure.

2. Methods

We designed a protocol to guide us in selecting studies that met specific inclusion criteria and established a series of inclusion and exclusion criteria. Only randomized controlled trials were included. The study population comprised children aged 0-18 years with IgE-mediated cow's milk allergy (CMA) confirmed by immediate clinical reaction and specific IgE to CMP. We divided patients into 2 groups: a control group, which was treated with an avoidance diet, and an active group, in which children received OIT. Patients with non IgE-mediated adverse reactions to CMP were excluded. Findings for both groups were compared in terms of tolerance to CMP and immunological outcomes.

2.1 Outcome Measures

Desensitization is defined as a change in the threshold dose of ingested food allergen necessary to cause allergic symptoms; this dose is dependent on ongoing antigen exposure. Tolerance is the induction of long-term immunologic changes associated with the ability to ingest a food without symptoms and without ongoing therapy [20,21].

We established 3 outcome measures: complete or partial tolerance acquired after desensitization; onset of symptoms during the course of OIT (with recording of the frequency of adverse effects and their severity in terms of the need for epinephrine); and variation in immunological parameters, namely, differences between specific IgE levels at baseline and after completion of OIT.

2.2. Search Methods

2.2.1 Electronic Search

We performed a systematic search with no language restrictions of the following bibliographic databases (November 2013): Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, MEDLINE via PubMed, EMBASE, and metaRegister of Controlled Trials (mRCT).

A search was conducted including the following terms:
Ovid MEDLINE (1950 to November 2013)

1. milk.mp.
2. immune tolerance/

3. immunotherapy/
4. desensitization, immunologic/
5. Remission Induction/
6. desensiti*.tw.
7. immunotherapy.tw.
8. (oral adj3 (toleran* or induc*)).tw.
9. or/2-8
10. 1 and 9

2.2.2 Manual Search

We performed a manual search of conference proceedings and review articles published during 2007-2013 in the following allergy journals: Journal of Investigational Allergology and Clinical Immunology, Journal of Allergy and Clinical Immunology, Allergy, and Allergologia et Immunopathologia.

2.2.3 Other Searches

We reviewed the reference lists of the articles included to identify potentially relevant citations. We contacted authors who conducted relevant studies of food allergy in order ascertain whether they knew of any additional unpublished articles that could provide useful information for our meta-analysis.

2.3 Data Collection and Analysis

Following our initial protocol, we extracted a dataset from each of the selected items and analyzed it. Data were extracted based on methodological quality, participants, inclusion and exclusion criteria, objectives, and the tools used and results obtained in the different studies (complete and partial tolerance acquired by patients after OIT, adverse effects during OIT and the need for epinephrine, and specific IgE levels at baseline and after treatment). The authors of the articles were contacted to provide data not explicit in their work that were required to meet the objectives of our individual patient data meta-analysis.

One reviewer systematically examined the titles and abstracts of the different publications and excluded those that did not meet the inclusion criteria. The full texts were then assessed, and a new selection was made according to the inclusion criteria. Three reviewers independently assessed the selected studies. Supplementary information was obtained from the authors of 4 of the 6 studies included [3,22-24] to provide information not explicit in the articles. In order to ensure the quality of the studies included, we assessed the risk of bias based on the criteria established by the Cochrane Handbook for Systematic Reviews of Interventions.

2.3.1 Statistical analysis

A random effect model was used to calculate heterogeneity for milk tolerance. We assessed heterogeneity between trials using the I^2 statistic: >50% represented substantial heterogeneity and >75% represented considerable heterogeneity. An individual patient data (IPD) meta-analysis was conducted to assess the change in IgE levels (initial minus final); IPD is considered the gold standard for synthesis. Most IPD analyses were performed in 2 stages, thus reducing the IPD of each study to aggregated data. Standard meta-analysis methods are used. An alternative method, the 1-step approach, combines all individual patient data in a regression model stratified by study; mixed regression models are used to incorporate random effects due to heterogeneity. Potential publication bias was assessed by visual inspection of a contour-enhanced funnel plot. Stata Statistical Software, Release 11 (StataCorp LP) was used for all analyses.

3. Results

3.1 Studies Included

The electronic search process yielded 278 articles, of which 256 were excluded based on the title or abstract. For the remaining 22, we obtained the complete article. The manual search yielded 13 articles. After applying the inclusion and exclusion criteria, we selected 6 studies [3,22-26] for inclusion in our study.

The characteristics of the studies included are summarized in Table 1.

The 6 studies were randomized controlled trials conducted between 2007 and 2012 in which the main objective was to assess the efficacy of OIT with cow's milk in patients with allergy to CMP. The diagnosis of allergy was confirmed by onset of symptoms after ingesting cow's milk and the presence of IgE antibodies specific to cow's milk. IgE-mediated allergy was confirmed by double-blind placebo-controlled food challenge in 4 of the studies [3,22,23,25], and by simple-blind placebo-controlled food challenge in the study of Morisset et al [26]. In the study of Salmivesi et al [24], the diagnosis was based on a challenge test with a positive result to cow's milk or accidental exposure with a severe systemic reaction. The efficacy of desensitization was evaluated by identifying the maximum tolerated dose of milk in the individual studies, as follows: 200 mL [3,23,24,26]; 150 mL [22]; and 500 mg [25]. Three of the articles included 60 patients [3,22,26], 1 included 30 [23], 1 included 20 [25], and 1 included 28 [24]. The population studied consisted of predominantly boys aged 1 to 17 years (except in the study of Salmivesi et al). The youngest patients (1-3 years) were analyzed in the study by Martorell et al [3]. The most recent clinical trial was that of Salmivesi et al, which was published in September 2012.

All the studies [3,22-26] included an assessment of the immunological variations that occurred after OIT (differences in specific serum IgE levels before and after treatment in the 2 groups of patients). In 5 studies [3,22-25] (all except that of Morisset et al [26]) the safety of OIT with cow's milk was assessed in terms of adverse reactions exhibited by patients during the treatment period. Patients who acquired partial tolerance were assessed in 3 studies: 20-200 mL [3], between 5 and 150 mL [22], and <200 mL [24].

3.2 Quality of Evidence of the Studies Included

Table 2 presents the assessment of risk of bias based on the criteria established by the Cochrane Handbook of Systematic Review of Interventions of the 6 clinical trials included in our study. There was no appreciable publication bias (Figure 1).

Table 1. Characteristics of the Studies Included

	Morisset et al [26]	Longo et al [22]	Skripak et al [25]	Pajno et al [23]	Martorell et al [3]	Salmivesi et al [24]
Year of publication	2007	2008	2008	2010	2011	2012
Number of patients	60	60	20	30	60	28
Age range (years)	1.1-6.5	5-17	6-17	4-10	2-3	6-14
Male/Female	39/21	39/21	12/8	17/13	34/26	12/16
Inclusion criteria	- Skin prick test to CM positive - Presence of specific IgE levels to CM - Positive labial or oral food challenge - Complete recovery from symptoms after 3 weeks of avoidance of CM	- History of severe allergic reactions after accidental exposure to milk - Milk-specific IgE levels >85 kU_A/L - DBPCFC positive to the lowest doses (≤0.8 mL of whole milk)	- Skin prick test to CM positive - CM-specific IgE levels >0.35 kU_A/L - DBPCFC positive to dose ≤2.5g of milk protein	- Clinical history - CM-specific IgE and skin testing to CM-positive - DBPCFC positive	- Immediate-type clinical symptoms - Skin test to CM readings ≥3 mm - sIgE levels to CM >0.35 kU_A/L - Persistence of CMP allergy in the 4 weeks before induction was tolerated - DBPCFC positive to cow's milk - Written informed consent from the parents	- Skin prick test to CM extract positive (> 3 mm) - CM protein specific IgE >3.5 kU_A/L - Challenge test with CM-positive or accidental exposure with a severe systemic reaction
Exclusion criteria	- Patients who react with ≤60 mL of milk	- Unreliable treatment and management of complications - Limited access to emergency facilities in the area where they lived - Poorly controlled asthma	- Anaphylaxis requiring hospitalization - History of intubation related to asthma - Current diagnosis of severe persistent asthma	- Sensitization to other foods	- Anaphylactic shock after ingestion of CM - Non–IgE-mediated adverse reactions to CM - Malignant or immunopathological diseases and/or immunodeficiencies - Therapy with immunosuppressors or β-blockers - Diseases contraindicating the use of epinephrine	Not available.
Groups of treatment	Group OD - Treatment (30)	Group A - SOTI (30)	Active treatment with OIT (13)	Active - OIT with CM (15)	Active - OD (30)	Active group - OIT (18)
(n)	Group A - Avoidance (30)	Group B - Milk-free diet (30)	Placebo (7)	Control - soy milk (15)	Control - milk-free diet (30)	Placebo group (10)
Dropouts	3	0	1	3	5	4
Maximum tolerated dose	200 mL	150 mL	500 mg	200 mL	200 mL	200 mL
SOTI duration, weeks	26	52	23	18	16	23
Main outcome	Rate of recovery induced by OD, compared to the natural course after avoidance over a 6-month period	Efficacy of SOTI for children with severe CMP-induced systemic reactions	Efficacy of OIT in desensitizing children with CMA	Patient-friendly desensitization regimen with weekly up-dosing and evaluation in a randomized controlled trial	Safety and efficacy of oral desensitization in 2-year-old children with cow's milk allergy, as an alternative to elimination diet	Efficacy of oral immunotherapy in schoolchildren with cow's milk allergy
Tools used to measure main outcome	SBPCFC	DBPCFC	DBPCFC	DBPCFC	DBPCFC	DBPCFC
Secondary outcomes	- Immunological changes	- Partial tolerance to CM - Safety (adverse reactions) - Immunological changes	- Safety (adverse reactions) - Immunological changes	- Immunological changes - Safety (adverse reactions)	- Partial tolerance to CM - Immunological changes - Safety (adverse reactions)	- Partial tolerance to CM - Immunological changes - Safety (adverse reactions)
Tools used to measure secondary outcomes	- Skin tests - Levels of sIgE levels to CM	- Tolerance between 5-150 mL of cow's milk - Adverse reactions. Need for epinephrine - sIgE levels to CM	- Adverse reactions. Need for epinephrine - sIgE levels to CM - Specific IgG4 levels to CM - Prick tests	- sIgE levels to CM - Adverse reactions. Need for epinephrine	- Tolerance between 20-200 mL of cow's milk - Skin test - Total IgE level - sIgE levels to CM and casein - Adverse reactions. Need for epinephrine	- Partial tolerance (<200 mL) - Symptoms presented by patients during SOTI - Specific IgE levels to CM

Abbreviations: CM, cow's milk; CMA, cow's milk allergy; CMP, cow's milk protein; DBPCFC, double-blind placebo-controlled food challenge; OD, oral desensitization; OIT, oral immunotherapy; SBPCFC, single-blind placebo-controlled food challenge; sIgE, specific IgE; SOTI, specific oral tolerance induction.

Table 2. Risk of bias based on the criteria established by the Cochrane Handbook for Systematic Review of Interventions

	Quality of Evidence From the Studies Included					
	Morisset et al [26]	Longo et al [22]	Skripak et al [25]	Pajno et al [23]	Martorell et al [3]	Salmivesi et al [24]
Sequence generation	Yes	Yes	Yes	Yes	Yes	Yes
Allocation sequence concealment	Unclear	Yes	Unclear	Yes	Yes	Yes
Blinding of patients/parents	Unclear	No	Yes	Yes	No	No
Blinding of personnel	Unclear	No	Yes	Yes	Yes	No
Incomplete outcome data	Unclear	Unclear	Yes	Yes	Yes	Yes
Selective outcome reporting	No	Yes	Yes	Yes	Yes	Yes
Outcome assessors	Unclear	Yes	Unclear	Yes	No	Unclear
Data collectors	Unclear	No	Unclear	Yes	Yes	Unclear
Data analysts	Unclear	No	Unclear	Yes	Yes	Unclear
Other threats to validity	No	No	No	No	No	No

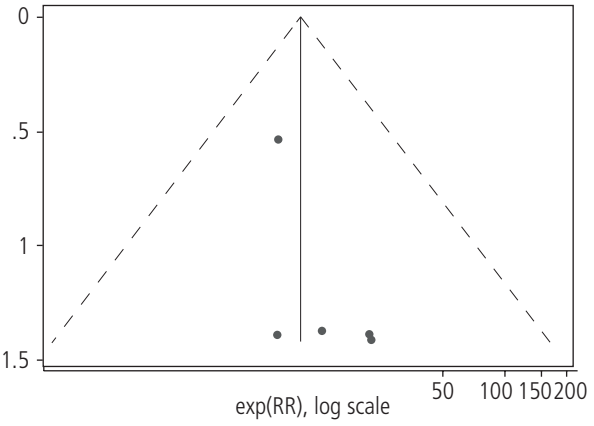

Figure 1. Publication bias. Funnel plot with pseudo 95% confidence limits.

3.3 Effect of Interventions/Conclusions

3.3.1 Immunological Changes (Variations in IgE Before and After Treatment)

One of the main objectives of this study was to evaluate the immunological changes that take place after OIT with cow's milk. Baseline and posttreatment cow's milk–specific serum IgE levels are shown in Table 3. The study by Morisset et al [26] was not included in the assessment of immunological changes, again owing to the selection criteria of patients with a baseline tolerance of 60 mL (unlike the other studies) and because we do not have the specific values of cow's milk–specific serum IgE for each of the patients.

In 3 of the articles [23-25], the authors found no significant differences in the variations in specific IgE before and after OIT. The results of Martorell et al [3] reveal a significant decrease in specific IgE milk levels after OIT (12 months of follow-up). Longo et al [22] observed a significant decrease in IgE levels in half of the patients treated with OIT, although they did use a cutoff IgE level of 100 kU_A/L, which can prevent detection of lower IgE levels in other patients.

The results of our 1-step individual patient data meta-analysis show a difference in the decrease in IgE levels between patients who were treated with OIT and those who were not of 8.1 kU_A/L (95%CI, –7.8 to 24), which is not statistically significant (*P*=.318). In the 2-step approach, the mean difference was 11.3 kU_A/L (95%CI, –1.9 to 24.5; *P*=.098) (Figure 2).

A greater decrease was observed in levels of cow's milk–specific serum IgE in patients treated with OIT than with placebo, although the difference was not statistically significant.

3.3.2 Amount of Cow's Milk Tolerated. Effectiveness of OIT

The other main objective of our meta-analysis was to determine whether OIT with cow's milk is sufficiently effective to be proposed as an alternative to an avoidance diet and symptomatic treatment for accidental exposure.

The results are summarized in Table 3 and Figure 3.

Studies show that OIT with cow's milk is more effective than an avoidance diet, since a greater percentage of patients treated with OIT acquire tolerance to cow's milk during the time taken to complete the study [3,22-26]. Excluding the trial by Morriset et al [26]—one of the inclusion criteria (selecting children with a baseline tolerance of 60 mL of milk) differs from those of the other studies—the results show that OIT multiplies the pooled relative risk by approximately 10-fold (RR, 10.2; 95%CI, 4.4-23.8) the possibility of achieving tolerance to CM.

In a sensitivity analysis, patients who were lost to follow-up were imputed as events. The pooled relative risk was 5.5 (95%CI, 2.6-11.7).

Table 3. Results

	Morisset et al [26]		Longo et al [22]		Skripak et al [25]		Pajno et al [23]		Martorell et al [3]		Salmivesi et al [24]	
Number of patients	60		60		20		30		60		28	
Groups	Active	Control	Active	Control	Active	Control	Active	Control	Active	Control	Active	Control
Number of patients in each group	28	32	30	30	13	7	15	15	30	30	18	10
Dropouts	1	2	0	0	1	0	2	1	1	4	2	2
Tolerant patients	24	18	11	0	6	0	10	0	27	3	12	0
Partially tolerant patients	ND	ND	27	0	ND	ND	ND	ND	1	0	4	0
Failure (no tolerance)	3	12	3	30	6	7	3	14	1	23	0	10
Adverse effects	3	0	30	6	4	0	10	0	24	0	16	2/3
Need for epinephrine	ND	ND	24 (neb) + 5 (im)	0	4	0	2	0	2	0		
Baseline CM-sIgE	ND	ND	101	101	34.8	14.4	39.0	40.1	15	23.6	18	12.6
CM-specific IgE after treatment	ND	ND	73.1	101	26.9	13.5	38.1	32.2	7	24.5	11	6.6
Baseline casein-sIgE	ND	ND	ND	ND	ND	ND	ND	ND	11.4	12.56	ND	ND
Casein-sIgE after treatment	ND	ND	ND	ND	ND	ND	ND	ND	2.61	19.1	ND	ND
Baseline CM-sIgG4	ND	ND	ND	ND	5	5.74	ND	ND	ND	ND	ND	ND
CM-sIgG4 after treatment	ND	ND	ND	ND	43.4	6.3	ND	ND	ND	ND	ND	ND
Baseline prick test	2.8 mm	2 mm	ND	ND	1:50	1:100	ND	ND	log 2.5	log 2.57	ND	ND
Prick test after treatment	1.4 mm	2.7 mm	ND	ND	1:3	1:50	ND	ND	log 0.962	log 2.75	ND	ND

Abbreviations: CM, cow milk; sIgE, specific IgE; neb, nebulized; im, intramuscular; ND, no data.

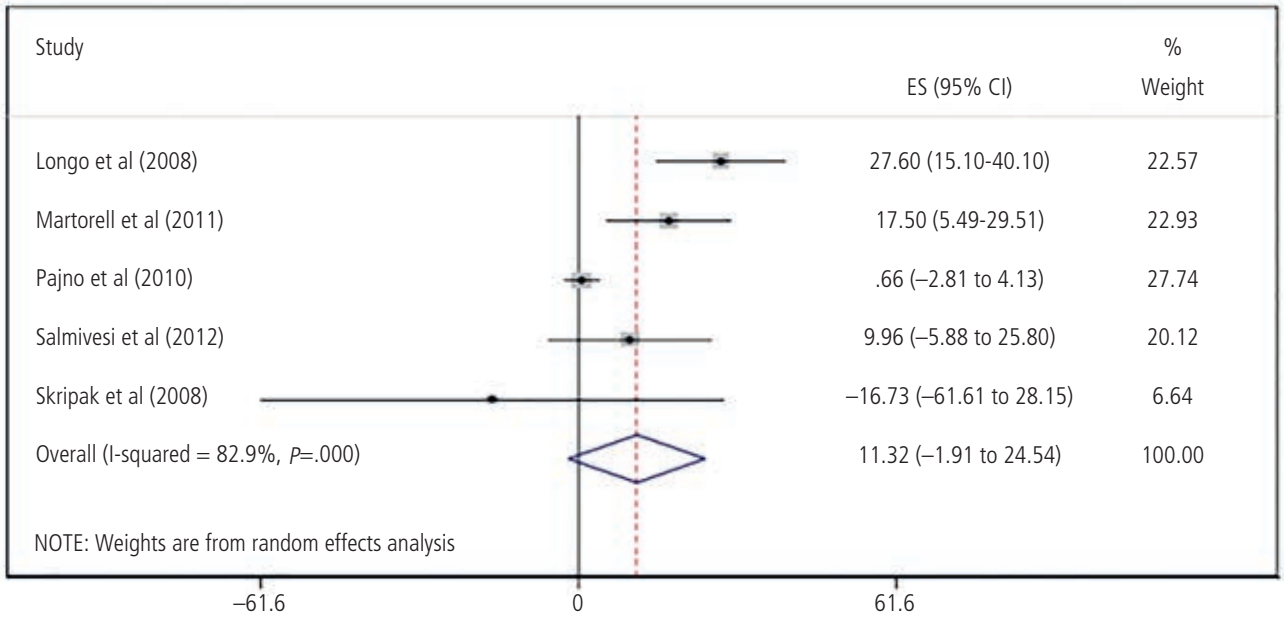

Figure 2. Results of immunological changes (variations in cow's milk-specific IgE levels before/after oral immunotherapy).

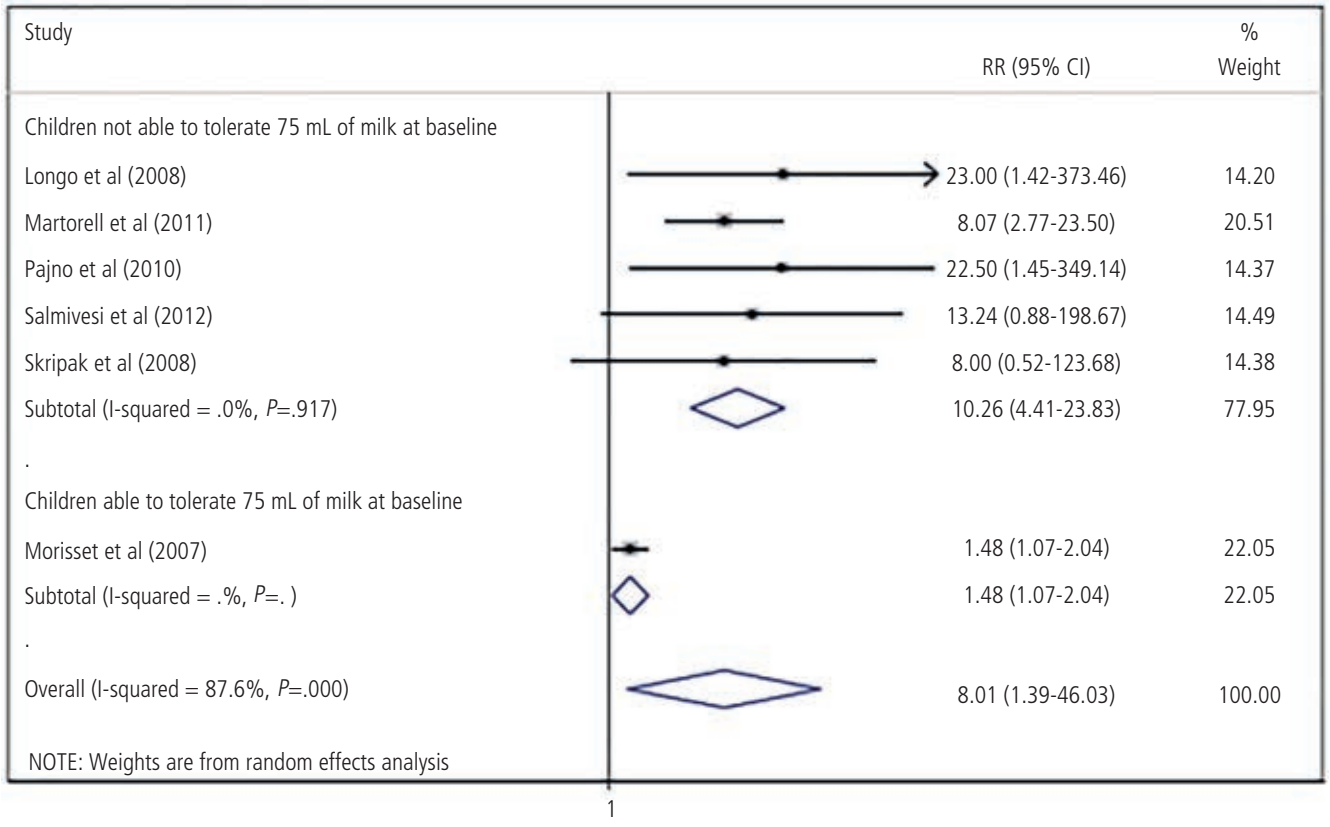

Figure 3. Results of effectiveness of oral immunotherapy with cow's milk.

In addition, in 3 of the studies, the number of patients who acquired partial tolerance is specified, thus allowing assessment of those patients who incrementally increased their tolerance threshold, despite not achieving complete tolerance [3,22,24].

3.3.1 Safety of OIT (Adverse Reactions. Need For Epinephrine)

The total number of patients who experienced adverse effects during the study and the number of patients requiring epinephrine are detailed in Table 3.

Although a significant number of adverse reactions were detected, in most cases these were mild.

The percentage of patients requiring treatment with parenteral epinephrine during OIT was specified in 4 studies: 6.7% [3], 13.3% [23], 16.7% [22], and 30.8% [25] (Table 3). None of the patients in the placebo group in the 4 articles required parenteral epinephrine.

3.3.1 Other Immunological Changes (Table 3)

Skripak et al [25] assessed variations in IgG4 levels and found a significant increase in the posttreatment group of patients who underwent OIT with cow's milk. Levels increased only minimally in the control group.

Martorell et al [3] assessed levels of specific IgE to cow's milk casein and found a significant decrease in the group of patients who underwent OIT with cow's milk (active group), with respect to the control group, after 12 months of follow-up.

Morisset et al [26], Skripak et al [25], and Martorell et al [3] found that the wheal in skin testing was smaller in patients who underwent OIT. A meta-analysis of the skin tests was not performed because of the differences in the presentation of results.

4. Discussion

In recent years, considerable research effort has been directed toward documenting the utility, effectiveness, benefits, and drawbacks of OIT with cow's milk. Research has also been aimed at improving the usefulness of the technique and establishing protocols for more widespread use.

We conducted a systematic review and meta-analysis of all controlled clinical trials published to date in which OIT with cow's milk was used for treatment of patients with IgE-mediated allergy to CMP. After comparing OIT with the conventional approach (avoidance), we conclude that this new strategy is an effective and reasonably safe alternative to the avoidance diet. OIT with cow's milk enables a greater number of patients to achieve tolerance without side effects.

Although 2 previously published meta-analyses synthesized data from clinical studies and drew more reliable conclusions on OIT with milk, we believe that our analysis provides important new insights [27,28]. We include a new study and, based on IPD, conduct a systematic review and meta-analysis in which the original data from each participant in the selected trials are reanalyzed and combined. This approach is considered the gold standard in evidence synthesis.

We evaluated immunological changes after treatment using IPD to show that OIT produces changes similar to those observed in patients taking immunotherapy against aeroallergens.

A tendency toward lower levels of milk-specific IgE was observed in OIT-treated patients but not in the control group. The absence of statistical significance could be explained by the high variability in IgE values resulting from missing individual data.

The authors who evaluated the decrease in casein-specific IgE found statistically significant differences after 1 year of follow-up [3].

It is not possible to analyze the evolution of IgG4 levels, since only 1 study shows significant differences for the increase in IgG4 with respect to the control group [23].

Further studies are needed to assess changes in milk-specific IgE and IgG4 to clarify the mechanisms underlying the effect of immunotherapy and their potential utility in the management of this technique.

In 2011, Fisher et al [4] published the first meta-analysis that determined whether there was sufficient evidence to state that OIT was a more effective technique than allergen avoidance in children with food allergy. The authors concluded that OIT cannot be recommended in daily practice for desensitization in children with IgE-mediated food allergy. However, they did evaluate the effect of OIT in all food allergies in general. The meta-analysis by Fisher et al included 3 trials [2,22,23], 1 of which we did not include (Staden et al [2]) because it assesses the efficacy of OIT in patients allergic both to cow's milk and to egg.

In a new meta-analysis published in March 2012, Brozek et al [27] investigated the effectiveness of OIT with cow's milk. The authors adopted a new approach to their previous specific analysis of OIT with cow's milk, which addressed the technique for the treatment of food allergy in general, by broadening their outcomes to include safety and the possibility of acquiring different degrees of tolerance (partial or complete). The analysis included 5 clinical trials, all of which were also included in our meta-analysis, and the authors found that the benefit of the OIT in patients with cow's milk allergy can be offset by the existence of frequent and occasionally severe side effects. The authors concluded that further studies with larger populations are warranted in order to ensure a more reliable assessment. For our meta-analysis, we included the 5 articles compiled by Brozek et al and an additional work that was recently published in 2013 [24].

Our results for full desensitization were slightly better than those reported by Yeung et al [28]. However, after a sensitivity analysis in which patients who were lost to follow-up were considered events, the pooled relative risk was 5.5 (95%CI, 2.6-11.7), which is very similar to that observed in Yeung et al. Desensitization rates were similar in all the studies, indicating that the procedure is effective in children.

Adverse reactions during OIT (both in the hospital and in the home phase) are common, although most are mild-moderate and easily managed [29-32]. We showed that OIT is a safe procedure when performed in the appropriate environment and with experienced medical staff. Although adverse reactions are not infrequent, most are mild and do not require treatment with epinephrine.

Our study is limited in that we could not perform a meta-analysis of safety or changes in skin reactivity to the antigen owing to differences in the presentation of results. However, this limitation could be corrected through consensus on measuring these variables in future OIT studies.

Our very broad search criteria make it unlikely that we missed any relevant information, and our findings probably reflect current best evidence on the use of OIT with cow's milk for IgE-mediated cow's milk allergy.

5. Conclusion

Our results and subsequent analysis enable us to conclude that OIT with cow's milk is effective for treatment of IgE-mediated cow's milk allergy: significantly more patients achieve tolerance with OIT than with an avoidance diet. OIT is reasonably safe, its side effects are mild-to-moderate and easily managed, and intramuscular epinephrine is rarely required. We found no significant differences with respect to lower levels of specific IgE to cow's milk in OIT-treated patients compared to patients who were not treated with this technique.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

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References

1. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, Plaut M, Cooper SF, Fenton MJ, Arshad SH, Bahna SL, Beck LA, Byrd-Bredbenner C, Camargo CA Jr, Eichenfield L, Furuta

GT, Hanifin JM, Jones C, Kraft M, Levy BD, Lieberman P, Luccioli S, McCall KM, Scheneider LC, Simon RA, Simons FE, Teach SJ, Yawn BP, Schwaninger JM. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 suppl):S1-58.
2. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. Allergy. 2007;62:1261-9.
3. Martorell A, De la Hoz, B, Ibañez MD, Bone J, Terrados MS, Michavila A, Plaza AM, Alonso E, Garde J, Nevot S, Echevarria L, Santana C, Cerdá JC, Escudero C, Guallar I, Piquer M, Zapatero L, Ferré L, Bracamonte T, Muriel A, Martínez MI, Félix R. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. Clin Exp Allergy. 2011;41:1297-304.
4. Fisher HR, Du Toit G, Lack G. Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance? Arch Dis Child. 2011;96:259-64.
5. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol. 1997;99:744-51.
6. Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, Davis FM, Hyun JD, Shanahan WR Jr. Avon Longitudinal Study of Parents and Children Study Team. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med. 2003;348:986-93.
7. Niggemann B, Staden U, Rolinck-Werninghaus C, Beyer K. Specific oral tolerance induction in food allergy. Allergy 2006;61:808-11.
8. Enrique E, Pineda F, Malek T, Bartra J, Basagaña M, Tella R, Castelló JV, Alonso R, de Mateo JA, Cerdá-Trias T, San Miguel-Moncín Mdel M, Monzón S, García M, Palacios R, Cisteró-Bahíma A. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immnol. 2005;116:1073-9.
9. Boyano-Martínez T, García-Ara C, Pedrosa M, Díaz-Pena JM, Quirce S. Accidental allergic reactions in children allergic to cow's milk proteins. J Allergy Clin Immunol. 2009;123:883-8.
10. Morrow-Brown H. Would oral desensitization for peanut allergy be safer than avoidance. Ann Allergy Asthma Immunol. 2007;98:203.
11. Patriarca G, Buonomo A, Roncallo C, Del Ninno M, Pollastrini E, Milani A, De Pasquale T, Gasbarrini G, Schiavino D, Nucera E. Oral desensitization in cow milk allergy: immunological findings. Int J Immunopath Pharmacol. 2002;15:53-8.
12. Patriarca G, Nucera E, Roncallo C, Pollastrini E, Bartolozzi F, De Pasquale T, Buonomo A, Gasbarrini G, Di Campli C, Schiavino D. Oral desensitizing treatment in food allergy: clinical and immunological results. Aliment Pharmacol Ther. 2003;17:459-65.
13. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. Allergy. 2004;59:980-7.
14. Patriarca G, Nucera E, Pollastrini E, Roncallo C, De Pasquale T, Lombardo C, Pedone C, Gasbarrini G, Buonomo A, Schiavino D. Oral specific desensitization in food-allergic children. Dig Dis Sci. 2007;52:1662-72.
15. Martorell Aragonés A, Félix Toledo R, Cerdá Mir JC, Martorell Calatayud A. Oral rush desensitization to cow milk. Following of desensitized patients during three years. Allergol Immunopathol. 2007;35:174-6.
16. Zapatero L, Alonso E, Fuentes V, Martínez MI. Oral desensitization in children with cow's milk allergy. J Investig Allergol Clin Immunol. 2008;18:389-96.
17. Caminiti L, Passalacqua G, Barberi S, Vita D, Barbeiro G, De Luca R, Pajno GB. A new protocol for specific oral tolerance induction in children with IgE-mediated cow's milk allergy. Allergy Asthma Proc. 2009;30:443-8.
18. Alvaro M, Giner MT, Vázquez M, Lozano J, Domínguez O, Piquer M, Días M, Jiménez R, Martíb MA, Alsina L, Plaza AM. Specific oral desensitization in children with IgE-mediated cow's milk allergy. Evolution in one year. Eur J Pediatr. 2012;171:1389-95.
19. Fiocchi A, Brozek J, Schünemann H, Bahna SL, von Berg A, Beyer K, Bozzola M, Bradsher J, Compalati E, Ebisawa M, Guzmán MA, Li H, Heine RG, Keith P, Lack G, Landi M, Martelli A, Rancé F, Sampson H, Stein A, Terracciano L, Vieths S. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. Pediatr Allergy Immunol. 2010;21(Suppl 21):1-125.
20. Scurlock AM, Jones SM. An update on immunotherapy for food allergy. Curr Opin Allergy Clin Immunol. 2010;10:587-93.
21. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol. 2011;127:18-27.
22. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, Ventura A. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol. 2008;121:343-7.
23. Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, Passalacqua G. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. Ann Allergy Asthma Immunol. 2010;105:376-81.
24. Salmivesi S, Korppi M, Mäkäela MJ, Paassilta M. Milk oral immunotherapy is effective in school-aged children. Acta Paediatr. 2013;102:172-6.
25. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, Matsui EC, Burks AW, Wood RA. A randomized, double blind, placebo controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2008;122:1154-60.
26. Morisset M, Moneret-Vautrin DA, Guenard L, Cuny JM, Frentz P, Hatahet R, Hanss Ch, Beadouin E, Petit N, Kanny G. Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases. A randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. Eur Ann Allergy Clin Immunol. 2007;39:12-9.
27. Brozek JL, Terracciano L, Hsu J, Kreis J, Compalati E, Santesso N, Fiocchi A, Schünemann HJ. Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and meta-analysis. Clin Exp Allergy. 2012;42:363-74.
28. Yeung JP, Kloda LA, McDevitt J, Ben-Shoshan M, Alizadehfar R. Oral immunotherapy for milk allergy. Cochrane Database

Syst Rev. 2012;11:CD009542.doi:10.1002/14651858.CD009542.pub2.
29. Barbi E, Longo G, Berti I, Matarazzo L, Rubert L, Saccari A, Lenisa I, Ronfani L, Radillo O, Ventura A. Adverse effects during specific oral tolerance induction: in home phase. Allergol Immunopathol. 2012;40:41-50.
30. Barbi E, Longo G, Berti I, Neri E, Saccari A, Rubert L, Matarazzo L, Montico M, Ventura A.. Adverse effects during specific oral tolerance induction: in-hospital "rush" phase. Eur Ann Allergy Immunol. 2012;44:18-25.
31. Flinterman AE, Knulst AC, Meijer Y, Bruijnzeel-Koomen CA, Pasmans SG. Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. Allergy. 2006;61:370-4.
32. Sopo SM, Onesimo R, Giorgio V, Fundarò C. Specific oral tolerance induction (SOTI) in pediatric age: clinical research or just routine practice? Pediatr Allergy Immunol. 2010;21:e446-9.

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