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/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.


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 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 LV en niños, evaluando los cambios inmunológicos, la adquisición...
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 bibilographic 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/
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 Immunopathologica.

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 [3,22-26] 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.

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

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<td>2008</td>
<td>2010</td>
<td>2011</td>
<td>2012</td>
</tr>
<tr>
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<td>20</td>
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<td>5-17</td>
<td>6-17</td>
<td>4-10</td>
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<td>6-14</td>
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<tr>
<td><strong>Male/Female</strong></td>
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<td>39/21</td>
<td>12/8</td>
<td>17/13</td>
<td>34/26</td>
<td>12/16</td>
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### 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
- Skin prick test to CM positive
- CM-specific IgE levels >0.35 kU/L
- DBPCFC positive to the lowest doses (≤0.8 mL of whole milk)
- 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/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/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 (n)
- 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)
- 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
- 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
- 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.

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.
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/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/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/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 Morisset 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

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<td>30</td>
<td>60</td>
<td>28</td>
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<tr>
<td>Groups</td>
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<td>Active  Control</td>
<td>Active  Control</td>
<td>Active  Control</td>
<td>Active  Control</td>
<td>Active  Control</td>
</tr>
<tr>
<td>Number of patients in each group</td>
<td>28 32</td>
<td>30 30</td>
<td>13 7</td>
<td>15 15</td>
<td>30 30</td>
<td>18 10</td>
</tr>
<tr>
<td>Dropouts</td>
<td>1 2</td>
<td>0 0</td>
<td>1 0</td>
<td>2 1</td>
<td>1 4</td>
<td>2 2</td>
</tr>
<tr>
<td>Tolerant patients</td>
<td>24 18</td>
<td>11 0</td>
<td>6 0</td>
<td>10 0</td>
<td>27 3</td>
<td>12 0</td>
</tr>
<tr>
<td>Partially tolerant patients</td>
<td>ND ND</td>
<td>27 0</td>
<td>ND ND</td>
<td>ND ND</td>
<td>1 0</td>
<td>4 0</td>
</tr>
<tr>
<td>Failure (no tolerance)</td>
<td>3 12</td>
<td>3 30</td>
<td>6 7</td>
<td>3 14</td>
<td>1 23</td>
<td>0 10</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>3 0</td>
<td>30 6</td>
<td>4 0</td>
<td>10 0</td>
<td>24 0</td>
<td>16 2/3</td>
</tr>
<tr>
<td>Need for epinephrine</td>
<td>ND ND</td>
<td>24 (neb)</td>
<td>ND ND</td>
<td>ND ND</td>
<td>ND ND</td>
<td>ND ND</td>
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<tr>
<td>Baseline CM-sIgE</td>
<td>ND ND</td>
<td>101 101</td>
<td>34.8 14.4</td>
<td>39.0 40.1</td>
<td>15 23.6</td>
<td>18 12.6</td>
</tr>
<tr>
<td>CM-specific IgE after treatment</td>
<td>ND ND</td>
<td>73.1 101</td>
<td>26.9 13.5</td>
<td>38.1 32.2</td>
<td>7 24.5</td>
<td>11 6.6</td>
</tr>
<tr>
<td>Baseline casein-sIgE</td>
<td>ND ND</td>
<td>ND ND</td>
<td>ND ND</td>
<td>ND ND</td>
<td>11.4</td>
<td>12.56</td>
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<td>Casein-sIgE after treatment</td>
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<td>ND ND</td>
<td>ND ND</td>
<td>2.61</td>
<td>19.1</td>
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<td>Baseline CM-sIgG4</td>
<td>ND ND</td>
<td>ND ND</td>
<td>5 5.74</td>
<td>ND ND</td>
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<td>CM-sIgG4 after treatment</td>
<td>ND ND</td>
<td>ND ND</td>
<td>43.4 6.3</td>
<td>ND ND</td>
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<td>Baseline prick test</td>
<td>2.8 mm</td>
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<td>1:50</td>
<td>1:100</td>
<td>ND ND</td>
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<tr>
<td>Prick test after treatment</td>
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<td>2.7 mm</td>
<td>ND ND</td>
<td>1:3</td>
<td>1:50</td>
<td>ND ND</td>
</tr>
</tbody>
</table>

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).
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.

Acknowledgments

We thank Giovanni B Pajno, MD (Allergy Unit, Department of Pediatrics, University of Messina, Italy), Egidio Barbi, MD (Pediatric Department, IRCCS, Burlo Garofolo, University of Trieste, Italy), and Marita Paassilta, MD, PhD (Allergy Centre, Tampere University Hospital, Finland) for providing raw data.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

Data from this study were presented at "Simposio Internacional de Alergia a Himenópteros" 2013, 24-26 October, Granada, Spain.

References

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